Title

Chapter 13 Positive Psychiatry and successful aging in people with schizophrenia

Authors

Jeste, Dilip V
Van Patten, Ryan
Lee, Ellen E

Publication Date

2020

DOI

10.1016/b978-0-12-800136-3.00013-2

Peer reviewed

Handbook of MENTAL HEALTH AND AGING

THIRD EDITION

Edited by
NATHAN HANTKE, AMIT ETKIN
AND RUTH O'HARA

Handbook of Mental Health and Aging

This page intentionally left blank

Handbook of Mental Health and Aging

Third Edition

Edited by

Nathan Hantke
Department of Neurology, Oregon Health and Science University, Portland, OR, United States; Mental Health and Neuroscience Division, VA Portland Health Care System, Portland, OR, United States

Amit Etkin
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Ruth O'Hara
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States; Stanford/VA Alzheimer's Center, Palo Alto, CA, United States

ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-800136-3

Publisher: Nikki Levy
Editorial Project Manager: Barbara Makinster
Production Project Manager: Punithavathy Govindaradjane
Cover Designer: Matthew Limbert

Typeset by MPS Limited, Chennai, India

Contents

This page intentionally left blank

List of Contributors

Vimal M. Aga Layton Aging and Alzheimer's Disease Center, Oregon Health and Science University, Portland, OR, United States

Lauren A. Anker Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States

Patricia A. Areán Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Sherry A. Beaudreau Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States; School of Psychology, University of Queensland, Brisbane, QLD, Australia

Claire Bird Department of Psychology, Marquette University, Milwaukee, WI, United States

Mousa S. Botros Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States; Mental Health and Behavioral Sciences Service, Miami VA Healthcare System, Miami, FL, United States; Mental and Behavioral Health Service, Jackson Health System, Miami, FL, United States

Nicholas T. Bott Clinical Excellence Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States; Department of Psychology, PGSP-Stanford Consortium, Palo Alto University, Palo Alto, CA, United States

Sarah Brown Bio-Medical Library, University of Minnesota, Minneapolis, MN, United States

Casey Buck Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Meryl A. Butters Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States

Laura M. Campbell SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, United States

Regina M. Carney Mental and Behavioral Health Service, Jackson Health System, Miami, FL, United States

Erin Cassidy-Eagle Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Christina F. Chick Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States

Breno S. Diniz Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Annemiek Dols Department of Psychiatry, Amsterdam UMC, Location Vrije Universiteit Medical Center, Amsterdam, The Netherlands

Katherine Dorociak Minneapolis VA Health Care System, Minneapolis, MN, United States

Spencer Eth Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States; Mental and Behavioral Health Service, Jackson Health System, Miami, FL, United States

Amit Etkin Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Lisa T. Eyler Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Desert Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, United States

Limor Gertner Neuropsychiatric Clinic, Soroka University Medical Center, Beer-Sheva, Israel

Danielle K. Glorioso Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States

Christine E. Gould Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Geriatric Research Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, United States

Julie E. Guzzardi Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States; Mental Health and Behavioral Sciences Service, Miami VA Healthcare System, Miami, FL, United States; Mental and Behavioral Health Service, Jackson Health System, Miami, FL, United States

Joachim F. Hallmayer Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States

Nathan Hantke Department of Neurology, Oregon Health and Science University, Portland, OR, United States; Mental Health and Neuroscience Division, VA Portland Health Care System, Portland, OR, United States

Laura Hein Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States

Alana Iglewicz Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Veterans Affairs San Diego Healthcare System, San Diego, CA, United States

Dilip V. Jeste Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States; Department of Neurosciences, University of California San Diego School of Medicine, La Jolla, CA, United States

Tylor J. Jilk Department of Public Health, Baylor University, Waco, TX, United States; Space Exploration Technologies, Hawthorne, CA, United States

Joshua T. Jordan Department of Psychiatry, University of California San Francisco, San Francisco, CA, United States; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Christine Juang Psychology Service, VA Palo Alto Health Care System, Palo Alto, CA, United States

Rosy Karna Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Makoto Kawai Stanford/VA Alzheimer's Research Center, VA Palo Alto Health Care System, Palo Alto, CA, United States; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Stanford Center for Sleep Sciences and Medicine, Redwood City, CA, United States

Jeffrey Kaye Department of Neurology, Oregon Health & Science University, Portland, OR, United States; Oregon Center for Aging & Technology, Portland, OR, United States

Susan Sharp Kolderup Home Based Primary Care, Memphis VA Medical Center, Memphis, TN, United States

Beth Ann LaBardi Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Ellen E. Lee Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States

Gregory B. Leong Department of Psychiatry and Behavioral Sciences, Keck School of Medicine of the University of Southern California, Los Angeles, CA, United States

Omer Linkovski Department of Psychiatry and Behavioral Sciences and Wu Tsai Neurosciences Institute, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States; Department of Medical Neurobiology (Physiology), Faculty of Medicine, The Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University, Jerusalem, Israel

Julia R. Loup Department of Psychology, The University of Alabama, Tuscaloosa, AL, United States

Flora Ma Geriatric Research Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, United States; Pacific Graduate School of Psychology, Palo Alto University, Palo Alto, CA, United States

Nehjla Mashal Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States; Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Felicia Mata-Greve Department of Psychology, Marquette University, Milwaukee, WI, United States

Leander K. Mitchell School of Psychology, University of Queensland, Brisbane, QLD, Australia

Raeanne C. Moore Department of Psychiatry, University of California San Diego School of Medicine, San Diego, CA, United States; VA San Diego Healthcare System, San Diego, CA, United States

Philippe Mourrain Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Beckman Center, Stanford University School of Medicine, Stanford, CA, United States

Martin S. Mumenthaler Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Sharon Naparstek Department of Psychiatry and Behavioral Sciences and Wu Tsai Neurosciences Institute, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States

Ruth O'Hara Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States; Stanford/VA Alzheimer's Center, Palo Alto, CA, United States

Nancy A. Pachana School of Psychology, University of Queensland, Brisbane, QLD, Australia

Kai Parker-Fong Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Renee Pepin Geisel School of Medicine at Dartmouth, Hanover, NH, United States

Elaine R. Peskind Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Murray A. Raskind Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Brenna N. Renn Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Meghan Riddle Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, United States; Department of Psychiatry, University of Kentucky College of Medicine, Lexington, KY, United States

Erin Y. Sakai Psychology Service, VA Palo Alto Health Care System, Palo Alto, CA, United States

Carl Salzman Department of Psychiatry, Harvard Medical School, Boston, MA, United States; Beth Israel Deaconess Medical Center & Massachusetts Mental Health Center, Boston, MA, United States

Logan Schneider Stanford/VA Alzheimer's Research Center, VA Palo Alto Health Care System, Palo Alto, CA, United States

Adriana Seelye Minneapolis VA Health Care System, Minneapolis, MN, United States; Department of Psychiatry, University of Minnesota, Minneapolis, MN, United States; Department of Neurology, Oregon Health & Science University, Portland, OR, United States; Oregon Center for Aging & Technology, Portland, OR, United States

Mujeeb U. Shad Department of Psychiatry, Oregon Health and Science University, Portland, OR, United States

Rammohan Shukla Department of Neuroscience, University of Toledo, Toledo, OH, United States

Etienne Sibille Department of Neuroscience, University of Toledo, Toledo, OH, United States; Departments of Psychiatry and of Pharmacology and Toxicology, Campbell Family Mental Health Research Institute of Centre for Addiction and Mental Health (CAMH), University of Toronto, Toronto, ON, Canada

Elizabeth Straus Department of Psychiatry, University of California San Diego School of Medicine, San Diego, CA, United States; VA San Diego Healthcare System, San Diego, CA, United States

Warren D. Taylor Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, United States; Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, United States

Lucas Torres Department of Psychology, Marquette University, Milwaukee, WI, United States

Jürgen Unützer Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Snezana Urosevic Minneapolis VA Health Care System, Minneapolis, MN, United States; Department of Psychiatry, University of Minnesota, Minneapolis, MN, United States

Ryan Van Patten Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States

Gordon X. Wang Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States; Beckman Center, Stanford University School of Medicine, Stanford, CA, United States

Lucy Y. Wang Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Katherine Wild Department of Neurology, Oregon Health & Science University, Portland, OR, United States; Oregon Center for Aging & Technology, Portland, OR, United States

Hongru Zhu Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Sidney Zisook Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States; Veterans Affairs San Diego Healthcare System, San Diego, CA, United States

Preface

The publication of the third edition of the *Handbook of Mental Health and Aging* marks four decades since the arrival of the inaugural edition. Supported by the National Institute of Mental Health, the first edition aimed to introduce the readers to the brand new field of Geriatric Mental Health, with the goal of providing an overview of topics within a field predicted to grow in significance. The editors' predictions proved correct, and the book provided a foundational background for practitioners and researchers to understand the broad range of factors associated with mental health care in older adults. By the publication of the second edition in 1992, the field of geriatric psychiatry had blossomed, as evidenced by the creation of multiple journals such as the *American Journal of Geriatric Psychiatry* and *International Journal of Geriatric Psychiatry* and increasing contributions to this domain of investigation. The editors captured this excitement, providing an integrated review of mental health in older adults. With 33 chapters, the authors provided a broad spectrum of content, including but not limited to age-related neurochemical changes in the brain, mood disorders in older adults, and an introduction on how to provide environmental interventions for cognitively impaired older adults. This second edition established itself as essential within the field, serving as the definitive reference work for researchers, clinicians, and advanced students working within mental health.

While many of the central topics discussed in the second edition remain very relevant today, our understanding of the process of aging and its interaction with mental health has grown substantially. Exciting developments in technology have accelerated our understanding of how dysfunction in neural circuitry can contribute to late-life mental health symptoms, and advances in nearly all areas of older adult care have had large impacts on the field over the past 20 years. The purpose of this current third edition is to provide an authoritative review of the current state of geriatric mental health, while also considering the future directions. The subject matter within this book is as broad as the older adults who we serve, yet reflects a natural evolution within an ever-expanding field. Conducting research and translating this work to provide optimal mental health care in older adults not only requires in-depth knowledge, but covers a broad range of domains that impact late-life mental health, including psychopathology, psychotherapy, pharmacology, cognitive function, neurodegenerative disorders, neurological changes associated with aging, appreciation of self-care, and end-of-life issues. In addition, in many ways, the treatment of mental health in older adults is a function of our society, influenced by caregiver support, community systems, sociocultural factors, and larger financial structures. The content of this book attempts to represent the complicated interaction between these factors at a level that aims to be valuable to clinicians, researchers, postdoctoral fellows, and advanced graduate students.

The current edition of this book, similar to past editions, is broadly divided into overarching themes or sections: conceptual factors associated with mental health, behavioral neuroscience and aging, psychopathology in late life, assessment in older adults, and intervention. Importantly, chapter authors were carefully selected to be content experts, leading researchers, prominent clinicians, and visionaries within the field. Within each chapter, there was a thoughtful emphasis on providing a synthesis of the current integration of research into clinical practice. In doing so, it is our intention to reflect the current cross-collaborative zeitgeist within the field and provide a comprehensive review of the diverse topics necessary to appreciate mental health care in older adults. The book opens with the discussion of large conceptual factors, such as the epidemiology of mental health disorder in aging and cultural factors that impact mental health. The book then transitions into neurobiological-based topics that play a vital role in aging, such as biomarkers, age-related structural changes in the brain, and current models of accelerated aging in mental health. Defined clinical topics, such as dementia, neuropsychology, and mood disorders, are presented as individual chapters set within related theories. The book finally closes with a discussion of the current and future trends within geriatric mental health, including the brain functional connectome, repetitive transcranial magnetic stimulation (rTMS), Precision Psychiatry, and treatment innovations.

Each chapter is designed to serve as a standalone introduction to its subject matter, and it is not necessary to read this book from front to back. Topics within each chapter are defined and provided within a foundational framework and then expanded to discuss the unique factors associated with older adults. As medicine continues to become more niched,

there is tendency to split subjects into their respective silos. Instead, in this book, we aimed to provide a forum where authors could integrate complicated interdisciplinary topics to communicate a holistic view of geriatric mental health. We are grateful to the excellent authors who contributed to this book; each embraced our vision to provide a definitive reference, synthesizing complicated topics that are all important for appreciating the processes in mental health and aging, yet are not commonly brought together within one book.

This book would not be possible without the incredible contribution of many people. Dr. Hantke would like to thank his wife Mindy for her endless encouragement, humor, and love during the process of bringing together this book and in the larger pursuit of the career that he loves. He would like to also thank his son Shaw for his inspiration and levity and his parents for their unending support. He would additionally like to thank his mentors and colleagues for their support and guidance at all stages of his career: Drs. Kristy Nielson, Naomi Chaytor, Ruth O'Hara, Sherry Beaudreau, Maheen Adamson, and many others.

Dr. O'Hara would like to thank all her colleagues who have inspired her work in aging for almost three decades, in particular the generous support and mentorship of Drs. George Alexopoulus, Lisa Eyler, Stuart Gilman, Dilip Jeste, Helena Kraemer, Barry Lebowitz, Charles Reynolds, Yvette Sheline, Etienne Sibille, Gwenn Smith, Warren Taylor, Larry Thompson, Dolores Gallagher-Thompson, Jared Tinklenberg, Jerome Yesavage, and Toni and Bob Zeiss. She is particularly grateful for her excellent collaboration with Dr. Sherry Beaudreau, who contributed in so many ways to this book, and Dr. Amit Etkin who brought state-of-the-art neuroscience expertise to his role as coeditor. However, this book would simply not have been possible without the outstanding leadership, content expertise, and tenacity of our Editor-in-Chief, Dr. Nathan Hantke, and I am forever grateful for his extraordinary hard work on this edition. Finally, I would like to thank Joseph McBride who taught me to be a better writer; my friends Joachim and Claudia, for always providing a home away from home; KJ, Natasha, Max, Aisling, Sabha, and Catherine, for all their affection and fun; my phenomenal, supportive and inspiring sisters, Gwenn, Susan, and Fiona; and my mother who had the vision and determination to bring us all to the United States and change our lives forever; and to my wonderful son, John William O'Hara McBride, my sine qua non.

Nathan Hantke, Amit Etkin and Ruth O'Hara

Chapter 1

Concepts and issues in mental health and aging

Nathan Hantke[1,2] **and Ruth O'Hara**[3,4,5]

[1]Department of Neurology, Oregon Health and Science University, Portland, OR, United States, [2]Mental Health and Neuroscience Division, VA Portland Health Care System, Portland, OR, United States, [3]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [4]Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States, [5]Stanford/VA Alzheimer's Center, Palo Alto, CA, United States

The second and last prior edition of this book was published in 1992, seemingly a lifetime ago within the field of geriatric mental health research, and perhaps truly a lifetime ago for some readers. Over the 28 year span leading to the current version, the field of mental health and aging has experienced an unprecedented level of change and growth. The fundamental taxonomy of many mental health disorders has been questioned, adjusted, and redefined. The detection of biomarkers has taken a center stage in health care, and the conceptualization of mental health research within multidimensional constructs (e.g., RDoC) is a radical departure from dichotomous-based classification models for psychiatric disorders (Cuthbert, 2015). Neuroimaging techniques have grown at an unprecedented rate. For example, the first publications on the technique of blood oxygen level–dependent imaging, vital in functional MRI, were released while the last edition of this book was in press (Kwong, 2012; Ogawa, Lee, Kay, & Tank, 1990). The role of mental health in whole-body well-being has gained traction, particularly as it applies to aging. The complex interplay of psychiatric symptoms, cognition, daily functioning, and aging is increasingly appreciated in medical care. Increasing thoughtfulness toward the importance of cultural competence, recognition of the impact of ethnic discrimination on mental health, and the integration of person-centered language into the lexicon of patient care are all relatively new, yet sorely needed changes within mental health care.

Yet, many fundamental aspects of mental health care in older adults remain little changed. Many chapters from the last edition are still directly important in today's health care system. Clinical care and research in older adults are sorely underfunded despite generations of warning of the now pending "silver tsunami" of baby boomers reaching older age. Dementia disorders, while heavily studied, continue to have no cure and place heavy burden upon patients, families, and the health care system despite modest strides in research. However, there has been substantial progress made in even the areas noted above, and many of the trends in research predicted by Dr. Barry Lebowitz and Dr. George Niederehe in the prior edition of this *Handbook* have come to fruition (Lebowitz & Niederehe, 1992). They accurately predicted increased attention to the relationship between sleep disorders and aging, which is now recognized as an important area of study and necessitated two chapters on the topic in the current edition. Drs. Lebowitz and Niederehe similarly successfully predicted increased recognition of the role of social isolation on mental health in older adults, and the increasing acknowledgment of caregiver burden within our society (Bott, Sheckter, & Milstein, 2017).

The goal of this chapter is not to provide new theories or provide a comprehensive review of topics; we will leave that to the authors of the following chapters. Instead, we aim to briefly synthesize the current state of the field and discuss the critical issues facing researchers and clinicians providing care to older adults. Mental health care is presently in an exciting time, as collaborations between neurochemistry, cognitive neuroscience, psychology, and psychiatry have recently resulted in fascinating breakthroughs with the potential to improve clinical care. We believe the following chapters, written by leaders in these areas, capture this zeitgeist. Importantly, we would like to first acknowledge Drs. James Birren, Bruce Sloane, and Gene Cohen, the previous editors of this *Handbook of Mental Health and Aging* (1980; 1992), who have left us gigantic shoes to fill and a robust foundation upon which to develop this book.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00001-6

Critical issues in mental health

The current edition of this book, similar to past editions, is broadly divided into overarching themes or sections: conceptual factors associated with mental health, behavioral neuroscience and aging, psychopathology in late-life, assessment in older adults, and intervention. The book begins with Drs. Renn, Areán, and Unützer discussing the epidemiology of select mental health disorders in late-life, including associated risk factors. As noted in their chapter, improvement in medical care has resulted in longer life expectancy and an associated need for more providers who specialize in providing mental health care for older adults. This increase in the geriatric population has significant implications for the health care system, a concern which has been espoused by multiple authors and work groups for the past decades (Institute of Medicine, 2012). Providers working with geriatric patients need related training to provide adequate care, as older adults often present with complicated medical problems that may exacerbate or mask mental health disorder. In addition, as discussed by the authors, the prevalence, risk factors, and presentation of mental health disorders may be very different in older adults as compared to younger adults.

In his chapter, Dr. Bott discusses the economic implications and history of U.S. health policy associated with geriatric mental health. There is growing evidence that preventative care leads to lower health care utilization, which in turn results in financial benefit. The creation of a health care infrastructure that is proactive to medical problems, as compared to reactive, is a complicated endeavor. Dr. Bott and colleagues discuss such a model for Alzheimer's disease care, providing a comprehension plan of targeting outpatient treatment of chronic medical issues, managing acute cognitive concerns, and providing caregiver support (Bott et al., 2019). They propose that this plan would theoretically save billions of health care dollars while concurrently improving the quality of care, utilizing coordination of care and protective interventions (Bott et al., 2019). Such programs aimed at improving the efficiency of mental health care through prevention and integrated care are at the forefront of proposed high-value care delivery policies, and a potential critical component of improving care for the growing number of older adults. Similar collaborate care models have already been shown to be very effective in treating depression in older adults (Hunkeler et al., 2006).

Mental health disorder in older adults

Clinicians and researchers who work with older adults appreciate the complex nature of mental health care within this population. Complicated medical problems (including cognitive impairment) may interact with and exacerbate mental health symptoms in older adults. Dr. Moore and her colleagues discuss such interactions in the context of stressors. The authors provide an excellent overview on how stress results in cumulative "wear and tear" on the older adult body, including immune dysregulation, inflammatory response, increased risk for cognitive dysfunction, and multiple other negative outcomes. Similarly, Drs. Hein, Dols, and Eyler discuss how bipolar disorder in older adults differs from that seen in younger adults, and discuss the current state of research on accelerated aging and cognitive impairment in older adults with bipolar disorder. This relationship between cognitive impairment, aging, and mental health is a common theme throughout the book and discussed in multiple other chapters.

The understanding of anxiety, depression, and suicidality in older adults has lagged behind the extensive empirical work seen in younger adults. What is known suggests that the etiology and symptom presentation may differ between younger and older adults, requiring special consideration when conceptualizing and diagnosing these disorders. Drs. Beaudreau and colleagues discuss how anxiety symptoms may present in older adults, and propose appropriate assessment and psychotherapy approaches, including an up-to-date review of the effectiveness of cognitive behavioral therapy for anxiety disorders in older adults. Drs. Jordan and Anker review the current research in suicide in late-life, including risk factors, current psychological theories, and recommended treatments. Within their subsection on neurodegeneration, the authors discuss recent research correlating structural differences shown on neuroimaging and associated executive dysfunction in those with suicidal ideation and those whom attempt suicide. Specifically, that executive dysfunction increases the overall likelihood of suicide in older adults (Gujral et al., 2014). Such findings reflect the growing appreciation of the relationship between cognition, mental health, and neural network dysfunction.

Drs. Van Patten, Lee, and Jeste discuss the relationship between schizophrenia and aging in their chapter, providing additional conceptual framework for utilizing positive psychiatry for this severe mental illness. Rooted in the well-established approach of humanistic psychology, positive psychiatry provides a refreshing perspective to healthy aging. Positive psychiatry characteristics, such as resilience and increased family support, are associated with better emotional health in aging. This long overdue movement toward assessing and treating the whole individual (medical, emotional, psychosocial, etc.) has resulted in exciting research showing that higher positive psychiatry–related characteristics result in better functional outcomes and serve as a protective factor against the negative effects of illness in older adults.

The interplay of neurobiology, cognition, and psychiatric symptoms

The growing appreciation of neurobiology in mental illness has resulted in increased study of related biomarkers. In their chapter, Drs. Diniz and Butters review the current understanding of the biological mechanisms underlying cognitive impairment in late-life depression, and the complex neurobiological relationship between depression and neurotrophic cascades. Cognitive impairment is relatively common in older adults with depression and is associated for increased risk for dementia (Kaup et al., 2016). A recently published case study reinforces the importance of integrating neuropsychological findings and structural brain imaging in the assessment of suspected depression-based dementia, discussing the cognitive correlates of vascular-based depressive symptoms (Sheline et al., 2010; Tanner, Mellott, Dunne, & Price, 2015). In Chapter 8, Accelerated brain molecular aging in depression, Drs. Shukla and Sibille propose that age-related changes in gene expression are the driving process behind late-life depression and associated cognitive dysfunction, providing an eloquent model of molecular aging that has profound implications for late-life neuropsychiatry.

The assessment of cognitive functioning plays a pivotal role in understanding and appreciating the aging process. Neuropsychological assessment has predominantly relied upon paper and pencil tests to assess cognitive function. The field was originally founded to assess deficits in function, often as a method to localize lesions. With the advent of refined neuroimaging techniques, neuropsychology has pivoted to assisting in differential diagnosis of cognitive-related disorders and the quantification of cognitive abilities in older adults, topics which are discussed in detail in this book. There is growing evidence that individuals with late-life psychiatric disorders have distinctly different cognitive difficulties beyond what would be expected for age. Dr. Chick, Ms. Buck, and Dr. O'Hara discuss in their chapter recent breakthroughs in the proposed reciprocal relationship between emotional processing and cognition. Growing evidence supports a shared etiology behind the onset of late-life mood disorders and disruption in neural networks. One paradigm-shifting example of this is the "Vascular Depression Hypothesis" long championed by Dr. George Alexopoulos (Alexopoulos, Bruce, Silbersweig, Kalayam, & Stern, 1999). This hypothesis posits that cerebrovascular disease burden may precipitate or perpetuate depression in older adults, a hypothesis that has been strongly supported by the now well-established observed relationship between white matter hyperintensities on neuroimaging, executive dysfunction, and late-life depression (Taylor, Aizenstein, & Alexopoulos, 2013). Vascular-driven depression may also be more treatment-resistant to SSRIs, such as sertraline, with greater cognitive dysfunction associated with worse treatment response (Sheline et al., 2010). On a broader level, such findings are important in the conceptualizing the mechanisms of interaction between cognitive function, neuropathology, and mental health and proposed mechanisms of treatment.

Technology has started shaping the way clinicians approach the assessment process and bridged the gap between office-based testing and ecological validity. The functional assessment of older adults is reviewed by Dr. Seelye and her colleagues in their chapter, providing a comprehensive overview of the current state the field's ability to assess and predict an older adult's capacity to perform tasks of everyday living. Smart-home technology involving the use of unobtrusive sensor systems now has the ability to provide data on changes in an individual's activity level and monitor performance of daily activities in vivo. In an example of this, a recent study utilized a remote activity system that monitored the behavior of older adults with dementia. Caregivers were then notified to changes in the individual's behavior, successfully alerting them of events such as falls and wandering (Gaugler et al., 2019). Research continues to move forward not only in monitoring behavior but also in utilizing passive monitoring to predict decline. Recent research showed evidence of sensor-based walking speed being able to predict future falls (Piau et al., 2019) and that passive monitoring of an individual's ability to navigate the internet can as a proxy of cognitive functioning, and thus everyday functioning in other areas (Woods, Kordovski, Tierney, & Babicz, 2019). While these kinds of technology are not yet integrated into clinical care, research continues at a rapid pace and the continued assimilation of technology into all daily activities suggests passive monitoring of status will likely only increase.

A reflection on intervention

Psychotherapy

Psychotherapy approaches have also undergone a significant period of growth over the last several decades, as reviewed by Drs. Mitchell and Pachana in their chapter. Third-wave psychotherapy approaches, such as acceptance and commitment therapy, dialectical behavior therapy, and mindfulness-based interventions are thought to represent a substantial shift from the dominant psychotherapy approaches. Interventions such as cognitive behavioral therapy emphasize the interaction of thoughts and mood, such that by addressing an individual's "cognitive distortions" and negative automatic thoughts regarding a situation, the individual will interpret a situation in a more balanced way and will subsequently

have improved mood. In contrast, third-wave interventions focus on the way an individual relates to his or her thoughts and emotions. Interventions are not focused on changing thoughts or mood, but instead on accepting a mood state and the transient nature of emotion. These strength-based approaches to mental health focused on enhancing quality of life, as compared to the alleviation of an illness, are increasingly gaining in popularity with older adults. In addition, motivational interviewing approaches, focused on evoking behavioral changes in the patient, have become increasingly popular among health care providers due to their utility across a variety of situations, including increasing treatment adherence, engagement in mental health, and decreasing substance use.

Of particular importance, psychotherapy research has increasingly focused on fostering evidence-based practice in older adults. Determining therapy completion rates, clinical outcomes, and decreases in symptom severity are carefully monitored via quantitative methods when determining the efficacy of a treatment for a given population. It appears likely that the promotion of evidenced-based practice will be a long-standing fixture within clinical care. Many health care systems, such as Veterans Affairs, have created clinical practice guidelines outlining approved evidence-based psychotherapy approaches, manualized treatment protocols, and entire programs aimed at the dissemination of standardized approaches. Dissemination and access to care have increased due to the intersection of technology and clinical care, as reviewed by Dr. Gould and her colleagues in their chapter in the present book. Computer applications, receiving mental health care via video teleconference, and internet-based interventions continue to increase in popularity, creating an entirely new burgeoning field of health care.

The role of care facilities for older adults who are no longer able to live at home are discussed by Dr. Cassidy-Eagle. In addition to reviewing appropriate care settings, she discusses proposed areas of growth to improve patient's quality of life and mental health, including increased social opportunities to provide increased meaning and decrease isolation. Dr. Botros and colleagues discuss the forensic and ethical issues that may present while providing care for older adults. By reviewing important concepts such as competency, financial capacity, and testamentary capacity, the authors provide an introductory framework for clinicians to consider when facing these daunting issues.

Summary

The understanding, conceptualization, and treatment of mental health disorders in older adults has made large strides over the past 30 years, and appears set for a period of accelerated growth due to advances in technology and our understanding of how dysfunction in neurobiology and neurocircuitry subserve mental health symptoms (as discussed in the final chapter of this book on the future of mental health). Importantly, providing mental health care in older adults requires special consideration and thoughtfulness. We hope this book provides an overview of the current state of mental health care in older adults, with each chapter providing a piece representative of the interlocking nature of the field and kindling future research that will guide clinical care and treatments.

References

Alexopoulos, G. S., Bruce, M. L., Silbersweig, D., Kalayam, B., & Stern, E. (1999). Vascular depression: A new view of late-onset depression. *Dialogues in Clinical Neuroscience*, *1*(2), 68–80.

Bott, N. T., Sheckter, C. C., & Milstein, A. S. (2017). Dementia care, women's health, and gender equity: The value of well-timed caregiver support. *JAMA Neurology*, *74*(7), 757–758. Available from https://doi.org/10.1001/jamaneurol.2017.0403.

Bott, N. T., Sheckter, C. C., Yang, D., Peters, S., Brady, B., Plowman, S., & Milstein, A. (2019). Systems delivery innovation for Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *27*(2), 149–161. Available from https://doi.org/10.1016/j.jagp.2018.09.015.

Cuthbert, B. N. (2015). Research domain criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97.

Gaugler, J. E., Zmora, R., Mitchell, L. L., Finlay, J. M., Peterson, C. M., McCarron, H., & Jutkowitz, E. (2019). Six-month effectiveness of remote activity monitoring for persons living with dementia and their family caregivers: An experimental mixed methods study. *Gerontologist*, *59*(1), 78–89. Available from https://doi.org/10.1093/geront/gny078.

Gujral, S., Dombrovski, A. Y., Butters, M., Clark, L., Reynolds, C. F., 3rd, & Szanto, K. (2014). Impaired executive function in contemplated and attempted suicide in late life. *The American Journal of Geriatric Psychiatry*, *22*(8), 811–819. Available from https://doi.org/10.1016/j.jagp.2013.01.025.

Hunkeler, E. M., Katon, W., Tang, L., Williams, J. W., Jr., Kroenke, K., Lin, E. H., & Unutzer, J. (2006). Long term outcomes from the IMPACT randomised trial for depressed elderly patients in primary care. *BMJ*, *332*(7536), 259–263. Available from https://doi.org/10.1136/bmj.38683.710255.BE.

Institute of Medicine. (2012). In J. Eden, K. Maslow, M. Le, & D. Blazer (Eds.), *The mental health and substance use workforce for older adults: In whose hands?* Washington (DC): National Academies Press (US).

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, *73*(5), 525−531. Available from https://doi.org/10.1001/jamapsychiatry.2016.0004.

Kwong, K. K. (2012). Record of a single fMRI experiment in May of 1991. *NeuroImage*, *62*(2), 610−612. Available from https://doi.org/10.1016/j.neuroimage.2011.07.089.

Lebowitz, B.D., & Niederehe, G. (1992). Concepts and issues in mental health and aging. In *Handbook of mental health and aging* (2nd ed., pp. 3−23). San Diego, CA.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(24), 9868−9872. Available from https://doi.org/10.1073/pnas.87.24.9868.

Piau, A., Mattek, N., Crissey, R., Beattie, Z., Dodge, H., & Kaye, J. (2019). When will my patient fall? Sensor-based in-home walking speed identifies future falls in older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. Available from https://doi.org/10.1093/gerona/glz128.

Sheline, Y. I., Pieper, C. F., Barch, D. M., Welsh-Bohmer, K., McKinstry, R. C., MacFall, J. R., & Doraiswamy, P. M. (2010). Support for the vascular depression hypothesis in late-life depression: Results of a 2-site, prospective, antidepressant treatment trial. *Archives Of General Psychiatry*, *67*(3), 277−285. Available from https://doi.org/10.1001/archgenpsychiatry.2009.204.

Tanner, J. J., Mellott, E., Dunne, E. M., & Price, C. C. (2015). Integrating neuropsychology and brain imaging for a referral of possible pseudodementia: A case report. *The Clinical Neuropsychologist*, *29*(2), 272−292. Available from https://doi.org/10.1080/13854046.2015.1008047.

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963−974. Available from https://doi.org/10.1038/mp.2013.20.

Woods, S. P., Kordovski, V. M., Tierney, S. M., & Babicz, M. A. (2019). The neuropsychological aspects of performance-based Internet navigation skills: A brief review of an emerging literature. *The Clinical Neuropsychologist*, *33*(2), 305−326. Available from https://doi.org/10.1080/13854046.2018.1503332.

This page intentionally left blank

Chapter 2

Epidemiology of selected mental disorders in later life

Brenna N. Renn, Patricia A. Areán and Jürgen Unützer

Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Introduction and scope of the chapter

Mental health and substance use disorders have traditionally held a lower priority than communicable and noncommunicable diseases such as cardiovascular disease and cancer. As global health began to shift from a focus on mortality alone to morbidity and associated burden in the 1990s, efforts to document and improve mental health became increasingly important (Bank, 1993; Patel et al., 2008). Mental health and substance use disorders comprise a substantial component of burden and disability. Epidemiological data from the most recent Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) (Whiteford et al., 2013) suggest that mental and substance use disorders accounted for 7.4% of the total worldwide disease burden in 2010. The chronicity of these disorders is particularly notable, making mental and substance use disorders leading causes of disability and accounting for the largest proportion of total years lived with disability (YLD; 22.9%) relative to cancer, infectious disease, chronic disease (e.g., cardiovascular disease and diabetes), injuries, and other communicable and noncommunicable disease.

Considering that the older adult segment of the population is growing, the individual and public health implications of such findings are substantial. According to the Institute of Medicine (2012), 5.6–8 million Americans aged 65 and older are living with a mental health and/or substance use disorder. An individual is typically referred to as an "older adult" at the age of 65. The US life expectancy at the time of this writing is nearly 79 years; importantly, if one makes it to the age of 65, they are expected to live an additional 19.4 years (20.6 years for women and 18.0 years for men) (Kochanek, Murphy, Xu, & Arias, 2017). Longer life expectancy means that people are living with such conditions for a longer period of time, some with a lifetime diagnosis of one or more psychiatric disorders. As such, older adults may present with more chronicity, complexity, and comorbidity than their younger counterparts. Previously, the senescence theory of aging posited that decline, deficits, or disorders are common, normal, and expected among older adults. However, a new paradigm of thinking, based in part by epidemiological studies showing a range of healthy aging, has emerged and challenges simplistic notions that later life is a period of inevitable loss, decline, and pathology. Thus professionals working with older adults can expect to work with a heterogeneous population of individuals in various decades of life.

This chapter presents the epidemiology of selected mental disorders in later life, which typically refers to ages 65 years and older (although some authorities use an age cutoff of 50, 55, or 60 years). The focus is on both the prevalence of the most common mental disorders as well as a review of the evidence for associated risk factors for these conditions. This chapter has been organized according to the most recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). We survey the epidemiology of disorders we deem most relevant to aging and mental health, with particular emphasis on depressive and neurocognitive disorders, given the prevalence and associated adverse outcomes in this age group.

Psychiatric epidemiology in later life

Epidemiology is the study of disease distribution and determinants in humans, typically drawn from examination of large groups of individuals. By measuring disease frequency and examining who within a population gets a disease,

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00002-8

epidemiological studies can inform hypotheses regarding possible causal and preventive factors. Such data can shed light on the etiology of illness and risk factors while helping to inform service needs. Like a good clinical practice in mental health requires attention to biological, psychological, and social factors, epidemiological research similarly evaluates factors related to the etiology or distribution of psychiatric illnesses. However, it is difficult to carry out intensive biological or psychiatric assessments in the context of large population-based studies; thus psychiatric epidemiology often relies on screening assessment instruments to evaluate symptomatology and disorders, rather than in-depth clinical interviews.

This chapter will use some common epidemiological terminology throughout. Briefly, *incidence* refers to the number of new cases, or individuals with the disease, that develop within a specified time period. *Prevalence* refers to the proportion of individuals who have a particular disease at a particular point in time (often referred to as *point prevalence*). *Period prevalence* broadens *point prevalence* to describe the proportion of individuals with preexisting and new onset of the disease over a particular time period (e.g., 1 year). When this period of time is expanded to include the proportion of all individuals with the disease in their lifetime, it is termed *lifetime prevalence*. In practice, this can be difficult to quantify, as it relies on accurate recall over many years and on sampling populations of various ages, many of whom are not at the end of their respective lifetimes. Often, epidemiological data are limited in that they can estimate prevalence but not the incidence or risk of a condition. For example, if a large survey found that depression was more prevalent among women than men, this does not in itself suggest a causal association between being female and developing depression. Nonetheless, these descriptive data can be probed for causal implications and inspire future research into suspected patterns or associations. More modern epidemiologic methods, including case−control studies, are designed specifically to gather data on casual hypotheses and risk factors. Epidemiological research may in turn generate new hypotheses to be tested in randomized controlled trials and other experiments with smaller groups of individuals.

Comorbidity (and the related construct of multimorbidity) is the occurrence of two or more disorders in one individual. This may refer to multiple psychiatric disorders (e.g., comorbid depression and anxiety) or to the overlap between mental and physical health disorders (e.g., comorbid depression and diabetes). The DSM-5 and prior editions have focused on narrowly defining mental disorders; however, psychiatric symptoms do not always fit into the specified categories or may be highly overlapping. The National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) in 2009 as an alternative to categorical diagnostic systems in mental health research. The current RDoC framework includes five constructs (negative valence systems, positive valence systems, cognitive systems, social processes, and arousal and regulatory systems) that integrate across dimensions of human behavior and mental illness. While the RDoC allows for new approaches to mental health research, it does not replace the current DSM-5 or other diagnostic systems [e.g., the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)].

Comorbidity is particularly important among older adults. Many older adults, particularly those with comorbid medical or neurological illness, have psychiatric symptoms that are clinically significant but fail to meet diagnostic criteria for a mental disorder. Moreover, it may be difficult to distinguish symptoms caused by a psychiatric disorder from those due to medical illness or medication use, as both are prevalent in older adults. Although many mental disorders have their peak periods of onset during adolescence and young adulthood (e.g., depressive disorders, anxiety disorders, bipolar disorder, psychotic disorders), the incidence of many chronic medical conditions (e.g., type 2 diabetes, cardiovascular disease, cancer) is greatest in midlife or later. Thus epidemiological studies shed light on physical illnesses as important comorbidities and possible contributors to or consequences of psychiatric symptoms or disorders (Renn, Feliciano, & Segal, 2011; Robinson & Jorge, 2016).

Data on the prevalence of mental disorders in the United States typically are drawn from several large-scale epidemiological studies. The Epidemiological Catchment Area Study (ECA) (Regier et al., 1988) from the 1980s was the first major national study to assess the prevalence of psychiatric problems in the United States. However, the generalizability of the ECA findings was limited, as data were collected at only five sites. The second study, called the National Comorbidity Survey (NCS) (Kessler, McGonagle, & Zhao, 1994), was carried out in 1990−92 on a national sample representative of English-speaking adults between the ages of 18 and 65 and was mostly concerned with the prevalence of cooccurring *DSM-III-R* psychiatric disorders. The NCS was replicated (NCS-R) (Kessler & Merikangas, 2004; Kessler, et al., 2004) a decade later (2001−03) to examine the prevalence of the *DSM-IV* and the *International Classification of Disease, version 10* (*ICD-10*) psychiatric disorders and provide age-of-onset estimates for mental health disorders in a new US sample of 10,000 adults. However, the information estimated by the NCS-R is limited with regard to differential prevalence of disorders between younger and older people. Although the NCS-R included individuals over the age of 60 and up to the age of 75, which is an improvement over the demographics in the previous

TABLE 2.1 12-Month and lifetime prevalence estimates for common psychiatric disorders among US adults.

Psychiatric disorder	12-Month prevalence among all adults (%)	Lifetime prevalence among all adults (%)	Lifetime prevalence ≥ 60 (%)
Major depressive disorder	6.7	16.6	10.6
Dysthymia[a]	1.5	2.5	1.3
Bipolar disorder (I or II)	2.6	3.9	1.0
Generalized anxiety disorder	3.1	5.7	3.6
Panic disorder	2.7	4.7	2.0
Social phobia[a]	6.8	12.1	6.6
Specific phobia	8.7	12.5	7.5
Posttraumatic stress disorder	3.5	6.8	2.5
Alcohol abuse[b]	3.1	13.2	6.2
Alcohol dependence[b]	1.3	5.4	2.2
Drug abuse[b]	1.4	7.9	0.3
Drug dependence[b]	0.4	3.0	0.2

Notes: Prevalence estimates are based on published results from the National Comorbidity Study—Replication (NCS-R) (Kessler, Berglund, et al., 2005; Kessler, Chiu, et al., 2005), which used DSM-IV-TR criteria for disorders.
[a]*Per DSM-5 naming conventions, dysthymia is now referred to as persistent depressive disorder; social phobia is now labeled social anxiety disorder.*
[b]*DSM-5 does not separate the diagnoses of substance abuse and dependence as in DSM-IV-TR. Rather, criteria are generally collapsed for what is called substance use disorder.*

ECA and NCS samples (Kessler & Merikangas, 2004), it included very little of our fastest-growing segment of the population, the "oldest old" (those 85 years old and older). Despite the *caveats* of these studies, it is important to highlight what is known about the prevalence of mental illness in older adults. See Table 2.1 for a summary of 12-month and lifetime prevalence estimates of common mental health disorders among the general US adult population derived from the NCS-R. Note that the prevalence estimates for those aged 60 and above may be biased by differential mortality (e.g., the relative risk of mortality is 2.22-fold greater for those with mental disorders than those without) (Walker, McGee, & Druss, 2015) or other sampling bias such as reluctance to participate.

At the time of this writing, the most recent prevalence statistics were drawn from the 2016 National Survey on Drug Use and Health (NSDUH) (CBHSQ, 2017), based on the data from 67,942 completed face-to-face interviews with US noninstitutionalized civilians aged 12 or older. The NSDUH disaggregates adolescent (aged 12−17) and adult (18 years and older) responses. This annual survey, directed by the Substance Abuse and Mental Health Services Administration (SAMHSA), an agency in the US Department of Health and Human Services, began in 1971 and is a source of statistical information regarding substance use and mental health [particularly major depressive disorder (MDD)].

Another cross-sectional nationally representative sample of the civilian noninstitutionalized US adult population is the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), which was sponsored and directed by the National Institute on Alcohol Abuse and Alcoholism. The NESARC-III collected information on substance use, DSM-5 substance use disorders, and related risk factors. The final sample size was 36,309. Finally, the Collaborative Psychiatric Epidemiology Surveys (CPES) (Alegria, Jackson, Kessler, & Takeuchi, 2016) combined the NCS-R with two other national studies (National Survey of American Life and the National Latino and Asian American Study) to comprise a nationally representative sample of 20,013 noninstitutionalized adults aged 18 and older in the United States, with a special emphasis on minority groups.

Most of these large-scale studies used interviews derived from DSM-IV criteria for psychiatric disorders; they have not been changed since the emergence of the DSM-5 in 2013. Thus our understanding of psychiatric epidemiology is largely based on diagnostic criteria that predate the current DSM-5. However, the definition of many common disorders, including depressive disorders, has undergone only small changes in recent DSM editions. Perhaps, the most notable change in the DSM-5 with relevance to geriatric practitioners is the classification and elaboration of neurocognitive disorders (both mild and major; the latter is equivalent to dementia). Thus data drawn from past studies still allow for reasonable inferences. When interpreting these results, however, it is important to keep in mind that population-based surveys that inform much of the epidemiological data often do not capture those most severely impacted by psychiatric and neurodegenerative disorders (i.e., those who are homeless, incarcerated, or in institutionalized health care settings).

Generally, there is not much evidence to suggest that the prevalence of mental disorders in older adults has changed over time (CBHSQ, 2017); however, population growth and aging have contributed to an increased burden of mental health and neurocognitive disorders. Specific substance use disorders (i.e., alcohol, cocaine, and opioid dependence) have also increased in prevalence since 1990 (Whiteford et al., 2013).

Selected disorders

Depressive disorders

Description of the disorder

Depressive disorders are perhaps the most widely studied and recognized mental health disorders. Their relatively common occurrence across settings and populations has earned them the nickname as the "common cold of psychopathology." MDD is the most serious of such disorders and is characterized by at least one major depressive episode with no history of mania. These depressive episodes are marked by at least five out of nine possible symptoms that must be present for most of the day, nearly every day, and the episode must last at least 2 weeks. One of these symptoms must be either depressed mood or lack of interest or pleasure in usual activities (*anhedonia*). Other depressive symptoms include somatic (e.g., sleep disturbances, changes in appetite), cognitive (e.g., difficulty concentrating), and/or affective symptoms (e.g., feelings of worthless, suicidal ideation) during that same period. The symptoms must cause clinically significant distress or be severe enough to interfere with the individual's social, educational, or occupational functioning. Lastly, symptoms should not be better accounted for by another condition (e.g., a medical condition, directly related to use or withdrawal of a substance, a psychotic disorder) (American Psychiatric Association, 2013).

Older adults with depression often present with less sadness than their younger counterparts (Gallo, Rabins, & Anthony, 1999). Rather, they may endorse anhedonia (loss of interest and pleasure), withdrawal, apathy, and somatic symptoms of fatigue and diffuse pain or malaise, all of which can make depression surprising disabling. According to the 2010 Global Burden of Diseases Study (Whiteford et al., 2013), depressive disorders explained the vast majority of disability-adjusted life years (40.5%) and YLDs (42.5%) relative to other mental health and substance use disorders, including anxiety disorders, schizophrenia, bipolar disorder, and alcohol and drug-use disorders. Despite the availability of effective treatments, including pharmacological and psychological treatments (e.g., cognitive behavioral therapy and problem-solving therapy) (Cuijpers, Karyotaki, Pot, Park, & Reynolds, 2014; Renn & Arean, 2017), depression remains a significant health care concern for older adults. Depression is associated with disability and functional decline, poor quality of life, increased morbidity and mortality, and increased utilization of health care services in later life (Chapman & Perry, 2008). Moreover, recent longitudinal data suggest that older adults with MDD have substantially worse outcomes than younger adults, even after controlling for other clinical, health, and social factors (Schaakxs et al., 2018).

Epidemiology

The 12-month prevalence of MDD among adults aged 18 and older was 6.7% in both the NCS-R and NSDUH data sets. Nearly two-thirds of those with major depression (4.3%, or 10.3 million of all US adults) had an episode with severe impairment in the past year (CBHSQ, 2017). NCS-R data estimate that one in six (16.6%) US adults will experience a major depressive episode in their lifetime, and an additional 2.5% will meet the criteria for persistent depressive disorder (formerly dysthymia) during their lifetime.

In general, the prevalence of MDD among community-dwelling older adults is lower than the levels observed in younger groups. Data from the NCS-R and NSDUH consistently demonstrate that the prevalence of depressive disorders varies between age groups, with the NCS-R reporting a peak in 12-month prevalence of MDD between the ages of 30–44 (Kessler, Berglund, et al., 2005). The NSDUH disaggregates older adults as those 50 years and older; 4.8% (5.3 million) adults in this age group had a past-year major depressive episode in 2015, which was similar to the proportion in 2005. An estimated 3.0% (3.3 million) adults aged 50 and older had a depressive episode with severe impairment in the last year. Older prevalence estimates suggest that minor depression is even more common than major depression among older adults, with upward of one in ten (9.8%) adults over the age of 55 affected by clinically relevant depressive symptoms not meeting diagnostic threshold for MDD (Beekman, Copeland, & Prince, 1999).

Associations and suspected risk factors for depression in later life

Depression is a relatively prevalent disorder seen among older adults across health care and social service settings; however, it is not a normal consequence of aging. Late-life depression often remains underdiagnosed and inadequately treated (Hybels & Blazer, 2003; Licht-Strunk et al., 2009). There is some evidence that late-life depression is more chronic and may be associated with increased relapse or recurrence (Ell, Aranda, Xie, Lee, & Chou, 2010; Mitchell & Subramaniam, 2005). Older adults with depression, particularly older men, are less likely to perceive a need for mental health care and thus have lower treatment unitization than younger cohorts (Klap, Unroe, & Unutzer, 2003). Moreover, treatment-resistant depression, defined as a depressive episode that has not responded to two adequately dosed antidepressant medications (Souery et al., 1999), affects about one-third of older adults with depression (Newman, 2016). Thus the public health consequences of underrecognized and poorly treated depression will continue to increase over time as the population continues to age.

Depressive disorders are associated with many conditions that are increasingly prevalent with age, including the presence of two or more chronic illnesses, as well as specific conditions such as congestive heart disease, myocardial infarction, type 2 diabetes, hypertension, chronic kidney disease, and neurological conditions such as Parkinson's disease. These chronic medical conditions increase the odds two- to threefold on average compared to healthy controls (Ali, Stone, Peters, Davies, & Khunti, 2006; Krishnan, 2002; Palmer et al., 2013; Rustad, Stern, Hebert, & Musselman, 2013). Age-related hearing loss has also been associated with increased odds of depression among older adults across a 10-year period (Brewster et al., 2018). Regardless of age, individuals reporting fair or poor self-rated health are much more likely to have a 12-month prevalence of a major depressive episode relative to those reporting excellent, very good, or good health (CBHSQ, 2017). Of course, overlapping somatic symptoms (e.g., sleep problems, weight changes, fatigue) can make the differential diagnosis of late-life depression difficult in the context of chronic disease, as such symptoms can be attributable to both the medical condition and depression. In the absence of reports of sadness or guilt, depression can go underrecognized in this age group.

Given that physical health status is one of the most commonly cited correlates to depression, it is perhaps unsurprising that prevalence of depression varies by settings. Primary care is often referred to as the de facto mental health services system (Regier, Goldberg, & Taube, 1978), with 5%−10% of primary care patients meeting criteria for MDD and 20% of all primary care visits having a clear mental health indication, including depression screening, treatment (psychotherapy, counseling, or prescription of a psychotropic drug), or other mental health reason for visit (Olfson, Kroenke, Wang, & Blanco, 2014). Although the prevalence of MDD is relatively low in community-dwelling older adults, it is substantially higher in populations with higher degrees of disability, making long-term care, medical inpatient, and palliative care relevant settings with a high prevalence of depression. Meta-analytic review of 4007 individuals with a mean age of 55 or older across palliative care settings estimated a 16.5% point prevalence of MDD and a 9.6% point prevalence of minor depression (Mitchell et al., 2011). Even more staggering are the estimates that half (54.4%) of people living in assisted living facilities have a diagnosis of depression, with new episodes occurring in 21.6% of the residents within the first 12 months of admittance (Hoover et al., 2010). The causes for higher prevalence and incidence of depressive disorders in long-term care facilities likely include loss of functional independence, loss of familiar surroundings, decreased access to pleasant activities or loved ones, and comorbid physical illnesses. Given the deleterious effect of depressive disorders on rehabilitation, comorbidity, and mortality, the high rate of these disorders in these settings is the cause for concern and necessitates more vigilant and proactive treatment of depression in long-term care.

Across age groups, depressive disorders are more prevalent among women compared to men. Lifetime prevalence data from the NCS-R found that women are at a 1.5-fold increased risk of developing a mood disorder over their lifetime compared to men, and a 1.7-fold increased risk of developing MDD specifically (Kessler, Berglund, et al., 2005). More recent 12-month prevalence estimates reported in the 2016 NSDUH data suggest that across US adults aged 18 and older, 8.5% of women and 4.8% of men had a major depressive episode during the past year. This gender gap appears consistent with age, such that 3.5% of women and 1.8% of men over the age of 65 reported a past-year major depressive episode (CBHSQ, 2017). Although the prevalence of depression varied between studies, a consistent theme emerges: More women than men report having depressive episodes, and this trend continues throughout the lifespan. Although the reasons for these differences are not fully established, some speculate that men and women differentially express and endorse symptoms of depression, such that men are more likely to report anger, aggression, irritability, and substance abuse than traditional symptoms of sadness and social withdrawal (Martin, Neighbors, & Griffith, 2013). Clearly, further work is needed to refine our conceptualization and assessment of depression across age groups, particularly in light of sociocultural changes.

The association of race and ethnicity with depression is unclear and continues to evolve in our increasingly diverse and multicultural country. According to the older NCS data, African Americans reported rates of depression similar to those of the non-Hispanic white population. More recent epidemiological data suggest varying prevalence estimates among racial and ethnic groups, with estimates demonstrating an increase in depressive disorders among all racial groups relative to earlier NCS data. The 2016 NSDUH (CBHSQ, 2017) data reported the highest 12-month prevalence of MDD among multiracial individuals (10.5%), followed by those identified as American Indian or Alaska Natives (8.7%), relative to non-Latino whites (7.4%). Native Hawaiian or Pacific Islander adults had a lower prevalence in 2016 (7.3%) that was comparable to non-Hispanic whites and elevated relative to the prevalence reported in 2015 among this ethnic group (5.2%). Other ethnic and racial minority groups reported lower levels of depression than their non-Hispanic white counterparts, with 5.6% of Hispanic/Latino, 5.0% of African American, and 3.9% of Asian adults experiencing a major depressive episode in the last year. Reexamination of NCS-R suggests that there are variations between Hispanic/Latino groups, with only Mexican immigrants showing a lower rate of mood disorders relative to US-born counterparts (Alegria et al., 2008). This study also confirmed that among individuals with depressive disorders, an alarming number did not receive any kind of mental health treatment or received inadequate treatment, highlighting the need for better assessment and treatment of depression for diverse groups. As the United States becomes increasingly diverse, caution is warranted in generalizing all ethnic or racial minority groups, as this may mask differences in vulnerability for depression due to multicultural issues including immigration status, acculturation, socioeconomic status, access to health care, substance use patterns, and myriad other factors including antiimmigrant and racial bias and discrimination. Further research is needed to understand risk and protective factors of depression related to these unique sociocultural intersections, particularly across aging birth cohorts.

Neurocognitive disorders

Description of the disorder

Although the DSM-5 uses the term neurocognitive disorder, the term dementia is still used in clinical practice and research settings for continuity and familiarity for both providers and patients. Dementia refers to a syndrome of decline in cognitive ability and behavior that are severe enough to interfere with daily functioning. The most common causes of dementia are Alzheimer's disease, frontotemporal dementia (caused by frontotemporal lobar degeneration), Lewy body disease, and vascular dementia (caused by cerebrovascular disease). Clinicians and researchers are also increasingly aware of dementia of mixed etiology (e.g., Alzheimer's disease and vascular dementia). Delirium is another neurocognitive disorder relevant to older adults and is characterized by a disturbance in attention, awareness, and orientation that develops over a short period of time and often fluctuates.

Epidemiology

The Aging, Demographics, and Memory Study (ADAMS) (Plassman et al., 2007) was the first US population−based study of dementia to sample all regions of the country and used a single standardized diagnostic protocol. These data are now over a decade old but estimated a 13.9% prevalence of dementia among individuals aged 71 and older, with 9.7% of the population suffering from Alzheimer's disease specifically. These data also demonstrated that dementia prevalence increased with age, from 5.0% of those aged 71−79 years to 37.4% of those aged 90 and older. More recent data estimate that Alzheimer's disease, the most common type of dementia, affects an estimated 5.4 million Americans, most of who are aged 65 or older. Indeed, it is the fifth leading cause of death in this age group. As the population continues to age, it is estimated that the number of people with Alzheimer's disease will triple by 2050 (Mehta & Yeo, 2017), with the most notable increase in those aged 85 and older (Hebert, Weuve, Scherr, & Evans, 2013) (see Fig. 2.1).

The prevalence of delirium is low in the community (1%−2%) but rises to 14% among adults aged 85 and older. It is more prevalent during hospitalization, often indicating a medical illness. Delirium occurs in 15%−53% of older adults postoperatively, 70%−87% of those in intensive care, 60% of those in nursing homes or postacute care, and 83% in those at end of life (American Psychiatric Association, 2013). Older adults in general are more susceptible to delirium than younger adults, and the risk increases in those with major and mild neurocognitive disorders.

Associations and suspected risk factors for neurocognitive disorders in later life

Age is the most notable and consistent risk factor for dementia. Women are more likely than men to have Alzheimer's disease, although this association may be due in part to greater longevity among women (Mehta & Yeo, 2017).

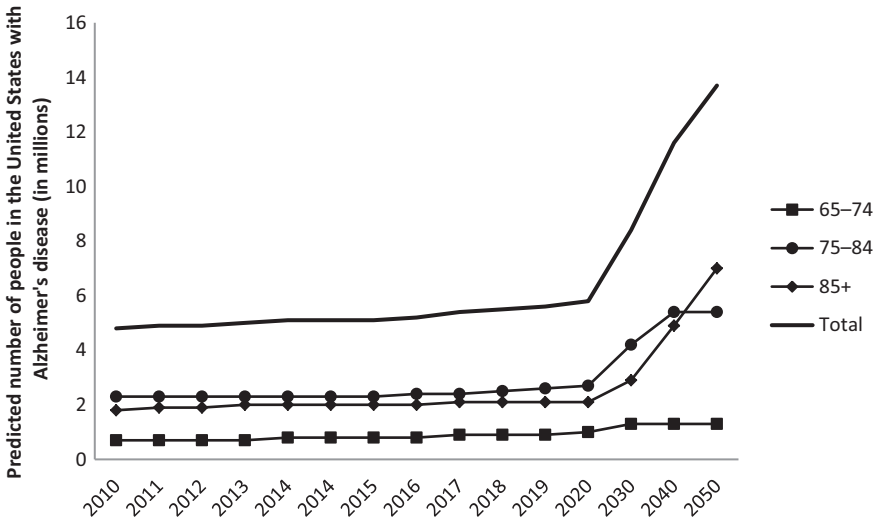


FIGURE 2.1 Projected number of US individuals with Alzheimer's disease, 2010–50, based on 2010 census data. *Created from data presented in Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology, 80(19), 1778–1783.*

Higher education is associated with a lower risk of dementia (Plassman et al., 2007), although some attribute this to the cognitive reserve hypothesis (Stern, 2012), by which susceptibility to Alzheimer's disease or other age-related brain pathologies is moderated by education and other lifestyle factors, allowing some people to tolerate more neural pathology than others while maintaining functioning.

To date, very little to no dementia prevalence data exist for certain ethnic, racial, and cultural groups, including American Indians or Alaska Natives, Asian American subgroups (e.g., Chinese Americans), or ethnic diversity within non-Latino white subgroups (e.g., immigrants from the Middle East or Eastern Europe). The literature does suggest increased prevalence of dementia among African American and Hispanic Caribbean American populations relative to other racial/ethnic groups (Mehta & Yeo, 2017). However, while ADAMS found a higher prevalence of dementia and Alzheimer's disease among African Americans, this difference by race disappeared once researchers controlled for the effects of sex and education (Plassman et al., 2007).

Other consistent risk factors for Alzheimer's disease are cardiovascular disease and associated physical health (such as poorly managed type 2 diabetes or high blood pressure), prior head trauma, and low educational attainment. Similar risk factors emerge for vascular dementia, in which case controlling risk for stroke and other heart disease factors become crucial. There is a growing interest in physical activity, education, and other lifestyle factors, such as social engagement, as potentially protective factors, particularly in Alzheimer's disease. Health in midlife may be particularly relevant, as a 2018 study of Swedish women found that high cardiovascular fitness drastically reduced the odds for all-cause dementia. Among those women who were eventually diagnosed, high midlife fitness delayed the age of dementia onset by 9.5 years compared to those of lower fitness levels (Hörder et al., 2018).

Mental health factors are also implicated in incident dementia, namely the complex relationship between depression and dementia. A prospective cohort investigation of African American and white community-dwelling older adults in the United States revealed that those with high and increasing depressive symptom trajectories over 5 years had a significantly increased risk (almost twofold) of developing incident dementia relative to those with minimal depression (Kaup et al., 2016).

Anxiety disorders

Description of the disorder

Anxiety disorders are a relatively common group of disorders that share features of excessive fear, anxiety, and avoidance behaviors. Notable disorders in this group include *generalized anxiety disorder* (GAD), which is marked by persistent anxiety and hard-to-control worry about an array of activities or events; *panic disorder*, in which the individual experiences recurrent unexpected panic attacks marked by four or more somatic or psychological symptoms of panic; *social anxiety disorder* (formerly social phobia), characterized by an intense fear or anxiety of social situations in which the individual may be observed or evaluated by another; and *specific phobias*, in which there is marked fear related to a specific object or situation (e.g., flying, needles).

Epidemiology

The prevalence of anxiety among US adult populations is the highest of any mental disorder, with more than one in four (28.8%) adults expected to meet diagnostic criteria during their lifetime (Kessler, Berglund, et al., 2005). NCS-R data (Kessler, Berglund, et al., 2005) suggest that specific phobia (12.5% lifetime prevalence) and social anxiety disorder/social phobia (12.1% lifetime prevalence) are the most common disorders, followed by a 5.7% lifetime prevalence of GAD. During a 12-month period, the prevalence of any anxiety disorder is 18.1% among US adults, including 8.7% for specific phobia, 6.8% for social phobia, and 3.1% for GAD (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). These 12-month prevalence estimates are somewhat lower (7.1%) for adults aged 65 and older from an earlier wave of NESARC (2001−02), which collapsed panic disorder, specific phobia, social phobia, and/or GAD (Lin et al., 2014).

Associations and suspected risk factors for anxiety disorders in later life

Anxiety disorders are prevalent at almost every decade of life, and the median age of onset for anxiety disorders (age 11 years) is much younger relative to substance use (age 20 years) or depressive disorders (age 30 years) (Kessler, Berglund, et al., 2005). As with the depressive disorders, the prevalence of an anxiety disorder generally declines with age but remains quite common. NCS-R surveillance data (Kessler, Berglund, et al., 2005) suggest that lifetime risk of an anxiety disorder is greatest for women, non-Hispanic whites, and those who were previously married, relative to their demographic counterparts. Among adults aged 55 and older captured in the NCS-R sample, 12-month prevalence of anxiety disorders was almost twice as common in women (14.7% vs 7.6% among men) (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010). Married or cohabitating older adults evidenced lower prevalence (8.9%) of any anxiety disorder in the last year, relative to those who were never married (14.6%) or who were divorced/separated/widowed (15.7%). There were no racial/ethnic differences found in anxiety prevalence among this nationally representative sample of 2575 older adults.

Older adults with anxiety disorders may not recognize them as such. Given the somatic presentation of anxiety (e.g., fatigue, sleep disturbance, muscle tension) among many in this age group, it may be that some prevalent cases are missed. Even when cases are detected, many likely go untreated, particularly among older adults. The secondary analysis of adults aged 55 and older from the NCS-R found that the vast majority (72.6%) of the sample meeting the criteria for any anxiety disorder did not use mental health services (Byers, Arean, & Yaffe, 2012). Unmet service need was greatest among older adults with specific phobia (79.5% nonuse), social phobia (69.7% nonuse), and GAD (65.6% nonuse). Those older adults who were racial/ethnic minorities expressed discomfort with mental health care, were married or cohabitating, reported middle-income status, reported a mild anxiety disorder, and had no chronic pain or cognitive complaints were least likely to use mental health services. As with other mental disorders, it is likely that low perceived need, moderate resources, and low motivation for mental health care may explain lack of mental health service use, despite diagnosable disorders.

Certain anxiety disorders may be more common among older adults with chronic health issues relative to their healthier counterparts. For example, the prevalence of panic disorder is almost 10 times greater among those with chronic obstructive pulmonary disorder (COPD) compared to the overall population prevalence (Livermore, Sharpe, & McKenzie, 2010). The clinical formulation is that panic occurs when an individual with COPD catastrophically misinterprets ambiguous physical sensations, such as dyspnea (shortness of breath), which increases arousal and creates a positive feedback loop that results in panic. Similarly, some clinicians believe that new onset of a panic disorder among older adults often coincides with cardiovascular disease and fear of incipient heart attack. Thus it is important for clinicians and researchers to discern the psychological and cognitive components of such somatic presentations.

Bipolar disorders

Description of the disorder

Bipolar disorder is a chronic and serious mental illness characterized by major depressive episodes and bouts of mania (i.e., acute periods of intense energy, euphoria, distorted thinking, and behavioral excesses; bipolar I) or hypomania (bipolar II). Older adults with bipolar disorders are a heterogeneous group. For some, the disorder may first manifest in younger adulthood and persist into later life. For others, it may present for the first time in older adulthood, although this is less common (Sajatovic & Blow, 2007). Typically, peak onset is between 15 and 24 years of age (mean age of 18 years) (American Psychiatric Association, 2013), although there is often a considerable lag between symptom onset and initiation of treatment. Compared to late-life anxiety and depressive disorders, empirical or epidemiological research on bipolar disorders among older adults is limited.

Epidemiology

The estimate of the 12-month prevalence of bipolar I or II disorder among US adults is 2.6% (Kessler, Chiu, et al., 2005). Among adults aged 65 and older, 12-month estimates are lower than the general adult population (0.4%−0.5% for bipolar I and 0.2% for bipolar II) (Blanco et al., 2017; Lin et al., 2014). NCS-R data (Kessler, Berglund, et al., 2005) found a decreasing lifetime prevalence of bipolar I and II disorder by age, such that prevalence was highest (5.9%) in the youngest ages (18−29 years) and decreased with successive age cohorts (4.5% among 30−44 year olds, 3.5% among 45−59 year olds) to a lifetime prevalence of 1.0% observed among those 60 and older. Similarly, lifetime prevalence estimates based on NESARC (2001−02) participants aged 65 and older range from 0.6% for bipolar II to 1.1% for bipolar I (Lin et al., 2014). These estimates have remained relatively stable over the last decade, with the newest figures from NESARC-III estimating a 0.4% 12-month and 0.8% lifetime prevalence of bipolar I among those aged 65 and older (Blanco et al., 2017).

Associations and suspected risk factors for bipolar disorders in later life

A family history of bipolar disorder is one of the most consistent and strongest risk factors for bipolar disorders, with a 10-fold risk among adults with relatives with either bipolar I or II (American Psychiatric Association, 2013). The lifetime risk of a bipolar disorder drastically reduces with age (Kessler, Berglund, et al., 2005). This is a result of both the typically young onset of the disorder and the lower life expectancy of individuals with this disorder, which are attributable in part to the substantially increased risk for suicide and other mortality in bipolar disorder (Kessing, Vradi, McIntyre, & Andersen, 2015).

Perhaps unsurprisingly, a greater prevalence of geriatric bipolar disorder is observed in certain acute care clinical settings, including the hospital emergency department, and among psychiatric inpatients. Although the use of substances generally declines with age, bipolar disorder is often comorbid with the use of substances across age cohorts. Bipolar disorder is often accompanied by cognitive impairment in older adults, which can complicate treatment and cause substantial disability. As such, the point prevalence of geriatric bipolar disorder is also thought to be higher in long-term care facilities (estimates range from 1.5%−3.0%) (Seitz, Purandare, & Conn, 2010; Tariot, Podgorski, Blazina, & Leibovici, 1993) where the cognitive impairment associated with bipolar disorder and other serious mental illness (e.g., schizophrenia) may make these individuals more common.

Although the etiology of bipolar disorder is unknown, clinicians and researchers suspect that late-onset geriatric bipolar disorder (e.g., occurring in adults aged 50 years or older) may differ from bipolar disorder with a young adult onset that has persisted into later life (Sajatovic & Kessing, 2010). Some have suggested that late-onset bipolar disorder is a subtype of bipolar disorder associated with medical and neurological disease (Sajatovic & Blow, 2007), and specifically with vascular risk factors such as hypertension and type 2 diabetes leading to heart disease and stroke (Cassidy & Carroll, 2002). However, the high comorbidity of bipolar disorder and chronic diseases such as diabetes and vascular disease may also be iatrogenic, as antipsychotic agents used in bipolar treatment may elevate the risk of such medical conditions (Daumit et al. , 2008).

Posttraumatic stress disorder

Description of the disorder

Posttraumatic stress disorder (PTSD) occurs when exposure to a trauma leads to intrusive symptoms, persistent avoidance of stimuli associated with the event, and negative alterations in cognition, mood, and physiological arousal or reactivity. Traumatic events include exposure to life-threatening events (e.g., combat, natural disasters, violence), serious injury, or sexual violence. Such exposure can be directly experienced, witnessed in another, or indirectly experienced through learning of a traumatic event occurring to a close family member or friend. Although PTSD can occur at any age, data from the NESARC-III estimated first onset to occur on average at the age of 23.7. The most commonly endorsed traumas from NESARC-III, in descending order, were sexual abuse before age 18, interpersonal violence victimization, seeing a dead body, witnessing someone else's serious injury, and experiencing one's own serious injury (Goldstein et al., 2016).

Epidemiology

NCS-R and NESARC-III data estimate a lifetime prevalence of 6.1%−6.8% for PTSD among US adults (Goldstein et al., 2016; Kessler, Berglund, et al., 2005). During a 12-month period, an estimated 3.5%−4.7% of US adults will

meet diagnostic criteria for PTSD (Goldstein et al., 2016; Kessler, Chiu, et al., 2005). As seen with other disorders reviewed herein, the prevalence of PTSD decreases with age, with a 2.2% 12-month prevalence and a 2.5%−3.2% lifetime prevalence observed for older adults aged 60 and older (Goldstein et al., 2016; Kessler, Berglund, et al., 2005).

Associations and suspected risk factors for posttraumatic stress disorder in later life

Odds of PTSD across the adult population were significantly elevated among women compared to men in the NESARC-III (Goldstein et al., 2016). Other associations with elevated PTSD endorsement included Native American or non-Hispanic white race/ethnicity and other sociodemographic variables, including having been previously married, having less than a high school education, rural dwelling, and those with family incomes <$70,000. These vulnerable groups may be at greater risk for encountering civilian trauma, such as intimate partner violence, other interpersonal violence, childhood abuse, and environmental disaster. PTSD is frequently comorbid with substance use disorders, other mental health disorders (namely, depressive, bipolar, anxiety, and personality disorders), and disability (Goldstein et al., 2016).

The lifetime prevalence of PTSD increases from early adulthood (6.3% in adults aged 18−29) to middle age (9.2% in adults aged 45−59) and then appears to steeply decline (2.5% of adults aged 60 and older) (Kessler, Berglund, et al., 2005). However, these cross-sectional surveillance data do not imply a causal relationship between age and PTSD risk. Importantly, the age cohort with the greatest prevalence of PTSD in the NCS-R was the baby boomers, who lived in a unique sociopolitical time (to include the Vietnam War) compared to the older generation of older adults captured in the NCS-R survey between 2001 and 2003. Indeed, veterans are often thought to be at greater risk of developing PTSD relative to civilians as a consequence of their exposure to combat and captivity. However, lifetime prevalence estimates (6.9%−7.95%) of PTSD among US veterans are very similar to those estimates reported for the general population, with lowest lifetime prevalence among those veterans aged 65 and older (3.75%) (Smith, Goldstein, & Grant, 2016; Wisco et al., 2014).

The decreasing prevalence of PTSD observed among older adults is in line with clinical consensus suggesting that subthreshold presentations of PTSD are more common in later life (American Psychiatric Association, 2013); nonetheless, these symptoms and related comorbidities impart substantial impairment and reduction in quality of life. Role changes (e.g., retirement, relocation), health problems, loss of functioning and independence, and other distressing events (e.g., illness or death of one's partner) may make coping with memories of earlier trauma more difficult for older adults and represent vulnerability factors for PTSD in later life.

Substance use disorders

Description of the disorder

The DSM-5 includes 10 classes of drugs in the classification of substance-related disorders: alcohol; caffeine; cannabis; hallucinogens (separating phencyclidine from other hallucinogens); inhalants; opioids; sedatives, hypnotics, and anxiolytics; tobacco; and other (or unknown) substances. The cardinal feature of a substance use disorder is continued use of a substance despite significant social, interpersonal, occupational, or functional problems related to the substance. Such disorders are marked by a cluster of cognitive, behavioral, and physiological symptoms, including cravings, tolerance, and withdrawal, and spending a great deal of time obtaining, using, or recovering from use. Substance use disorders are associated with poorer mental health; more impaired social, role, and emotional functioning; and worse quality of life (Grant et al., 2016).

Substance use among older adults is an area of increasing clinical and public health concern. Although many older adults reduce substance use as they age, some older adults begin or continue using substances in a manner hazardous to their health. Physiological changes associated with aging present unique risks for harm with even minimal amounts of substance use among older adults. Although alcohol use by adults is legal, it can be problematic among older adults, who are more sensitive to the effects of alcohol, including dangerous interactions with other medications or exacerbation of medical conditions. Other substance-related concerns in this population include misuse of psychotherapeutic medications (e.g., opioids, tranquilizers, stimulants, and sedatives) in a way that was not directed by a doctor. Although substance use has traditionally been lower among older adults compared to the general population, cohort effects may complicate or change this presentation. Notably, there is a relatively higher use of substances among the Baby Boom generation (born 1946−64) compared to previous generations (Wu & Blazer, 2011). These individuals came of age during the 1960s and 1970s, a period of permissive attitudes about drugs and alcohol. Moreover, the myth that older adults do not use mood-altering substances can be clinically detrimental to geriatric care and likely result in

underidentification. Identification of substance use among older age groups can also be complicated by overlapping symptoms with medical problems that are more common in older adults.

Epidemiology

Substance use disorders are lowest among those aged 65 and older relative to younger age groups, for both alcohol and drug use. However, the prevalence of substance use has remained high among baby boomers as they have aged relative to previous cohorts (SAMHSA, 2013).

Alcohol use disorder is the most common of substance use disorders. Lifetime and 12-month prevalence estimates of DSM-5 alcohol use disorders among US adults are 29.1% and 13.9%, respectively (Grant et al., 2015). As in the general population, alcohol remains the most commonly used substance among older adults, despite increasing levels of illicit and prescription drug misuse among this age group. Slightly more than one in eight (13.4%) older adults report a lifetime alcohol use disorder, compared to 28.2%−37.0% of younger adults (Grant et al., 2015). NSDUH (CBHSQ, 2017) estimates that 3.4% of adults aged 50 and older met criteria for alcohol use disorder in the past year; this was much higher among men (5.1%) than women (2.0%) in this age group.

The overall prevalence of any alcohol use (not limited to alcohol use disorder) increased in the United States from the early 2000s to 2013. The largest increase occurred among adults aged 65 and older compared to other age groups, with the proportion of drinkers in this age group increasing 10 percentage points (from 45.1% reporting past-year alcohol use in 2001−02 to 55.2% in 2012−13) (Dawson, Goldstein, Saha, & Grant, 2015). The prevalence of monthly heavy episodic drinking also increased among older adults during this timeframe (from 6.1% to 11.8%).

With regard to drug-use disorder, lifetime and 12-month prevalence for US adults are estimated at 9.9% and 3.9%, respectively (Grant et al., 2016). Only 2.0% of adults aged 65 and older reported any lifetime history of drug-use disorder relative to 9.7%−14.2% of younger adults (Grant et al., 2016). As seen with alcohol use disorder, NSDUH estimates of adults aged 50 and older similarly demonstrate much higher 12-month prevalence of substance use disorder among men (5.7%) than women (2.6%) in this age group (4.1% overall for adults aged 50 and older).

Alcohol, cannabis, opioids, and cocaine have the highest prevalence of use. Tobacco use is also quite common in both the general population (23.5%) and among older adults (14%) (CBHSQ, 2017). Marijuana use is considerably more prevalent than other drugs, and the reported use is increasing since the early 2000s, particularly among middle-aged (45−64) and older adults (65 and older). Among the latter group, 1.3% reported marijuana use between 2012 and 2013 (Hasin et al., 2015). However, these data may underestimate true prevalence, as respondents in these national surveys may underreport illicit substance use. Moreover, these data may not capture social and legal changes reflected in the increased legalization of marijuana that began in 2012 in Colorado and Washington. At the time of this writing, nine US states and Washington, DC, have legalized marijuana; it has been decriminalized in an additional 13 states. Additionally, more than half (29) of the states have provisions for marijuana use for medical purposes.

Opioid misuse has also received national attention, particularly as it is intertwined with the related public health issue of chronic pain management. Indeed, the most commonly cited reason for opioid misuse is the relief of physical pain. The past-year prevalence of opioid misuse has increased from 1.8% to 4.1% among the general US adult population since the early 2000s (Saha et al., 2016). As with all substance use, the prevalence of opioid misuse is lowest among adults aged 65 compared to other age groups; nonetheless, misuse of opioids and other substances among older adults is fraught with unique medical vulnerabilities, including confusion, respiratory distress, falls, and interactions with other medications and medical conditions. One in 20 (5%) adults aged 65 and older report a lifetime prevalence of DSM-5 opioid use disorder (compared to 11.36%−14.78% of younger adults) (Saha et al., 2016).

Associations and suspected risk factors for substance use in later life

Alcohol and other substance use disorders in the general population are associated with myriad mental health conditions, including anxiety, depressive, and bipolar disorders, as well as schizophrenia and antisocial personality disorders (American Psychiatric Association, 2013). Substance use disorders in the general population tend to be greatest for men, white and Native American individuals, those with lower education and income and those who were previously or never married (Grant et al., 2016). The overall patterns of alcohol use are higher for men than women, although there is evidence of a converging gender gap in younger birth cohorts (Keyes, Li, & Hasin, 2011). Alcohol use increased with education and income and is most frequent among those who were never married.

As in the general population, risk factors related to substance use among older adults include white race and being the recipient of mental health treatment in the past year (perhaps related to the comorbidity of psychiatric illness and substance use). Little else is known about psychiatric comorbidity with substance use among older adults; however,

substance use in this age group appears to be correlated with depressive disorders (CBHSQ, 2017; Kuerbis, Sacco, Blazer, & Moore, 2014).

Among adults aged 50 and older, cannabis users are more likely to be younger, male, non-Hispanic, and use tobacco, alcohol, or other drugs compared to noncannabis users (Han et al., 2017). Physical risk factors for general substance use in later life include chronic pain, physical disabilities, poor health status, and polypharmacy. Authorities also note psychosocial risk factors for misuse, including bereavement, unexpected or forced retirement, transitions in care or living situation, social isolation, and an avoidant coping style (Kuerbis et al., 2014). Risk factors may vary by substance; understanding such risks can help researchers and practitioners assess and respond to unhealthy use that does not meet diagnostic criteria for substance use disorder but is otherwise problematic or dangerous.

Suicide

Description of the disorder

Although not a mental health disorder per se, suicidal thoughts and behavior are a concerning finding across mental and substance use disorders, regardless of age. Suicide is a tragedy for all involved and ranks in the top 10 leading causes of death in the United States (Kochanek et al., 2017). Suicide attempts are more likely to result in death among older adults than younger individuals This is in part because older adults tend to plan more carefully and use more lethal means, and so are less likely to be discovered and rescued. Additionally, their physical frailty means that they are less likely to recover from an attempt.

Epidemiology

In 2016 the highest age-adjusted suicide rate (19.72 per 100,000 individuals) was among adults between 45 and 54 years of age. The second-highest rate (18.98 per 100,000 individuals) occurred in those 85 years or older (CDC, 2016). Across the general population, men die by suicide 3.5 times more often than women, and white men in particular accounted for 70% of suicides in 2016 (CDC, 2016). According to the most recent data from the Centers for Disease Control and Prevention (CDC), suicide completion rates are highest among whites (15.17 per 100,000 individuals) and American Indians and Alaska Natives (13.37 per 100,000 individuals). Asian and Pacific Islanders (6.62 per 100,000 individuals) and black or African American individuals (6.03 per 100,000 individuals) evidenced much lower rates of suicide. (Note: the CDC records Hispanic ethnicity separately from the racial categories above, as individuals in all of these groups may also be Hispanic). See Fig. 2.2 for age-adjusted rates of suicide death by age groups from 1999 to 2016.

Data from NSDUH (CBHSQ, 2017) suggest that 2.4% of adults aged 50 and older endorsed suicidal thoughts in a 1-year period and were less likely to report these thoughts compared to younger adults. In 2016, 0.5% of adults aged 50 and older made suicide plans and 0.2% of adults in this age group attempted suicide.

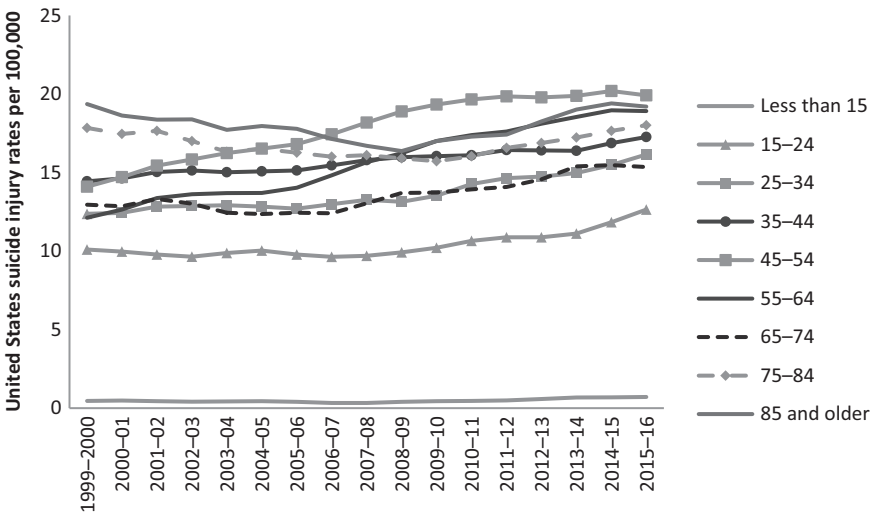


FIGURE 2.2 Age-adjusted rate of suicide death by age groups from 1999 to 2016. *Created from data produced by the National Center for Injury Prevention and Control, derived from the NCHS vital statistics system for the number of deaths.*

Associations and risk factors for suicide in later life

Data on suicide injury drawn from the CDC (2016) point to drastically increased odds of suicide death for white men aged 85 and older (age-adjusted rate, 52.47 per 100,000) relative to men (47.96 per 100,000) and women (3.47 per 100,000) of all races in this age group. African American men in this "oldest old" age group have a much lower prevalence of suicide death relative to their white counterparts (8.83 per 100,000).

Particular mental disorders are associated with an increased risk of suicide. For example, studies of suicide in bipolar disorder across the lifespan suggest that the risk of a completed suicide is greatest 7−12 years postdisease onset, and the highest prevalence of completed suicides occur in those under the age of 35 (Depp & Jeste, 2004; Tsai, Kuo, Chen, & Lee, 2002). Depression and other mental health problems (including substance use) likewise increase the risk of suicide at any age. Older adults with depression, anxiety, and alcohol use disorder are the age group most likely to complete suicide. Examination of CPES data found that older adults (aged 55 and older) who were exposed to serious accidents or illnesses were three times more likely to endorse suicidal ideation compared to those older adults who were not exposed to similar trauma (Beristianos, Maguen, Neylan, & Byers, 2016). This robust finding held after controlling for sociodemographic variables, comorbid mental health disorders (PTSD, MDD, and substance use disorders), and experience of other traumas. In particular, knowledge of having a life-threatening illness was associated with increased odds of endorsing late-life ideation. Practitioners working with older adults should note age-relevant risk factors for suicide, including social isolation, physical illness, disability, and pain, and initiate support and treatment plans accordingly.

Summary and future directions

Mental disorders in older adults impart a significant individual and public health burden. As life expectancy increases and the large baby boomer cohort ages, such burden and associated adverse outcomes have increasing effects. Unfortunately, the workforce of health care providers equipped to work with older adults is insufficient to meet this demand (Institute of Medicine, 2012), creating a dire health services need. Notably, 70% of older adults from the NCS-R with prevalent mood and anxiety disorders did not use mental health services. Nonservice use was related to being from a racial/ethnic minority group and being from lower or middle-income group (compared to high-income status) (Byers et al., 2012). Other epidemiological data suggest that relationship loss or strife is a key predictor of services use in middle and older age (Byers, Lai, Nelson, and Yaffe, 2017). Mental health service use among older adults is determined in part by complex sociocultural factors, including ethnicity/race, marital status, health insurance, perceived family support, comorbid psychiatric disorders, chronic medical conditions, and perceived cognitive impairment, warranting special attention in future epidemiological investigations of this increasingly diverse age group. The aging of the population suggests the importance of continued epidemiological monitoring of mental health and the use of mental health services among older adults, to include the diversity among the young-old through the oldest-old cohorts.

Epidemiological methods document the distribution of psychiatric disorders in the population and can help to inform service needs. Moreover, they are a complement to basic science research and experimental studies, in order to best infer what risks and determinants may contribute to psychiatric disease in the population. The epidemiological data reviewed in this chapter generally demonstrate a declining prevalence of mental illness among older adults relative to younger age groups, with the exception of neurocognitive disorders, for which age is the biggest risk factor. Data consistently demonstrate lower levels of depression, anxiety, and substance use among older adults compared to their young and middle-aged adults. Some may find this counterintuitive, given the increased incidence of worsened physical health and loss in later life. Possible explanations for this general decline of mental illness observed in older age groups include (1) cohort effects, in which characteristics observed in prior birth cohorts may change as the young-old (i.e., baby boomers) age; (2) differential mortality or "healthy survivor bias," in which the probability of survival into older adulthood is lower for individuals with mental illness than those without; (3) lack of institutionalized older adults represented in national samples; and (4) other methodological and clinical issues in assessing older adults, including stigma or other underreporting related to endorsing mental health symptoms or disorders, heterogeneity of symptom presentations relative to younger cohorts (including somatic presentations of mental illness), and difficulty recalling symptoms.

The future of psychiatric epidemiology and mental health research in general will be shaped by the growing need to refine psychiatric diagnoses. For example, recent findings from genome-wide association studies across nearly 1.2 million individuals suggest significant overlap across psychiatric disorders, most notably bipolar disorder, MDD, schizophrenia, and attention deficit/hyperactivity disorder (Brainstorm Consortium et al., 2018). Cognitive and personality traits showed robust correlations with certain disorders such as neuroticism with both anxiety and depressive disorders.

Such a high degree of shared pathogenesis and heritability calls into question the current diagnostic categories and points to shared or overlapping brain mechanisms in what were previously considered distinct disorders. Genetic epidemiology is an emerging discipline which integrates the fields of epidemiology and genetics to consider joint actions of genetic and environmental factors in causing disease, including mental illness. Advances in genetics and neuroscience will increasingly need to be applied to psychological and biological processes in population-based studies. Conversely, epidemiology can generate hypotheses to be tested by basic scientists and in experimental studies in humans.

Acknowledgments

The preparation of this chapter was supported by the National Institute of Mental Health (grant no. T32MH073553).

References

Alegría, M., Chatterji, P., Wells, K., Cao, Z., Chen, C., Takeuchi, D., et al. (2008). Disparity in depression treatment among racial and ethnic minority populations in the United States. *Psychiatric Services*, *59*(11), 1264–1272.

Alegria, M., Jackson, J. S., Kessler, R. C., and Takeuchi, D. (2016). Collaborative Psychiatric Epidemiology Surveys (CPES), 2001–2003 [United States]. Inter-university Consortium for Political and Social Research [distributor].

Ali, S., Stone, M. A., Peters, J. L., Davies, M. J., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with Type 2 diabetes: A systematic review and meta-analysis. *Diabetic Medicine: A Journal of the British Diabetic Association*, *23*(11), 1165–1173.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. (5th ed.). Washington, DC: American Psychiatric Publishing.

Bank, W. (1993). *Investing in health: World development indicators.*. New York, NY: World Bank.

Beekman, A. T., Copeland, J. R., & Prince, M. J. (1999). Review of community prevalence of depression in later life. *British Journal of Psychiatry.*, *174*, 307–311.

Beristianos, M. H., Maguen, S., Neylan, T. C., & Byers, A. L. (2016). Trauma exposure and risk of suicidal ideation among older adults. *The American Journal of Geriatric Psychiatry.*, *24*(8), 639–643.

Blanco, C., Compton, W. M., Saha, T. D., Goldstein, B. I., Ruan, W. J., Huang, B., et al. (2017). Epidemiology of DSM-5 bipolar I disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions—III. *Journal of Psychiatric Research*, *84*, 310–317.

Brainstorm Consortium., Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., et al. (2018). Analysis of shared heritability in common disorders of the brain. *Science.*, *360*(6395).

Brewster, K. K., Ciarleglio, A., Brown, P. J., Chen, C., Kim, H. O., Roose, S. P., et al. (2018). Age-related hearing loss and its association with depression in later life. *The American Journal of Geriatric Psychiatry.*, *26*(7), 788–796.

Byers, A. L., Arean, P. A., & Yaffe, K. (2012). Low use of mental health services among older Americans with mood and anxiety disorders. *Psychiatric Services.*, *63*(1), 66–72.

Byers, A. L., Lai, A. X., Nelson, C., & Yaffe, K. (2017). Predictors of mental health services use across the life course among racially-ethnically diverse adults. *The American Journal of Geriatric Psychiatry.*, *25*(11), 1213–1222.

Byers, A. L., Yaffe, K., Covinsky, K. E., Friedman, M. B., & Bruce, M. L. (2010). High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Archives of General Psychiatry.*, *67*(5), 489–496.

Cassidy, F., & Carroll, B. J. (2002). Vascular risk factors in late onset mania. *Psychological Medicine.*, *32*(2), 359–362.

Center for Behavioral Health Statistics and Quality (CBHSQ). (2017). *2016 National survey on drug use and health: detailed tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Centers for Disease Control and Prevention (CDC). Data & statistics fatal injury report for 2016. 2016.

Chapman, D. P., & Perry, G. S. (2008). Depression as a major component of public health for older adults. *Preventing Chronic Disease*, *5*(1), A22.

Cuijpers, P., Karyotaki, E., Pot, A. M., Park, M., & Reynolds, C. F., 3rd (2014). Managing depression in older age: Psychological interventions. *Maturitas.*, *79*(2), 160–169.

Daumit, G. L., Goff, D. C., Meyer, J. M., Davis, V. G., Nasrallah, H. A., McEvoy, J. P., et al. (2008). Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia Research*, *105*(1–3), 175–187.

Dawson, D. A., Goldstein, R. B., Saha, T. D., & Grant, B. F. (2015). Changes in alcohol consumption: United States, 2001–2002 to 2012–2013. *Drug and Alcohol Dependence*, *148*, 56–61.

Depp, C. A., & Jeste, D. V. (2004). Bipolar disorder in older adults: A critical review. *Bipolar Disorders*, *6*(5), 343–367.

Ell, K., Aranda, M. P., Xie, B., Lee, P. J., & Chou, C. P. (2010). Collaborative depression treatment in older and younger adults with physical illness: Pooled comparative analysis of three randomized clinical trials. *The American Journal of Geriatric Psychiatry.*, *18*(6), 520–530.

Gallo, J. J., Rabins, P. V., & Anthony, J. C. (1999). Sadness in older persons: 13-Year follow-up of a community sample in Baltimore, Maryland. *Psychological Medicine.*, *29*(2), 341–350.

Goldstein, R. B., Smith, S. M., Chou, S. P., Saha, T. D., Jung, J., Zhang, H., et al. (2016). The epidemiology of DSM-5 posttraumatic stress disorder in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Social Psychiatry and Psychiatric Epidemiology*, *51*(8), 1137–1148.

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., et al. (2015). Epidemiology of DSM-5 Alcohol Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry.*, *72*(8), 757–766.

Grant, B. F., Saha, T. D., Ruan, W. J., Goldstein, R. B., Chou, S. P., Jung, J., et al. (2016). Epidemiology of DSM-5 Drug Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry.*, *73*(1), 39–47.

Han, B. H., Sherman, S., Mauro, P. M., Martins, S. S., Rotenberg, J., & Palamar, J. J. (2017). Demographic trends among older cannabis users in the United States, 2006–13. *Addiction.*, *112*(3), 516–525.

Hasin, D. S., Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., et al. (2015). Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry.*, *72*(12), 1235–1242.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology.*, *80*(19), 1778–1783.

Hoover, D. R., Siegel, M., Lucas, J., Kalay, E., Gaboda, D., Devanand, D. P., et al. (2010). Depression in the first year of stay for elderly long-term nursing home residents in the USA. *International Psychogeriatrics.*, *22*(7), 1161–1171.

Hörder, H., Johansson, L., Guo, X., Grimby, G., Kern, S., Östling, S., et al. (2018). Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women. *Neurology.*, *90*(15), e1298–e1305.

Hybels, C. F., & Blazer, D. G. (2003). Epidemiology of late-life mental disorders. *Clinics in Geriatric Medicine*, *19*(4), 663–696.

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., et al. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry.*, *73*(5), 525–531.

Kessing, L. V., Vradi, E., McIntyre, R. S., & Andersen, P. K. (2015). Causes of decreased life expectancy over the life span in bipolar disorder. *Journal of Affective Disorders*, *180*, 142–147.

Kessler, R. C., Berglund, P., Chiu, W. T., Demler, O., Heeringa, S., Hiripi, E., et al. (2004). The US National Comorbidity Survey Replication (NCS-R): Design and field procedures. *International Journal of Methods in Psychiatric Research*, *13*(2), 69–92.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry.*, *62*(6), 593–602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry.*, *62*(6), 617–627.

Kessler, R. C., McGonagle, K. A., Zhao, S., et al. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry.*, *51*(1), 8–19.

Kessler, R. C., & Merikangas, K. R. (2004). The National Comorbidity Survey Replication (NCS-R): Background and aims. *International Journal of Methods in Psychiatric Research.*, *13*(2), 60–68.

Keyes, K. M., Li, G., & Hasin, D. S. (2011). Birth cohort effects and gender differences in alcohol epidemiology: A review and synthesis. *Alcoholism: Clinical and Experimental Research*, *35*(12), 2101–2112.

Klap, R., Unroe, K. T., & Unutzer, J. (2003). Caring for mental illness in the United States: A focus on older adults. *The American Journal of Geriatric Psychiatry.*, *11*(5), 517–524.

Kochanek, K. D., Murphy, S. L., Xu, J., & Arias E. (2017). Mortality in the United States, 2016.

Krishnan, K. R. (2002). Biological risk factors in late life depression. *Biological Psychiatry.*, *52*(3), 185–192.

Kuerbis, A., Sacco, P., Blazer, D. G., & Moore, A. A. (2014). Substance abuse among older adults. *Clinics in Geriatric Medicine.*, *30*(3), 629–654.

Licht-Strunk, E., Van Marwijk, H. W., Hoekstra, T., Twisk, J. W., De Haan, M., & Beekman, A. T. (2009). Outcome of depression in later life in primary care: Longitudinal cohort study with three years' follow-up. *BMJ.*, *338*, a3079.

Lin, J. C., Karno, M. P., Grella, C. E., Ray, L. A., Liao, D. H., & Moore, A. A. (2014). Psychiatric correlates of alcohol and tobacco use disorders in U.S. adults aged 65 years and older: Results from the 2001–2002 National Epidemiologic Survey of Alcohol and Related Conditions. *The American Journal of Geriatric Psychiatry.*, *22*(11), 1356–1363.

Livermore, N., Sharpe, L., & McKenzie, D. (2010). Panic attacks and panic disorder in chronic obstructive pulmonary disease: A cognitive behavioral perspective. *Respiratory Medicine.*, *104*(9), 1246–1253.

Martin, L. A., Neighbors, H. W., & Griffith, D. M. (2013). The experience of symptoms of depression in men vs women: Analysis of the National Comorbidity Survey Replication. *JAMA Psychiatry.*, *70*(10), 1100–1106.

Institute of Medicine. (2012). *The mental health and substance use workforce for older adults: In whose hands?* Washington, DC: The National Academies Press.

Mehta, K. M., & Yeo, G. W. (2017). Systematic review of dementia prevalence and incidence in United States race/ethnic populations. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(1), 72–83.

Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., et al. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *The Lancet Oncology*, *12*(2), 160–174.

Mitchell, A. J., & Subramaniam, H. (2005). Prognosis of depression in old age compared to middle age: A systematic review of comparative studies. *American Journal of Psychiatry.*, *162*(9), 1588–1601.

Newman, B. M. (2016). Treatment-resistant depression in the elderly: Diagnostic and treatment approaches. *Current Geriatric Reports*, *5*(4), 241–247.

Olfson, M., Kroenke, K., Wang, S., & Blanco, C. (2014). Trends in office-based mental health care provided by psychiatrists and primary care physicians. *The Journal of Clinical Psychiatry.*, *75*(3), 247–253.

Palmer, S., Vecchio, M., Craig, J. C., Tonelli, M., Johnson, D. W., Nicolucci, A., et al. (2013). Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. *Kidney International*, *84*(1), 179−191.

Patel, V., Garrison, P., de Jesus Mari, J., Minas, H., Prince, M., Saxena, S., et al. (2008). The Lancet's series on global mental health: 1 year on. *Lancet.*, *372*(9646), 1354−1357.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., et al. (2007). Prevalence of dementia in the United States: The aging, demographics, and memory study. *Neuroepidemiology.*, *29*(1−2), 125−132.

Regier, D. A., Goldberg, I. D., & Taube, C. A. (1978). The de facto US mental health services system: A public health perspective. *Archives of General Psychiatry.*, *35*(6), 685−693.

Regier, D. A., Hirschfeld, R. M., Goodwin, F. K., Burke, J. D., Jr., Lazar, J. B., & Judd, L. L. (1988). The NIMH Depression Awareness, Recognition, and Treatment Program: Structure, aims, and scientific basis. *American Journal of Psychiatry.*, *145*(11), 1351−1357.

Renn, B. N., & Arean, P. A. (2017). Psychosocial treatment options for major depressive disorder in older adults. *Current Treatment Options in Psychiatry.*, *4*(1), 1−12.

Renn, B. N., Feliciano, L., & Segal, D. L. (2011). The bidirectional relationship of depression and diabetes: A systematic review. *Clinical Psychology Review.*, *31*(8), 1239−1246.

Robinson, R. G., & Jorge, R. E. (2016). Post-stroke depression: A review. *American Journal of Psychiatry.*, *173*(3), 221−231.

Rustad, J. K., Stern, T. A., Hebert, K. A., & Musselman, D. L. (2013). Diagnosis and treatment of depression in patients with congestive heart failure: A review of the literature. *The Primary Care Companion for CNS Disorders*, *15*(4).

Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., Jung, J., et al. (2016). Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *The Journal of Clinical Psychiatry.*, *77*(6), 772−780.

Sajatovic, M., & Blow, F. C. (2007). *Bipolar disorder in later life.*. Baltimore, MD: Johns Hopkins University Press.

Sajatovic, M., & Kessing, L. V. (2010). Bipolar disorder in the elderly. In L. N. Yatham, & M. Maj (Eds.), *Bipolar disorder: Clinical and Neurobiological Foundations.* (p. 488). West Sussex: Wiley-Blackwell.

Schaakxs, R., Comijs, H. C., Lamers, F., Kok, R. M., Beekman, A. T. F., & Penninx, B. (2018). Associations between age and the course of major depressive disorder: A 2-year longitudinal cohort study. *The Lancet Psychiatry.*, *5*(7), 581−590.

Seitz, D., Purandare, N., & Conn, D. (2010). Prevalence of psychiatric disorders among older adults in long-term care homes: A systematic review. *International Psychogeriatrics*, *22*(7), 1025−1039.

Smith, S. M., Goldstein, R. B., & Grant, B. F. (2016). The association between post-traumatic stress disorder and lifetime DSM-5 psychiatric disorders among veterans: Data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). *Journal of Psychiatric Research*, *82*, 16−22.

Souery, D., Amsterdam, J., de Montigny, C., Lecrubier, Y., Montgomery, S., Lipp, O., et al. (1999). Treatment resistant depression: Methodological overview and operational criteria. *European Neuropsychopharmacology*, *9*(1−2), 83−91.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006−1012.

Substance Abuse and Mental Health Services Administration (SAMHSA). (2013). *Results from the 2012 national survey on drug use and health: Summary of national findings*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Tariot, P. N., Podgorski, C. A., Blazina, L., & Leibovici, A. (1993). Mental disorders in the nursing home: Another perspective. *American Journal of Psychiatry.*, *150*(7), 1063−1069.

Tsai, S. Y., Kuo, C. J., Chen, C. C., & Lee, H. C. (2002). Risk factors for completed suicide in bipolar disorder. *The Journal of Clinical Psychiatry.*, *63*(6), 469−476.

Walker, E. R., McGee, R. E., & Druss, B. G. (2015). Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. *JAMA Psychiatry.*, *72*(4), 334−341.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., et al. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet.*, *382*(9904), 1575−1586.

Wisco, B. E., Marx, B. P., Wolf, E. J., Miller, M. W., Southwick, S. M., & Pietrzak, R. H. (2014). Posttraumatic stress disorder in the US veteran population: Results from the National Health and Resilience in Veterans Study. *The Journal of Clinical Psychiatry.*, *75*(12), 1338−1346.

Wu, L. T., & Blazer, D. G. (2011). Illicit and nonmedical drug use among older adults: A review. *Journal of Aging and Health.*, *23*(3), 481−504.

Chapter 3

Culture and ethnicity in the mental health of older adults

Lucas Torres, Claire Bird and Felicia Mata-Greve
Department of Psychology, Marquette University, Milwaukee, WI, United States

Culture and ethnicity in the mental health of older adults

The US population continues to live longer and healthier lives resulting in a growth in the proportion of older adults (APA Presidential Task Force, 2008). The older adult population has seen marked demographic changes given that racial and ethnic minority individuals are considered the fastest-growing segment within this group (Jimenez, Alegria, Chen, Chan, & Laderman, 2010). In the coming decades, older adults will be increasingly diverse in terms of cultural values, attitudes toward help-seeking and healing practices, and communication preferences (Vasquez, Marin, & Garcia-Vazquez, 2010). In addition to culture and ethnicity, the older adult group will include "heterogeneity in a number of critical areas, including health status, sexual orientation, gender identity, gender expression, disability, availability and involvement of family members as partners in care, physical activity, occupational status, educational background, financial resources, knowledge about technology, and trust of mental health professionals" (APA Presidential Task Force, 2008, p. 8). It is increasingly important to acknowledge that membership into these diverse groups includes histories and life course experiences associated with inequities, disadvantages, and stressors that culminate in health disparities later in life (Jackson, Govia, & Sellers, 2011).

Mental health difficulties are an area of concern among the growing older adult population. Previous research has documented differences in prevalence rates across ethnic groups, although much of this work has been critiqued for utilizing samples of younger adults (Riolo, Nguyen, Greden, & King, 2005). As an example, one study found that older White Americans showed greater rates of depression, anxiety, and substance use than older Asian Americans and African Americans, but comparable to Latinx[1] older adults. In fact, Latinx older adults had higher 12-month prevalence rates for depression than any other ethnic group (Jimenez et al., 2010). Still, ethnic minority older adults underutilize medical and mental health services, perhaps because of structural factors (i.e., financial, access to care) and cultural variables (APA Presidential Task Force, 2008; Hiroto & Yarry, 2017). Until recently, minimal empirical research has focused on the role of race, ethnicity, and culture on the mental health of older adults (Ferrer, Grenier, Brotman, & Koehn, 2017).

To clarify the use of terms, *race* has been defined as a physical characteristic shared by a group of people (Cokley, 2007). Scholars have largely conceptualized race as a social construct with research disputing the notion that biological differences exist across groups (Smedley & Smedley, 2005). Still, race has significant political and psychological implications. *Ethnicity* refers to a group of people with a common ancestry and shared cultural traditions (Cokley, 2007). *Culture*, on the other hand, is a broader construct that includes shared attitudes, beliefs, and norms. Although often used interchangeably, ethnicity is specific to a social context and heritage, whereas culture involves elements of one's worldview, such as communication patterns, affective styles, and individualism/collectivism (Hall & Barongan, 2002). Culture and worldview determine our definitions of abnormality and explanations for psychological difficulties, expressions of distress, and coping and help-seeking behaviors.

The purpose of the current chapter is to provide an overview of the mechanisms and factors likely to influence the mental health and access to care of ethnic minority older adults. The first aim is to explore cultural factors, namely

1. Latinx is an all-encompassing and gender neutral term that refers to individuals who identifty as Latina/o or Hispanic.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00003-X

racial/ethnic discrimination, cultural adaptation, and religion/spirituality, that may contribute to mental health problems including cognitive decline. The second aim of the chapter is to review access to mental health care and potential barriers, namely attitudes toward treatment, mental health stigma, cultural mistrust, and structural barriers to care. These topic areas are not intended to be exhaustive but instead provide an overview of key experiences and systems that are associated with the mental health of ethnic minority older adults.

Cultural factors associated with mental health

As mentioned earlier, the first aim of this review is to examine some of the cultural factors that have been linked with mental health among ethnic minority older adults. While there are many cultural factors that have potential to influence mental health, minimal research has explored these constructs among ethnic minority older adults. The existing empirical literature has focused on racial/ethnic discrimination, cultural adaptation, ethnicity's relationship with cognition, and religion/spirituality, described below.

Racial/ethnic discrimination

Racial/ethnic discrimination involves unfair or differential treatment due to one's membership in a racial or ethnic group (Contrada et al., 2000). It is a broad term that encompasses several types of experiences ranging from systemic or structural inequities to subtle and covert forms of everyday discrimination that occur at an interpersonal level. The link between racial/ethnic discrimination and poor mental health outcomes, including depression, anxiety, posttraumatic stress disorder, and substance use, has been well established (Paradies et al., 2015; Pascoe & Smart Richman, 2009).

Systemic racial/ethnic discrimination. As defined by the US Equal Employment Opportunity Commission, systemic discrimination is defined as patterns within structural procedures of an organization or broader community that continually maintain disadvantage for already marginalized groups. In the case of older ethnic minority adults, lessened health education campaigns and community prevention efforts may influence how they access mental health treatment.

Moreover, the long and pervasive history of systemic discrimination in the US health care system might contribute to how ethnic minority older adults view and access mental health care. Historical examples aid this suggestion. As an infamous case, in the 1930s the Tuskegee study examined the effects of syphilis among African American men for many years. In the 1950s, when a cure was released, the African American participants were purposefully not informed of the new treatment by the researchers. Instead, researchers followed the disease's progression (Brandt, 1978). As another example, physicians sterilized Native American women with tubal ligations or hysterectomies during other routine procedures without their consent or knowledge in the 1960s and 1970s. Scholars estimate that approximately one-quarter of Native American women within reproductive ages were sterilized in the 1970s alone (Lawrence, 2000). The current cohort of older adults may have lived through these events. Therefore, the legacy of these and other examples of historical and systemic discrimination might negatively influence how older ethnic minority adults view health care professionals.

Everyday racial/ethnic discrimination. It is defined as chronic, covert, slights that include being treated with less respect or receiving a different level of treatment than others (Essed, 1991). These experiences, which are often ambiguous and subtle, contribute to the added stress burden experienced by many ethnic minority older adults. Previous studies illustrated how ethnic minority older adults experience everyday racial/ethnic discrimination within mental health services. In fact, findings from the Health and Retirement study reported that 63% of older adults indicated experiences of everyday racial/ethnic discrimination with older African Americans endorsing more instances when compared to other ethnic minority groups (Luo, Xu, Granberg, & Wentworth, 2012). Furthermore, this study found that everyday racial/ethnic discrimination was associated with health changes 2 years later, namely increased depressive symptoms and poorer self-rated health, independent of general life stress. Despite these psychological consequences, older African American adults were less likely than older White American adults to receive help from mental health providers (Woodward, Chatters, Taylor, Neighbors, & Jackson, 2010).

One way in which older adults may experience everyday discrimination is through biases of treatment providers. Studies continue to demonstrate that mental health providers likely hold implicit biases and stereotypes of marginalized groups. For example, it is well known that mental health professionals may have preconceived notions, whether conscious or not, toward older adults (cf., Laganá & Shanks, 2002) and racial/ethnic minorities (Snowden, 2003). The attitudes that mental health providers hold may influence their interactions with ethnic minority older adults seeking treatment. In fact, studies suggest that treatment providers treat similar conditions vastly different depending on the patient's ethnicity. As an example, Kales and colleagues (2000) found that among those with psychotic disorders,

African Americans were scheduled for fewer psych-related follow-up visits than White Americans. Furthermore, African Americans were prescribed higher medication doses, which likely contributed to higher nonadherence rates of the medications due to elevated side effects. In sum, ethnic minority older adults continue to experience negative day-to-day discriminatory interactions that are associated with increased mental health problems and their likelihood of seeking or adhering to mental health treatment.

Intersectional considerations. Intersectionality acknowledges that an individual may have more than one membership to a marginalized social group, which influences their lived experience given the interlocking systems of inequities associated with each identity (Crenshaw, 1989). Ethnic minority older adults likely experience age-related and racial/ethnic discrimination. Age-related discrimination has been thought to be an explanatory factor for why older adults of all racial/ethnic backgrounds are less likely to seek mental health treatment when compared to younger cohorts (Robb, Chen, & Haley, 2002). One qualitative study reported that ethnic minority older adults did not seek mental health services in order to protect their own individual and cultural identity (Koehn, 2009). These participants sought to present as healthy and independent to avoid age-related stereotypes or biases. Furthermore, women and individuals who identify as lesbian, gay, bisexual, or transgender may have to manage added difficulties stemming from gender discrimination and/or homophobia. For instance, lesbian/bisexual older adult women reported higher levels of psychological distress when compared to their heterosexual counterparts (Wallace, Cochran, Durazo, & Ford, 2011). Mental health care providers should be cognizant of their own biases and that ethnic minority older adults may experience discrimination associated with multiple marginalized backgrounds.

Cultural adaptation

The process of cultural adaptation has been described as a lifelong phenomenon by which ethnic minority individuals adjust and manage to live in multiple cultures (Berry, 1997). Current models describe a bidimensional process by which ethnic minority individuals negotiate contact with the mainstream culture and, concurrently, maintenance of the traditional culture of origin (Berry, 2003). Specifically, *acculturation* is defined as the process by which individuals adopt the values, customs, and traditions of the mainstream culture in which they are living (Berry, 1997). On the other hand, *enculturation* is thought to be the process where an individual maintains the practices of their heritage culture (Gonzales, Knight, Birman, & Sirolli, 2004). Unfortunately, many methodological challenges have been cited in the research examining cultural adaptation. For example, some research has taken a one-dimensional approach in which acculturation is examined with no acknowledgment of enculturation. Still, experiences of acculturation and enculturation fit the lived experiences of ethnic minority individuals, making it critically important to consider how country of origin, pattern of migration, similarities and differences between the mainstream and heritage culture, and language fluency influence the cultural adaptation process across groups (Hunt, Schneider, & Comer, 2004; Schwartz, Unger, Zamboanga, & Szapocznik, 2010).

Cultural adaptation and mental health. Given some of the aforementioned methodological challenges (cf., Schwartz et al., 2010), disparate findings exist regarding the relation of acculturation and enculturation with mental health outcomes across ethnic minority groups. To illustrate, among older adults, greater enculturation has been linked to higher depression symptoms among Muslim Americans (Abu-Bader, Tirmazi, & Ross-Sheriff, 2011). Older Muslim adults that adhere strongly to their heritage culture may experience additional stress adapting to the US culture post-9/11 given the anti-Muslim sentiment and discrimination that arose after the terrorist attacks. For Asian American older adults, low acculturation has been cited as a risk factor for depression, whereas high acculturation has emerged as a protective factor (Casado & Leung, 2001; Harada et al, 2012; Jang & Chiriboga, 2011).

The empirical research on the cultural adaptation of Latinx older adults is difficult to parse apart given the inconsistencies that exist among findings. For instance, reports have suggested that high acculturation predicts depression (Gallagher-Thompson et al., 1997) and is associated with increased alcohol consumption (Bryant & Kim, 2013). Conversely, other research has indicated that Latinx older adults with high enculturation had a greater risk of depression symptoms than those reporting high acculturation (Gonzalez, Haan, & Hinton, 2001). Again, many studies fall short of considering a multitude of factors pertinent to acculturation, such as age of immigration, years spent in the United States, historical considerations of the cultural group, language fluency of the individual, and/or adjustment of the individual (Gelfand & Yee, 1991).

Rather than viewing cultural adaptation as a risk or protective factor on mental health, researchers and clinicians may consider other related factors such as amount of time lived in the United States or ethnic density of an individual's neighborhood. As an example, Gelfand and Yee (1991) found that low acculturation predicted higher depression among Korean American older adults in the United States. However, when they controlled for neighborhood density, they

found that this link no longer existed for those that lived in a neighborhood with a high population of other Korean Americans. Similarly, Kwag and Jang (2012) found that Latinx older adults with low acculturation were more likely to be depressed when they lived in a low-density Latinx neighborhood. Schwartz and colleagues (2010) explained that if an individual lives in an area where their cultural values and practices are maintained, acculturation and enculturation may be less of an issue for mental health. In sum, the trend demonstrates that if an individual is low in acculturation but has high activity and proximity with their own race/ethnicity, the link between cultural adaptation and mental health becomes less salient.

Symptom presentation. Scholars have suggested that cultural adaptation and level of acculturation may influence the presentation of mental health symptoms among ethnic minority older adults. Chiriboga, Jang, Banks, and Kim (2007) examined how Mexican American older adults endorsed depression symptomatology in the Center for Epidemiologic Scale for Depression (Radloff, 1977). Interestingly, those who endorsed high levels of acculturation were more likely to endorse items with high face validity (e.g., "I am depressed"). In contrast, those with low acculturation were more likely to endorse items of interpersonal struggles and discomfort. Another study found that, on average, Latinx older adults were less likely to endorse items reflecting positive emotionality compared to their White American counterparts (MacIntosh & Strickland, 2010). Similarly, Jang, Kim, and Chiriboga (2005) assessed how Korean American older adults completed two common self-report measures of depression. They found that those with low acculturation were more likely to endorse low frequency of positive items than those with high acculturation (e.g., I feel hopeful). Different cultural values, such as in emotional expression, may influence how individuals endorse symptoms of depression. For example, with Korean American older adults, it might be that they are socialized to not display positive affect (Jang et al., 2005).

In addition, researchers have examined how various cultures, inside and outside of the United States, may express mental health difficulties in the form of physical or somatic complaints. Ryder and colleagues (2008) found that individuals from China were more likely to report somatic symptoms of depression compared to individuals in Canada. Similarly, another study found that clinically depressed Asian Americans were more likely to endorse somatic symptoms, while White Americans were more likely to report affective symptoms (Kalibatseva, Leong, & Ham, 2014). Parallel findings emerged among older Japanese-American men: older Japanese-American men living in Hawaii who identified strongly with Japanese culture were less likely to endorse symptoms of depression compared to older Japanese-American men that identified with US culture. However, these older Japanese-American men with lower levels of acculturation were more likely to report physical complaints (Harada et al., 2012). It might be due to the notion that US culture places a stronger emphasis on endorsing affective symptoms of depression than other cultures (Ryder et al., 2008). Thus, increasing acculturation levels to the United States may encourage ethnic minority older adults to identify and report more affective symptoms.

Empirical findings suggesting differential symptom presentation have caused clinicians and researchers to think critically about the mental health questionnaires that are administered to ethnic minority older adults. Still, more research is needed to examine the measurement invariance of commonly used measures across cultural groups of older adults (e.g., Kim, DeCoster, Huang, & Bryant, 2013; MacIntosh, & Strickland, 2010). Using cultural adaptation as a lens in which to understand symptom presentation has significant clinical implications and may enhance communication between health care providers and patients (Gelfand & Yee, 1991).

Cognition and ethnicity

Cognitive decline, particularly, dementia and Alzheimer's disease, in common among older adults yet has been shown to vary widely across ethnicity. Latinx and African American older adults are 1.5 and 2 times more likely to experience Alzheimer's disease or other dementia, respectively, in comparison to White American older adults (Alzheimer's Association, 2010). Puerto Rican older adults have been found to be at particularly high risk for the diagnosis of Alzheimer's disease and experience greater severity of cognitive impairment in comparison to African American and White American older adults (Livney et al., 2011). Empirical research has indicated that low socioeconomic status (SES) and less years of education are significant risk factors associated with cognitive decline (Haan et al., 2011; Karlamangla et al., 2009). Still, some work has sought to identify the cultural factors that can protect ethnic minority older adults from cognitive decline. For instance, bilingualism has been found to serve a protective function among Latinx older adults and has been associated with delayed age of dementia onset (Bialystok, Craik, & Freedman, 2007). This buffering effect has been attributed to an expanded cognitive reserve that allows bilingual individuals to compensate for cognitive impairments as the disease begins to develop. Still, bilingualism does not appear to slow down the

deterioration observed in dementia but instead may slow down the corresponding functional impairment (Torres, Hoelzle, & Vallejo, 2016).

Ethnic minority older adults suffering from dementia tend to underutilize treatment and often experience inadequate quality care. A systematic review examining the use of health services and access to dementia treatments reported that ethnic minority older adults with dementia are 40% less likely to enter 24-hour care, are rarely represented in clinical trials for treatment, and are less likely to be prescribed appropriate medication to treat their dementia (Cooper, Tandy, Balamurali, & Livingston, 2010). A study examining the influence of culture on caregiving of older Chinese Americans found that stigma, the view of dementia as "normal aging," and the expectation of familial caregiving often deters individuals from seeking medical attention when experiencing symptoms of dementia (Sun, Ong, & Burnette, 2012). Health service professionals should have an increased awareness of the stigma associated with dementia among ethnic minority populations. It is also suggested that providers should be aware of cultural beliefs surrounding dementia and Alzheimer's disease including their client's adherence to such attitudes that may impact their course of treatment. In addition, structural inequities, including SES or a lack of community resources, often serve as barriers to care which, in turn, contribute to greater severity of symptoms (Livney et al., 2011).

Religion and spirituality

Although often studied together and used interchangeably, religion and spirituality are different constructs that have a significant impact on the lives of many individuals. *Religion* is considered to be a fixed set of beliefs and practices, which is often associated with an organized institution or group (Hill & Pargament, 2003). *Spirituality*, on the other hand, may be described as one's "personal, subjective side of the religious experience," or holding a personal connection to a higher power (Hill & Pargament, 2003, p. 64). Spirituality is thought to lead to connection with spiritual practices, sense of inner peace with self, and has been associated with greater well-being for older adults (Fry, 2000). Research has demonstrated that religion and spirituality are positively correlated with age, such that as individuals age, they become more religious and/or spiritual (Moberg, 2005; Nelson-Becker, 2005). Religion and spirituality have been thought to be particularly salient among ethnic minority older adults. For instance, Mexican American and African American older adults reported praying more often for gratitude and material items when compared to their White American counterparts (Krause, 2012). African American older adults have reported higher levels of religiosity and spirituality compared to their younger counterparts, as approximately 75% of the sample of older adults endorsed engaging in prayer or meditation each day (Skarupski, Fitchett, Evans, & De Leon, 2010). Higher levels of religiosity and spirituality appear to be generally beneficial through many adaptive mechanisms.

Religion and spirituality have been thought to serve a protective function with physical and mental health regardless of ethnicity, gender, SES, or age (Ellison & Levin, 1998). Pargament (2002) suggested that marginalized groups, such as ethnic minority older adults, may reap significant benefits because religion and spirituality offer order in their lives, promote well-being, and provide emotional resources. Religion and/or spirituality have been positively linked to life satisfaction among a national sample of African American (Skarupski, Fitchett, Evans, & de Leon, 2013) and Native American older adults (Yoon & Othella, 2004). Older African American and Caribbean Blacks endorsed greater rates of religious coping and levels of spirituality in comparison to their White American older adult counterparts (Taylor, Chatters, & Jackson, 2007).

Religion and spirituality have been consistently linked to positive aspects of well-being and mental health among ethnic minority older adults. To demonstrate, higher levels of spirituality have been associated with lower depression symptoms among African American older adults (Skarupski et al., 2013) and a diverse sample of older adults in the United States (Lynch, Hernandez-Tejada, Strom, & Egede, 2012; Mofidi et al., 2006). A similar pattern has been reported with religiosity such that higher levels are related to lower depression among older adults representing different ethnic groups, particularly African Americans (Husaini, Blasi, & Miller, 1999; Nelson, 1989; Roff et al., 2004). Among Latinx older adults, church attendance was positively linked to decreased depression symptoms (Aranda, 2008). In sum, religion and spirituality are largely cited as protective factors to mental health for ethnic minority older adults. The mechanisms by which religion and spirituality contribute to positive psychological outcomes are important to consider. Although numerous factors play a role, the empirical literature has largely cited social support and religious coping as important to reaping the benefits of religion and spirituality (cf., Ellison & Levin, 1998).

Social support. It, in general, has been linked to increased life satisfaction and decreased negative affect across the lifespan (Siedlecki, Salthouse, Oishi, & Jeswani, 2014). Social support has been found to underlie the connection between religiosity and life satisfaction, particularly among Korean American older adults, suggesting that it is a key reason for the ability of religion to serve a protective function (Park, Roh, & Younsook, 2012). Identification with a

specific religion often entails involvement with a faith community that can provide emotional support and access to resources. For instance, one study showed that frequency of contact with friends from one's church community was a strong predictor of well-being for African American older adults (Ortega & Rushing, 1983). Church communities often provide spaces for formal and informal gatherings, which provide older adults the opportunity for increased interpersonal interactions (Ellison & Levin, 1998). In fact, attending church has been connected to emotional and tangible support for African American older adults (Hayward & Krause, 2013).

Religious coping. Scholars estimate that being religious or spiritual allows individuals to develop and maintain additional coping resources, such as prayer and meditation (cf., Bjorklof, Engedal, Selbaek, Kouwenhoven, & Helvik, 2013; Ellison & Levin, 1998). Even longitudinally, some studies have found that features of religious coping predict increased physical health and decreased depression at a later date (Bosworth, Kwang-Soo, McQuoid, Hays, & Steffens, 2003; Hayward & Krause, 2016). Unfortunately, the bulk of empirical research has focused on White American samples with fewer studies examining the unique experiences of ethnic minority older adults in relation to religious coping. As an exception, one qualitative study with Chinese immigrant older adults in the United States found that these individuals reported increased religious coping strategies, such as reflecting on their values, faith, and cultural beliefs in response to stressors (Lee & Chan, 2009).

Access to mental health care

The second aim of this chapter is to review access to mental health care, which has been posited as contributing to health disparities. Shavers, Bakos, and Sheppard (2010) conducted a review of pain management among ethnic minority older adults and found that miscommunication and/or misperceptions about health status, cultural differences regarding the effectiveness of treatment, and attitudes toward treatment, among others, were barriers to care encountered by many ethnic minority older adults. Additionally, ethnic minority older adults contend with numerous structural or systemic hurdles that function to create and sustain health inequities.

Mental health stigma and negative attitudes toward treatment

Differential outcomes regarding quality care have been observed across ethnic minority older adults. For instance, Akinolgil and colleagues (2012) reported that, among a national sample, ethnic minority older adults were less likely to receive a diagnosis of depression and receive treatment when compared to their White American counterparts. Similarly, in a large sample of Asian American older adults, Filipino and Korean Americans reported greater symptoms of mental distress in comparison to White Americans and were less likely to have seen a primary care physician or to have taken medications (Sorkin, Nguyen, & Ngo-Metzger, 2011).

Negative feelings or perceptions of mental health treatment can influence one's decision to seek out professional psychological services, which appear to be especially prominent within ethnic minority communities. In a large national sample, African American older adults who had never sought mental health treatment had higher negative attitudes toward treatment (Conner, Copeland, et al., 2010). Specifically, African Americans in this study reported higher mistrust and beliefs of ineffectiveness toward mental health treatment compared to White Americans. Additionally, a focus group with African American older adults reported myths about treatment including that it would not be helpful and that certain medications, such as antidepressants, would be addictive or lead to negative side effects (Conner, Lee, et al., 2010). The participants also indicated a general mistrust in medical treatment and negative beliefs regarding mental health professionals.

Cultural mistrust. As alluded to previously, a large barrier to mental health care within ethnic minority communities is a mistrust of mental health professionals. A study conducted with Chinese and Tamil communities found that they expressed mistrust of mental health services (Sadavoy, Meier, & Ong, 2004). In a separate study examining stigma and mental health care, African American older adults reported more mistrust in mental health services and believed it to be more ineffective than White American participants (Conner, Copeland, et al., 2010). Asian/Pacific Islander and Latinx older adults have also reported not seeking mental health services because they did not feel comfortable when talking to a professional (Sorkin, Murphy, Nguyen, & Biegler, 2016). Much cultural mistrust stems from the many historical examples of discrimination (i.e., Tuskegee study) experienced by ethnic minority individuals when interacting with the health care system.

Due to this mistrust of health care providers and mental health professionals, many ethnic minority older adults will seek out support or help from other leaders in the community or informal networks of support (Woodward et al., 2010). As an example, Chinese and Tamil older adults expressed a preference for confiding in a family member or friend

before seeking professional services (Sadavoy et al., 2004). In a diverse sample of older adults, most selected seeing a medical professional (nonpsychiatrist) as a first choice (40%) for any mental health concerns, with the next most popular choice being a religious leader (32%; Gum et al., 2010).

Mental health stigma. It involves negative beliefs, attitudes, or perceptions of individuals who may have a mental illness (Corrigan, 2004). Mental health stigma may influence the attitudes toward treatment among ethnic minority older adults. For example, in a large national sample, African Americans reported more internalized stigma regarding mental health, compared to White Americans, which was related to less positive attitudes about mental health treatment (Conner, Copeland, et al., 2010). Internalized stigma occurs when individuals with mental health difficulties endorse stereotypes about mental illness, anticipate social rejection, and believe they are a devalued member of society (Livingston & Boyd, 2010). Moreover, in a qualitative focus group with African Americans, participants reported not wanting to appear as "crazy" to friends and family, resulting in a higher likelihood that they would hide symptoms of depression (Conner, Lee, et al., 2010). These participants reported that depression was viewed as a weakness in their community. Similarly, a study examining over 75,000 older adults found that Asian/Pacific Islanders and African Americans were more likely than White Americans to report concerns about someone finding out they had a mental illness (Sorkin et al., 2016).

Another factor contributing to mental health stigma among communities of ethnic minority older adults involves the fear of being seen as a burden on the family. Koehn (2009) found that ethnic minority older adults reported not seeking care because they did not want to pressure children or burden their family. In a large scale study, Latinx older adults were more likely to report that mental health conditions are a source of weakness and a burden on the family (Sorkin et al., 2016). Moreover, Japanese-American older adults have reported that they may be hesitant to ask for help to avoid appearing demanding (Machizawa & Lau, 2010).

In summary, mental health stigma, cultural mistrust, and negative attitudes toward treatment serve as barriers to seeking and receiving quality mental health care for ethnic minority older adults. Establishing strong community partnerships can help to reduce stigma and mistrust by integrating community leaders or community health workers as part of the treatment team to assist and support ethnic minority older adults in times of crisis. In this way, community liaisons can bridge patients with health care providers in a genuine and culturally appropriate manner. Further, health care professionals may consider integrating mental health screenings in primary care and medical settings. Embedding mental health care providers within primary care can facilitate availability and accessibility to services.

Structural barriers to care

Socioeconomic status. Measurement of SES varies widely across research; however, it is most commonly assessed through income, education, and/or occupation. SES is linked to many physical and mental health outcomes, such that higher SES has been associated with better health (Marmot, 2002; Williams & Jackson, 2005). African American older adults relying on Medicare have been found to live in areas where providers are less likely to be board-certified and often provide low-quality care (Williams & Jackson, 2005). In fact, physical health status may influence mental health among ethnic minority older adults. As an example, Bierman and Lee (2018) found that severe chronic pain was more strongly associated with greater risk for depressive symptoms among African American and Latinx older adults than White American older adults. Additionally, using an intersectional perspective, Hinze, Lin, and Andersson (2012) found that less than a high school education was associated with decreased health outcomes for older African American women. On the other hand, higher than a high school education was related to better health outcomes for White American men and African American women. Attributing health disparities to SES is often at the cost of concluding that race or ethnicity does not play a role in differential health outcomes. However, as a critique of this conclusion, Bonilla-Silva and Baiocchi (2007) suggest that structural inequities lie at the intersection of class and ethnicity.

Health insurance. Often, a consequence of low SES includes a lack of health insurance, which greatly limits the professional services available to an individual. In a large national sample, Akinolgil and colleagues (2012) found that African American older adults were less likely than White Americans to have private supplemental insurance that covers charges larger than standard Medicare-approved amounts. Despite nearly universal access to health care via Medicare, disparities exist regarding the quality of care and coverage available for ethnic minority older adults (Herd, Robert, & House, 2011). For example, Virnig, Huang, Lurie, and Musgrave (2004) found that ethnic minority older adults on Medicare received less follow-up care following a hospitalization for mental illness, lower antidepressant and medication management for newly diagnosed depression, and lower continuation-phase treatment. As another example, African American older adults have been found to be less satisfied with medication prices, drug coverage, and ability to find a pharmacy that accepts their coverage in comparison to White Americans (Taira et al., 2017). Relatedly, one's

immigration status may impede their ability to obtain insurance coverage. Specifically, individuals without US citizenship or documentation are often uninsured or underinsured. Moreover, even when insured, they tend to have worse access to emergency and ambulatory care (Ku & Matani, 2001).

Availability and accessibility of services. Another structural factor that has been identified in the empirical research as a barrier to mental health care involves availability of services, awareness of services, and accessibility of services (Sadavoy et al., 2004). In terms of accessibility, ethnic minority older adults have expressed difficulty with "navigation" of the health care system, particularly regarding online scheduling and communication systems and transportation (Koehn, 2009). Ethnic minority older adults may not have ready access to transportation. Choi and Gonzalez (2005) note that older adults with mental health diagnoses, especially depression, may lack the motivation to seek out transportation services. Bartels and colleagues (2004) recommended considering integrating mental health care within a primary care clinic to ease some of the challenges with transportation. In sum, clinics and mental health providers may consider having reliable transportation referrals and if needed, instruct older adults how to use these services.

Ethnic minority older adults have often mentioned the lack of culturally appropriate services in the client's preferred language. The inability to express psychological distress in the individual's native or preferred language is a significant barrier to quality care. As a solution, many clinicians employ the use of interpreters to facilitate communication and treatment. While a systematic review shows that professional interpreters largely improve clinical care (Karliner, Jacobs, Chen & Mutha, 2007), some qualitative studies reveal important concerns. For example, ethnic minority older adults have expressed the pressure to supply their own interpreter, which if a family member can bring about conflict, embarrassment, and/or shame (Sadavoy et al., 2004). That is, older adult may choose to not disclose private information in front of their family member, thus interfering with the quality of care. Empirical research has demonstrated some negative consequences when using family members as interpreters or language brokers including an increased sense of burden and depressive symptoms, although some positive outcomes have also been noted (Kim, Hou, & Gonzalez, 2017). Other considerations for using interpreters within a mental health setting involve taking steps to ensure that the message is being accurately conveyed by the interpreter to facilitate information gathering and treatment. It is vital that the interpreter understands the nature of confidentiality so that the ethnic minority client is assured that the conversation remains private. Moreover, when considering psychotherapy specifically, an interpreter with limited mental health training may be in a difficult position where they are expected to facilitate or carry out complex interventions (Searight & Armock, 2013).

Discussion

With the growth and diversity of the older adult population in the United States, the need has increased to better understand the individual cultural factors and systemic inequities that contribute to mental health and help-seeking among this population. Unfortunately, the experiences of ethnic minority older adults have been largely overlooked in the mental health research or minimized to broad demographic categories (i.e., African American, Latinx). Thus, the current empirical knowledge may be limited and previous models, developed with mainly White American individuals, may not apply to the current cohort of ethnic minority older adults. In an effort to advance the empirical research, comprehensive frameworks that include intersectional approaches to studying aging have been developed (Ferrer et al., 2017). For example, the *intersectional life course perspective* provides a nuanced description of the lives of ethnic minority older adults that consider structural and institutional forces in relation to mental health. In this way, including key transitions, such as immigration, within life course stages can provide a deeper understanding regarding the role of policies, consequences of relocation, and/or discrimination experiences (Ferrer et al., 2017).

Cultural factors play a significant role in the mental health of ethnic minority older adults. As discussed previously, discrimination is associated with numerous health consequences. Discrimination can occur across many levels, from institutional to interpersonal, and include overt or subtle forms. As such, it is important for clinicians and scholars to understand that these experiences are common and often amplified in a social environment that is stratified by ethnic categories (Thrasher et al., 2012). The chronicity of discriminatory experiences adds to the stress burden experienced by ethnic minority older adults, which is later manifested in mental health (and physical health) problems (Williams & Jackson, 2005). Further, intersectionality perspectives provide a more comprehensive understanding of the experiences of marginalization that are associated with being a member of multiple identities or social categories (Crenshaw, 1989). Although the current chapter has focused on ethnic discrimination, ethnic minority older adults can experience unfair treatment based on age, sexual orientation, language use, immigrant status, or socioeconomic class, to name a few identities.

As reviewed, the empirical literature is equivocal on whether acculturation and enculturation function as protective or risk factors. Instead, cultural adaptation should be conceptualized as a multifaceted construct that manifests within the broader environmental context. Still, cultural adaptation will influence how ethnic minority older adults describe and present their symptoms, their understanding of the root causes of difficulties, and who they reach out to for assistance. Religious and spiritual beliefs have been generally associated with positive health outcomes among ethnic minority older adults. Still, clinicians may feel uncomfortable discussing or exploring spirituality. Peteet and colleagues (2018) offered suggestions for integrating spirituality into the health care of older adults from a multicultural perspective: conduct religious/spiritual assessment by a "spiritual care team," obtain spirituality history, coordinate meetings to focus on spiritual needs, and possibly refer to chaplains or pastoral counselors. Making it a practice to ask about religion and spirituality can help the clinician build on existing sources of support. Furthermore, clinicians can consider incorporating spiritual themes within individual treatment plans (i.e., religious meditation as a component of mindfulness exercises). Understanding the complex dynamics within cultural adaptation and religion/spirituality can help clinicians identify and make use of community resources that match the unique needs of their clients.

Access to mental health care is influenced by numerous factors among ethnic minority adults. Mental health stigma, negative attitudes toward treatment, and cultural mistrust contribute to the help-seeking behaviors exhibited by ethnic minority older adults. Empirical work has indicated that interventions which seek to reduce the stigma about treatment effectiveness show greater adherence, particularly antidepressant medication, among older adults (Sirey, Bruce, & Kales, 2010). A community collaborative approach can help to decrease the stigma and mistrust associated with mental health care. Collaborative care models facilitate access to treatment through a combination of psychoeducation, patient activation, treatment monitoring, and mobilization of community resources; all of which have been found to be associated with greater adherence to depression treatment and reduced symptomatology among ethnic minority older adults (Areán et al., 2005). In general, it is important to build community partnerships with leaders and informal networks (i.e., health care professionals, religious leaders) to determine mental health needs, provide education on treatment, and increase accessibility to resources.

From an intersectional life course perspective, structural inequities function as significant barriers at various time points to receiving adequate psychological services. In the United States, SES and ethnicity are markedly intertwined and associated with mental health disparities. Experiences of ethnic discrimination, poverty, and other related stressors have a dose−response relationship such that the accumulation of these negative experiences contributes to mental health difficulties across the life course (Angel, Mudrazija, & Benson, 2016). Scholars have begun to conceptualize SES not only as a determinant but also as a cause of health status given the consistent link between low SES and poor outcomes (Herd et al., 2011).

In conclusion, continued work is necessary to reduce mental health disparities and increase access to quality care for ethnic minority older adults. Future empirical work is needed that examines the sociopolitical factors that impede and facilitate the quality of life of individuals who experience chronic and systemic forms of marginalization over the life course (Jackson et al., 2011). To this end, it is essential to conduct research with ethnic minority older adults that integrates social justice throughout the process—from formulating research questions, to carrying out studies in ways that are respectful and empowering, to drawing on communities to interpret major findings (Thrasher et al., 2012). The key is the development of an awareness of how discrimination and structural inequities underlie and cause health disparities. In this way, research avoids the all too common problem of conflating the causes of disparities to ethnic differences as opposed to the result of institutional disadvantages. In terms of general practical recommendations, clinicians are encouraged to espouse cultural humility when working with ethnic minority older adults. Cultural humility involves a lifelong process of self-reflection characterized by openness, curiosity, and genuine desire to understand the clients' lives (Gallardo, 2013; Owen et al., 2016). In this way, clinicians can engage in active listening skills that are attuned to the various aspects of a client's identity including structural and contextual factors (APA, 2017).

References

Abu-Bader, S. H., Tirmazi, M. T., & Ross-Sheriff, F. (2011). The impact of acculturation on depression among older Muslim immigrants in the United States. *Journal of Gerontological Social Work*, *54*(4), 425−448.

Alzheimer's Association. (2010). Alzheimer's disease facts and figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *6*, 158−194.

Akinolgil, A., Olfson, M., Siegel, M., Zurlo, K. A., & Walkup, J. T. (2012). Racial and ethnic disparities in depression care in community dwelling elderly in the U.S. *American Journal of Public Health*, *102*(2), 319−328.

American Psychological Association. (2017). *Multicultural guidelines: An ecological approach to context, identity, and intersectionality*. Retrieved from <http://www.apa.org/about/policy/multicultural-guidelines.pdf>.

American Psychological Association Presidential Task Force on Integrated Health Care for an Aging Population. (2008). *Blueprint for change: Achieving integrated health care for an aging population*. Washington, DC: American Psychological Association.

Angel, J. L., Mudrazija, S., & Benson, R. (2016). Racial and ethnic inequalities in health. In L. K. George, & K. F. Ferraro (Eds.), *Handbook of aging and the social sciences* (8th ed., pp. 123–141). New York, NY: Academic Press.

Aranda, M. P. (2008). Relationship between religious involvement and psychological well-being: A social justice perspective. *Health & Social Work*, *33*(1), 9–21.

Areán, P. A., Ayalon, L., Hunkeler, E., Lin, E. H., Tang, L., Harpole, L., & Unützer, J. (2005). Improving depression care for older, minority patients in primary care. *Medical Care*, *43*, 381–390.

Bartels, S. J., Coakley, E. H., Zubritsky, C., Ware, J. H., Miles, K. M., Areán, P. A., … Quijano, L. (2004). Improving access to geriatric mental health services: a randomized trial comparing treatment engagement with integrated versus enhanced referral care for depression, anxiety, and at-risk alcohol use. *American Journal of Psychiatry*, *161*(8), 1455–1462.

Berry, J. W. (2003). Conceptual approaches to acculturation. In K. Chun, P. Balls Organista, & G. Marín (Eds.), *Acculturation: advances in theory, measurement, and applied research* (pp. 17–37). Washington, DC: American Psychological Association.

Berry, J. W. (1997). Immigration, acculturation, and adaptation. *Applied Psychology*, *46*(1), 5–34. Available from https://doi.org/10.1111/j.1464-0597.1997.tb01087.x.

Bierman, A., & Lee, Y. (2018). Chronic pain and psychological distress among older adults: A national longitudinal study. *Research on Aging*, *40*(5), 432–455. Available from https://doi.org/10.1177/0164027517704970.

Bialystok, E., Craik, F. I. M., & Freedman, M. (2007). Bilingualism as a protection against the onset of symptoms of dementia. *Neuropsycholgia*, *45*, 459–464.

Bjorklof, G. H., Engedal, K., Selbaek, G., Kouwenhoven, S. E., & Helvik, A. S. (2013). Coping and depression in old age: A literature review. *Dementia and Geriatric Cognitive Disorders*, *35*, 121–154.

Bonilla-Silva, E., & Baiocchi, G. (2007). *Anything but racism: How sociologists limit the significance of racism. Handbooks of the sociology of racial and ethnic relations* (pp. 79–100). Boston, MA: Springer.

Bosworth, H. B., Kwang-Soo, P., McQuoid, D. R., Hays, J. C., & Steffens, D. C. (2003). The impact of religious practice and religious coping on geriatric depression. *International Journal of Geriatric Psychiatry*, *18*, 905–914.

Brandt, A. M. (1978). Racism and research: The case of the Tuskegee syphilis study. *The Hastings Center Report*, *8*(6), 21–29.

Bryant, A. N., & Kim, G. (2013). The relation between acculturation and alcohol consumption patterns among older Asian and Hispanic immigrants. *Aging & Mental Health*, *17*(2), 147–156.

Casado, B. L., & Leung, P. (2001). Migratory grief and depression among elderly Chinese American immigrants. *Journal of Gerontological Social Work*, *36*(1-2), 5–26.

Chiriboga, D. A., Jang, Y., Banks, S., & Kim, G. (2007). Acculturation and its effect on depressive symptom structure in a sample of Mexican American elders. *Hispanic Journal of Behavioral Sciences*, *29*(1), 83–100.

Cooper, C., Tandy, A. R., Balamurali, T. B., & Livingston, G. (2010). A systematic review and meta-analysis of ethnic differences in use of dementia treatment, care, and research. *The American Journal of Geriatric Psychiatry*, *18*(3), 193–203.

Cokley, K. (2007). Critical issues in the measurement of ethnic and racial identity: A referendum on the state of the field. *Journal of Counseling Psychology*, *54*, 224–234.

Conner, K. O., Copeland, V. C., Grote, N. K., Koeske, G., Rosen, D., Reynolds, C. F., & Brown, C. (2010). Mental health treatment seeking among older adults with depression: The impact of stigma and race. *The American Journal of Geriatric Psychiatry*, *18*(6), 531–543.

Conner, K. O., Lee, B., Mayers, V., Robinson, D., Reynolds, C. F., Albert, S., & Brown, C. (2010). Attitudes and beliefs about mental health among African American older adults suffering from depression. *Journal of Aging Studies*, *24*(4), 266–277.

Contrada, R. J., Ashmore, R. D., Gary, M. L., Goups, E., Egeth, J. D., Sewell, A., & Chasse, V. (2000). Ethnicity-related sources of stress and their effects on well-being. *Current Directions in Psychological Science*, *9*(4), 136–139. Available from https://doi.org/10.1111/1467-8721.00078.

Corrigan, P. (2004). How stigma interferes with mental health care. *American Psychologist*, *59*(7), 614–625.

Crenshaw, K. (1989). *Demarginalizing the intersection of race and sex: A black feminist critique of antidiscrimination doctrine, feminist theory, and antiracist politics* (pp. 140–167). University of Chicago Legal Forum. Retrieved from <https://philpapers.org/archive/CREDTI.pdf?ncid = txtlnkusaolp00000603>.

Ellison, C. G., & Levin, J. S. (1998). The religion-health connection: Evidence, theory, and future directions. *Health Education & Behavior*, *25*(6), 700–720.

Essed, P. (1991). *Understanding everyday racism: An interdisciplinary theory*. Thousand Oaks, CA: Sage.

Ferrer, I., Grenier, A., Brotman, S., & Koehn, S. (2017). Understanding the experiences of racialized older people through an intersectional life course perspective. *Journal of Aging Studies*, *41*, 10–17.

Fry, P. S. (2000). Religious involvement, spirituality, and personal meaning for life: Existential predictors of psychological well being in community-residing and institutional care elders. *Aging & Mental Health*, *4*(4), 375–387.

Gallagher-Thompson, D., Tazeau, Y. N., Basilio, L., Hansen, H., Polich, T., Menendez, A., & Villa, M. L. (1997). The relationship of dimensions of acculturation to self-reported depression in older, Mexican American-women. *Journal of Clinical Geropsychology*, *3*(2), 123–137.

Gallardo, M. E. (Ed.), (2013). *Developing cultural humility: Embracing race, privilege and power*. SAGE Publications.

Gelfand & Yee. (1991). Trends and forces: The influence of immigration, migration, and acculturation on the fabric of aging in America. *Generations*, *15*(4), 7–10.

Gonzales, N. A., Knight, G. P., Birman, D., & Sirolli, A. A. (2004). Acculturation and enculturation among Latino youth. In K. I. Maton, C. J. Schellenbach, B. J. Leadbeater, & A. L. Solarz (Eds.), *Investing in children, youth, families, and communities: Strengths-based research and policy* (pp. 285–302). Washington, DC: American Psychological Association.

Gonzalez, H. M., Haan, M. N., & Hinton, L. (2001). Acculturation and the prevalence of depression in older Mexican Americans: Baseline results of the Sacramento Area Latino Study on Aging. *Journal of American Geriatrics Society*, *49*(7), 948–953.

Gum, A. M., Ayalon, L., Greenberg, J. M., Palko, B., Ruffo, E., & Areán, P. A. (2010). New and emerging professionals: Preferences for professional assistance for distress in a diverse sample of older adults. *Clinical Gerontologist: The Journal of Aging and Mental Health*, *33*(2), 136–151.

Haan, M. N., Zeki A-Hazzouri, A., & Aiello, A. E. (2011). Life-span socioeconomic trajectory, nativity, and cognitive aging in Mexican Americans: the Sacramento Area Latino Study on Aging. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *66*(suppl_1), i102–i110.

Hayward, R. D., & Krause, N. (2013). Patterns of change in religious service attendance across the life course: Evidence from a 34-year longitudinal study. *Social Science Research*, *42*(6), 1480–1489.

Hayward, R. D., & Krause, N. (2016). Classes of individual growth trajectories of religious coping in older adulthood: Patterns and predictors. *Research on Aging*, *38*(5), 554–579. Available from https://doi.org/10.1177/0164027515593347.

Hiroto, K. E., & Yarry, S. J. (2017). Cultural differences in aging experiences of ethnic and sexual minority older adults. In B. Yochim, & E. Woodhead (Eds.), *Psychology of aging: a biopsychosocial perspective*. New York: Springer.

Hall, G. C., & Barongan, C. (2002). *Multicultural psychology*. Upper Saddle River, NJ: Pearson.

Harada, N., Takeshita, J., Ahmed, I., Chen, R., Ross, G. W., & Masaki, K. J. A. (2012). Does cultural assimilation influence prevalence and presentation of depressive symptoms in older Japanese American men? The Honolulu-Asia Aging Study. *The American Journal of Geriatric Psychiatry*, *20*(4), 337–345.

Herd, P., Robert, S. A., & House, J. S. (2011). Health disparities among older adults: Life course influences and policy solutions. In R. H. Binstock, & L. K. George (Eds.), *Handbook of aging and the social sciences* (7th ed., pp. 121–134). New York, NY: Academic Press.

Hill, P. C., & Pargament, K. I. (2003). Advances in the conceptualization and measurement of religion and spirituality: Implications for physical and mental health research. *American Psychologist*, *58*(1), 64–75.

Hinze, S. W., Lin, J., & Andersson, T. E. (2012). Can we capture the intersections? Older Black women, education, and health. *Women's Health Issues*, *22*(1), e91–e98.

Hunt, L. M., Schneider, S., & Comer, B. (2004). Should "acculturation" be a variable in health research? A critical review of research on US Hispanics. *Social Science & Medicine*, *59*(5), 973–986.

Husaini, B. A., Blasi, A. J., & Miller, O. (1999). Does public and private religiosity have a moderating effect on depression? A bi-racial study of elders in the American south. *The International Journal of Aging and Human Development*, *48*(1), 63–72.

Jackson, J. S., Govia, I. O., & Sellers, S. L. (2011). Racial and ethnic influences over the life course. In R. H. Binstock, & L. K. George (Eds.), *Handbook of Aging and the Social Sciences* (7th ed., pp. 91–103). Oxford, UK: Elsevier.

Jang, Y., & Chiriboga, D. A. (2011). Social activity and depressive symptoms in the Korean American older adults: The conditioning role of acculturation. *Journal of Aging and Health*, *23*(5), 767–781.

Jang, Y., Kim, G., & Chiriboga, D. (2005). Acculturation and manifestation of depressive symptoms among Korean American older adults. *Aging & Mental Health*, *9*(6), 500–507.

Jimenez, D. E., Alegría, M., Chen, C. N., Chan, D., & Laderman, M. (2010). Prevalence of psychiatric illnesses in older ethnic minority adults. *Journal of the American Geriatrics Society*, *58*(2), 256–264.

Kales, H. C., Blow, F. C., Bingham, C., Roberts, J. S., Copeland, L. A., & Mellow, A. M. (2000). Race, psychiatric diagnosis, and mental health care utilization in older patients. *The American Journal of Geriatric Psychiatry*, *8*(4), 301–309.

Kalibatseva, Z., Leong, F. T. L., & Ham, E. H. (2014). A symptom profile of depression among Asian Americans: Is there evidence for differential item functioning of depressive symptoms? *Psychological Medicine*, *44*(12), 2567–2578.

Karlamangla, A. S., Miller-Martinez, D., Aneshensel, C. S., Seeman, T. E., Wight, R. G., & Chodosh, J. (2009). Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. *American Journal of Epidemiology*, *170*, 331–342.

Karliner, L. S., Jacobs, E. A., Chen, A. H., & Mutha, S. (2007). Do professional interpreters improve clinical care for patients with limited English proficiency? A systematic review of the literature. *Health Services Research*, *42*(2), 727–754.

Kim, F., DeCoster, J., Huang, C.-H., & Bryant, A. N. (2013). A meta-analysis of the factor structure of the Geriatric Depression Scale (GDS): The effects of language. *International Psychogeriatrics*, *25*, 71–81.

Kim, S. Y., Hou, Y., & Gonzalez, Y. (2017). Language brokering and depressive symptoms in Mexican-American adolescents: Parent-child alienation and resilience as moderators. *Child Development*, *88*, 867–881.

Koehn, S. (2009). Negotiating candidacy: Ethnic minority seniors' access to care. *Ageing and Society*, *29*(4), 585–608.

Krause, N. (2012). Assessing the prayer lives of older Whites, older Blacks, and older Mexican Americans: A descriptive analysis. *The International Journal for the Psychology of Religion*, *22*(1), 60–78.

Ku, L., & Matani, S. (2001). Left out: Immigrants' access to health care and insurance. *Health Affairs*, *20*(1), 247–256.

Kwag, K. H., & Jang, Y. (2012). Acculturation and depressive symptoms in Hispanic older adults: Does perceived ethnic density moderate their relationship. *Journal of Immigrant and Minority Health*, *14*(6), 1107–1111.

Laganá, L., & Shanks, S. (2002). Mutual biases underlying the problematic relationship between older adults and mental health providers: Any solution in sight? *The International Journal of Aging and Human Development*, *55*(3), 271–295.

Lawrence, J. (2000). The Indian Health Service and the sterilization of Native American women. *American Indian Quarterly*, *24*(3), 400–419.

Lee, E. K. O., & Chan, K. (2009). Religious/spiritual and other adaptive coping strategies among Chinese American older immigrants. *Journal of Gerontological Social Work*, *52*(5), 517–533.

Livingston, J. D., & Boyd, J. E. (2010). Correlates and consequences of internalized stigma for people living with mental illness: A systematic review and meta-analysis. *Social Science & Medicine*, *71*(12), 2150–2161.

Livney, M. G., Clark, C. M., Karlawish, J. H., Cartmell, S., Negrón, M., Nuñez, J., … Arnold, S. E. (2011). Ethnoracial differences in the clinical characteristics of Alzheimer's disease at initial presentation at an urban Alzheimer's disease center. *The American Journal of Geriatric Psychiatry*, *19*(5), 430–439.

Luo, Y., Xu, J., Granberg, E., & Wentworth, W. M. (2012). A longitudinal study of social status, perceived discrimination, and physical and emotional health among older adults. *Research on Aging*, *34*, 275–301.

Lynch, C. P., Hernandez-Tejada, M. A., Strom, J. L., & Egede, L. E. (2012). Association between spirituality and depression in adults with type 2 diabetes. *The Diabetes Educator*, *38*(3), 427–435.

Machizawa, S., & Lau, D. T. (2010). Psychological needs of Japanese American elders: Implication for culturally competent interventions. *Journal of Cross-Cultural Gerontology*, *25*(2), 183–197.

MacIntosh, R. C., & Strickland, O. J. (2010). Differential item responses on CES-D inventory: A comparison of elderly Hispanics and non-Hispanic Whites in the United States and item usage by elderly Hispanics across time. *Aging & Mental Health*, *14*(5), 556–564.

Marmot, M. (2002). The influence of income on health: Views of an epidemiologist. *Health Affairs*, *21*(2), 31–46.

Moberg, D. O. (2005). Research in spirituality, religion, and aging. *Journal of Gerontological Social Work*, *45*(1-2), 11–40.

Mofidi, M., DeVellis, R. F., Blazer, D. G., DeVellis, B. M., Panter, A. T., & Jordan, J. M. (2006). Spirituality and depressive symptoms in a racially diverse US sample of community-dwelling adults. *Journal of Nervous and Mental Disease*, *194*(12), 975–977.

Nelson, P. B. (1989). Ethnic differences in intrinsic/extrinsic religious orientation and depression in the elderly. *Archives of Psychiatric Nursing*, *3*(4), 199–204.

Nelson-Becker, H. (2005). Religion and coping in older adults. *Journal of Gerontological Social Work*, *45*(1-2), 51–67.

Ortega, S. T., & Rushing, W. A. (1983). Race differences in elderly personal well-being: Friendship, family, and church. *Research on Aging*, *5*(1), 101–118.

Owen, J., Tao, K. W., Drinane, J. M., Hook, J., Davis, D. E., & Kune, N. F. (2016). Client perceptions of therapists' multicultural orientation: Cultural (missed) opportunities and cultural humility. *Professional Psychology: Research and Practice*, *47*(1), 30–37.

Paradies, Y., Ben, J., Denson, N., Elias, A., Priest, N., Pieterse, A., & Gee, G. (2015). Racism as a determinant of health: a systematic review and meta-analysis. *PLoS One*, *10*(9), e0138511.

Pargament, K. I. (2002). The bitter and the sweet: An evaluation of the costs and benefits of religiousness. *Psychological Inquiry*, *13*(3), 168–181.

Park, J., Roh, S., & Younsook, Y. (2012). Religiosity, social support, and life satisfaction among elderly Korean immigrants. *The Gerontologist*, *52*(5), 641–649.

Pascoe, E. A., & Smart Richman, L. (2009). Perceived discrimination and health: A meta-analytic review. *Psychological Bulletin*, *135*(4), 531–554. Available from https://doi.org/10.1037/a0016059.

Peteet, J. R., Zaben, F. A., & Koenig, H. G. (2018). Integrating spirituality into the care of older adults. *International Psychogeriatrics*, 1–8. Available from https://doi.org/10.1017/S1041610218000716.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. Available from https://doi.org/10.1177/014662167700100306.

Riolo, S. A., Nguyen, T. A., Greden, J. F., & King, C. A. (2005). Prevalence of depression by race/ethnicity: Findings from the national health and nutrition examination survey III. *American Journal of Public Health*, *95*, 998–1000.

Robb, C., Chen, H., & Haley, W. E. (2002). Ageism in mental health and health care: A critical review. *Journal of Clinical Geropsychology*, *8*(1), 1–13.

Roff, L. L., Klemmack, D. L., Parker, M., Koenig, H. G., Crowther, M., Baker, P. S., & Allman, R. M. (2004). Depression and religiosity in African American and White community-dwelling older adults. *Journal of Human Behavior in the Social Environment*, *10*(1), 175–189.

Ryder, A. G., Yang, J., Zhu, X., Yao, S., Yi, J., Heine, S. J., & Bagby, R. M. (2008). The cultural shaping of depression: Somatic symptoms in China, psychological symptoms in North America? *Journal of Abnormal Psychology*, *117*(2), 300–313.

Sadavoy, J., Meier, R., & Ong, A. Y. M. (2004). Barriers to access to mental health services for ethnic seniors: The Toronto study. *The Canadian Journal of Psychiatry*, *49*(3), 192–199.

Searight, H. R., & Armock, J. A. (2013). Foreign language interpreters in mental health: a literature review and research agenda. *North American Journal of Psychology*, *15*, 17–38.

Schwartz, S. J., Unger, J. B., Zamboanga, B. L., & Szapocznik, J. (2010). Rethinking the concept of acculturation: Implications for theory and research. *American Psychologist*, *65*(4), 237–251.

Shavers, V. L., Bakos, A., & Sheppard, V. B. (2010). Race, ethnicity, and pain among the US adult population. *Journal of Health Care for the Poor and Underserved*, *21*(1), 177–220.

Siedlecki, K. L., Salthouse, T. A., Oishi, S., & Jeswani, S. (2014). The relationship between social support and subjective well-being across age. *Social Indicators Research*, *117*(2), 561–576.

Sirey, J. A., Bruce, M. L., & Kales, H. C. (2010). Improving antidepressant adherence and depression outcomes in primary care: the treatment initiation and participation (TIP) program. *The American Journal of Geriatric Psychiatry*, *18*, 554–562.

Skarupski, K., Fitchett, G., Evans, D. A., & De Leon, C. F. (2010). Daily spiritual experiences in a biracial, community-based population of older adults. *Aging & Mental health*, *14*(7), 779–789.

Skarupski, K. A., Fitchett, G., Evans, D. A., & de Leon, C. F. (2013). Race differences in the association of spiritual experiences and life satisfaction in older age. *Aging & Mental Health*, *17*(7), 888–895.

Smedley, A., & Smedley, B. D. (2005). Race as biology is fiction, racism as a social problem is real: Anthropological and historical perspectives on the social construction of race. *American Psychologist*, *60*(1), 16–26.

Snowden, L. R. (2003). Bias in mental health assessment and intervention: Theory and evidence. *American Journal of Public Health*, *93*(2), 239–243.

Sorkin, D. H., Nguyen, H., & Ngo-Metzger, Q. (2011). Assessing the mental health needs and barriers to care among a diverse sample of Asian American older adults. *Journal of General Internal Medicine*, *26*(6), 595–602.

Sorkin, D. H., Murphy, M., Nguyen, H., & Biegler, K. A. (2016). Barriers to mental health care for an ethnically and racially diverse sample of older adults. *Journal of American Geriatrics Society*, *64*(10), 2138–2143.

Sun, F., Ong, R., & Burnette, D. (2012). The influence of ethnicity and culture on dementia caregiving: a review of empirical studies on Chinese Americans. *American Journal of Alzheimer's Disease & Other Dementias®*, *27*(1), 13–22.

Taira, D. A., Shen, C., King, M., Landsittel, D., Mays, M. H., Sentell, T., & Southerland, J. (2017). Access to medications for medicare enrollees related to race/ethnicity: Results from the 2013 Medicare Current Beneficiary Study. *Research in Social and Administrative Pharmacy*, *13*(6), 1208–1213.

Taylor, R. J., Chatters, L. M., & Jackson, J. S. (2007). Religious and spiritual involvement among older African Americans, Caribbean blacks and non-Hispanic Whites: Findings from the national survey of American life. *The Journals of Gerontology: Series B*, *62*(4), S238–S250.

Thrasher, A. D., Clay, O. J., Ford, C. L., & Stewart, A. L. (2012). Theory-guided selection of discrimination measures for racial/ethnic health disparities research among older adults. *Journal of Aging and Health*, *24*(6), 1018–1043.

Torres, L., Hoelzle, J., & Vallejo, L. G. (2016). Dementia and Latinos. In F. R. Ferraro (Ed.), *Minority and Cross-Cultural Aspects of Neuropsychological Assessment* (second edition). New York: , Taylor & Francis.

Vasquez, L. A., Marin, M., & Garcia-Vazquez, E. (2010). Advances in multicultural assessment and counseling with culturally diverse older adults. In J. G. Ponterotto, J. M. Casas, L. A. Suzuki, & C. M. Alexander (Eds.), *Handbook of multicultural counseling* (pp. 667–675). Thousand Oaks, CA: SAGE Publications.

Virnig, B., Huang, Z., Lurie, N., & Musgrave, D. (2004). Does Medicare Managed Care provide equal treatment for mental health across races? *Archives of General Psychiatry*, *62*(2), 201–205.

Wallace, S. P., Cochran, S. D., Durazo, E. M., & Ford, C. L. (2011). *The health of aging lesbian, gay and bisexual adults in California. Policy Brief (UCLA Center for Health Policy Research)* (pp. 1–8). .

Williams, D. R., & Jackson, P. B. (2005). Social sources of racial disparities in health. *Health Affairs*, *24*(2), 325–334.

Woodward, A. T., Chatters, L. M., Taylor, R. J., Neighbors, H. W., & Jackson, J. S. (2010). Differences in professional and informal help seeking among older African Americans, Black Caribbean, and non-Hispanic Whites. *Journal of the Society for Social Work and Research*, *1*(3), 124–139.

Yoon, D. P., & Othelia, L. (2004). Religiousness/spirituality and subjective well-being among rural elderly Whites, African Americans and Native Americans. *Journal of Human Behavior in the Social Environment*, *10*(1), 191–211.

Further reading

Arean, P. A., Ayalon, L., Jin, C., Linkins, K., Chen, G., & Levkoff, S. (2008). Integrated specialty mental health care among older minorities improves access but not outcomes: Results of the PRISMe study. *International Journal of Geriatric Psychiatry*, *23*(10), 1086–1092.

Ayalon, L., Areán, P. A., & Alvidrez, J. (2005). Adherence to antidepressant medications in Black and Latino elderly patients. *The American Journal of Geriatric Psychiatry*, *13*(7), 572–580.

Ayalon, L., & Gum, A. M. (2011). The relationships between major lifetime discrimination, everyday discrimination, and mental health in three racial and ethnic groups of older adults. *Aging & Mental Health*, *15*(5), 587–594.

Chavez-Korell, S., Benson-Flórez, G., Rendón, A. D., & Farías, R. (2014). Examining the relationships between physical functioning, ethnic identity, acculturation, familismo, and depressive symptoms for Latino older adults. *The Counseling Psychologist*, *42*(2), 255–277.

Hinton, D. E., & Lewis-Fernández, R. (2010). Idioms of distress among trauma survivors: Subtypes and clinical utility. *Culture, Medicine, and Psychiatry*, *34*(2), 209–218. Available from https://doi.org/10.1007/s11013-010-9175-x.

Jimenez, D. E., Le Cook, B., Kim, G., Reynolds, C. F., Alegreia, M., Coe-Odess, S., & Bartels, S. J. (2015). Relationship between general illness and mental health service use and expenditures among racially-ethnically diverse adults >65 years. *Psychiatric Services*, *66*(7), 727–733.

Kang, S., Kim, I., & Kim, W. (2016). Differential patterns of healthcare service use among Chinese and Korean immigrant elders. *Journal of Immigrant and Minority Health*, *18*(6), 1455–1461.

Krause, N. (2002). Church-based social support and health in old age: Exploring variations by race. *The Journals of Gerontology: Series B*, *57*(6), S332–S347.

Mair, C. A. (2010). Social ties and depression: An intersectional examination of black and white community-dwelling older adults. *Journal of Applied Gerontology*, *29*(6), 667–696.

Nguyen, D. (2011). Acculturation and perceived mental health need among older Asian immigrants. *The Journal of Behavioral Health Services & Research*, *38*(4), 526–533.

Powe, B. D. (2001). Cancer fatalism among elderly African American women: Predictors of the intensity of the perceptions. *Journal of Psychosocial Oncology*, *19*(3-4), 85–95. Available from https://doi.org/10.1300/J077v19n03_07.

Schieman, S., Bierman, A., & Ellison, C. G. (2010). Religious involvement, beliefs about god, and the sense of mattering among older adults. *Journal for the Scientific Study of Religion*, *49*(3), 517–535.

Spoont, M. R., Nelson, D. B., Murdoch, M., Sayer, N. A., & Nugent, S. (2015). Are there racial/ethnic disparities in VA PTSD treatment retention? *Depression and Anxiety*, *32*(6), 415–425.

Trask, B. S., Hepp, B. W., Settles, B., & Shabo, L. (2009). Culturally diverse elders and their families: Examining the need for culturally competent services. *Journal of Comparative Family Studies*, *40*(2), 293–303.

Woodall, A., Morgan, C., Sloan, C., & Howard, L. (2010). Barriers to participation in mental health research: Are there specific gender, ethnicity, and age related barriers? *BMC Psychiatry*, *10*, 103.

Chapter 4

Stress, mental health, and aging

Raeanne C. Moore[1,2], **Elizabeth Straus**[1,2] **and Laura M. Campbell**[3]

[1]Department of Psychiatry, University of California San Diego School of Medicine, San Diego, CA, United States, [2]VA San Diego Healthcare System, San Diego, CA, United States, [3]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, United States

Introduction

Globally, the population is aging at an unprecedented rate. It is expected that by 2060 the US population of adults aged 65 and older will nearly double, from 46.3 to 98 million. While people are living longer lives, research indicates they are not necessarily living healthier lives (World Health Organization, 2015). In addition to greater risk for chronic medical disease and neurodegenerative disorders, aging adults experience a greater risk of mental health problems, including depression, anxiety, and stress. It is estimated that between 15% and 20% of older adults experience some type of mental health problem, and there is a high prevalence of comorbid mental health problems among these older adults.

Life stress (also referred to as daily stress), in particular, which is common to people of all ages, can be especially prevalent in older age. Older adults commonly experience change in physical health status and abilities such as loss in capacities, chronic pain, reduced mobility, decline in functional ability, and frailty. Even if they have not experienced a change in physical health status, many older adults are burdened with a constant worry about developing health problems, which can be detrimental to their overall health and well-being. For example, as people are becoming more aware of prevalence rates and risk factors for Alzheimer's disease (AD) and related dementias, there is a growing prevalence of what some refer to as "dementia worry" (Molden & Maxfield, 2017), or fear of developing dementia. In addition, older adults are more likely than their younger counterparts to experience stressful life events such as decreases in socioeconomic status, bereavement, and changes in family support. The cumulative effect of these stressors can negatively affect physiological and psychological functioning and can result in social isolation and loneliness. In turn, isolation and loneliness are well-established risk factors for morbidity, including myocardial infarction and stroke, and mortality. Life stressors are also risk factors for the onset or exacerbation of psychiatric illnesses, including depressive disorders, anxiety, and posttraumatic stress disorder (PTSD). Given the pervasive role of stress on health in late life, it is imperative to consider the myriad of issues that impact the relationship between stress and mental health in older adults.

In this chapter, we describe what is known about the biological mechanisms and genetic susceptibilities that underlie the relationships between stress, age, and mental health problems, with the *caveat* that the understanding of these relationships is still somewhat limited. Of note that throughout this chapter, reference to "stress" refers to daily stressors that occur in the context of routine challenges to daily life. Daily stressors differ from major life events in that they can have immediate impacts on psychological and physical functioning, with their cumulative effect on the development of serious mental health outcomes. These not only include the development of depression and anxiety, but also higher chronicity of symptoms and greater recurrence of symptoms over time (Brown, Varghese, & McEwen, 2004; Juruena, 2013; Varghese & Brown, 2001). We also discuss the associations of stress, aging, and cognitive functioning, including both objective cognitive functioning and the impact of subjective cognitive concerns, including dementia worry. The impact of stress on psychological distress, namely depression, and everyday functioning is discussed, as well as the special case of the veteran population. In addition to stress as a risk factor for negative outcomes, we highlight the protective role of positive psychological traits. Lastly, we describe evidence-based treatments to decrease stress and improve mental health in older adults.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00004-1

Biological impact of stress in late life

Stress affects the brain and body throughout the lifespan; however, the body and brain may be particularly sensitive to stress in older age. When stressed, the hypothalamic-pituitary-adrenal (HPA) axis is activated, causing the release of glucocorticoids. The neurotoxicity hypothesis (previously the glucocorticoid cascade hypothesis) proposes that prolonged exposure to glucocorticoids is neurotoxic particularly to the hippocampus and prefrontal cortex, which may in turn be particularly detrimental for cognition in older adults (Lupien, McEwen, Gunnar, & Heim, 2009; O'Hara, 2006). Cumulative "wear and tear" on multiple systems in the body (e.g., neuroendocrine, cardiac, immune, metabolic) in reaction to repeated responses to environmental stressors is conceptualized as allostatic load. Allostatic load indices, with higher scores indicating more abnormalities on physiological tests, have been used to quantify level of damage on physiological systems in order to understand the relationship between stress, the body, and medical and psychological outcomes (Juster, McEwen, & Lupien, 2010; McEwen, 1998). In older adults, both HPA axis activation and greater allostatic load have been linked to a number of poor outcomes and comorbidities such as worse cognitive and physical functioning (e.g., frailty), as well as greater risk of cardiovascular disease and mortality (Gaffey, Bergeman, Clark, & Wirth, 2016; Juster et al., 2010; Lupien et al., 2009) (see Fig. 4.1).

Cellular aging and stress

Telomeres are segments of DNA at the end of the chromosome that shorten with each cellular replication; thus telomere length is used as a proxy marker of cellular aging. Shorter telomere length is also associated with many poor health outcomes such as cancer and cardio-metabolic dysfunction (D'Mello et al., 2015; Wang, Dong, & Cao, 2016; Wentzensen, Mirabello, Pfeiffer, & Savage, 2011). There is ample evidence to suggest that both chronic (e.g., caregiving, trauma) and perceived stress is associated with shorter telomere length across the lifespan (Epel & Prather, 2018; Mathur, Epel, & Kind, 2016; Oliveira et al., 2016; Schutte & Malouff, 2016).

It is more challenging to study the relationship between telomere length and stress in older adults compared to younger adults because conditions related to telomere shortening are more common in older adults. Among older adults,

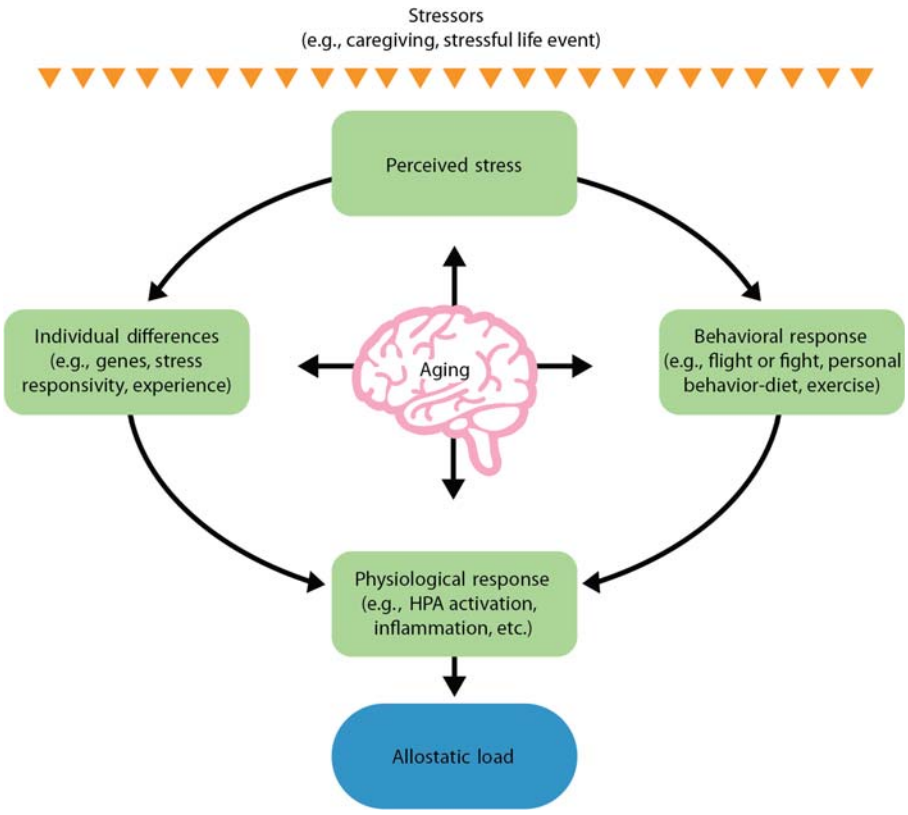


FIGURE 4.1 The allostatic load model adapted from McEwen (1998) and Gaffey et al. (2016). *Adapted from McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load.* Annals of the New York Academy of Sciences, 840 *(1), 33–44; Gaffey, A. E., Bergeman, C. S., Clark, L. A., & Wirth, M. M. (2016). Aging and the HPA axis: Stress and resilience in older adults. Neuroscience & Biobehavioral Reviews, 68, 928–945.*

there is also the cumulative effect of multiple decades of possible stressors that could confound findings. Therefore, it is unsurprising that studies examining early life stressors and telomere length in older adults report mixed findings (Savolainen, Eriksson, & Kananen, 2014; Schaakxs et al., 2016; Verhoeven, van Oppen, Puterman, Elzinga, & Penninx, 2015). However, the relationship between perceived stress, recent life stressors, and chronic stress with shorter telomere length is more consistent, with the majority of studies finding greater stress is related to shorter telomeres (Damjanovic, Yang, & Glaser, 2007; Jones, Janson, & Lee, 2017; Puterman, Lin, Krauss, Blackburn, & Epel, 2015; Verhoeven et al., 2015). Additionally, in a study in middle-aged and older adults by Steptoe, Hamer, Lin, Blackburn, and Erusalimsky, (2017), cortisol responsivity (i.e., greater cortisol response to a stressful situation) was not related to baseline telomere length. However, participants with greater cortisol responsivity demonstrated more rapid telomere shortening at follow-up 3 years later, suggesting that cortisol responsivity may partially mediate the relationship between stress and telomere shortening (Steptoe et al., 2017). Conversely, two studies by Puterman and colleagues (2010, 2015) found that positive health behaviors such as exercise, good diet, and adequate sleep attenuated the negative association between stress and telomere shortening in postmenopausal women, indicating that positive health interventions may be helpful for preventing accelerated cellular aging due to stress (Puterman et al., 2010, 2015).

The immune system and inflammation

Both aging and stress are related to immune dysregulation and increased inflammation. Therefore older adults may be particularly vulnerable to the adverse effects of stress with respect to immune dysregulation and inflammatory responses (Gouin, Hantsoo, & Kiecolt-Glaser, 2008; Graham, Christian, & Kiecolt-Glaser, 2006; Wolkowitz, Epel, Reus, & Mellon, 2010). Indeed, studies have shown that older adults who are chronically stressed have worse response to vaccines, impaired control over latent viruses, and slower wound healing than age-matched controls (Gouin et al., 2008; Graham et al., 2006). Additionally, several studies have shown that both chronic stress and perceived stress are related to increased inflammatory markers in older adults (Casaletto, Staffaroni, & Elahi, 2018; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012; Gouin et al., 2008; Kiecolt-Glaser et al., 2003). A recent longitudinal study by Casaletto and colleagues (2018) found that older adults with high self-reported perceived stress levels had increased elevations in inflammatory markers at follow-up. Additionally, increased inflammation was associated with worse cognitive performance in those with high stress levels (Casaletto et al., 2018). Increased inflammation is associated with several age-related diseases such as cardiovascular disease and diabetes as well as increased mortality (Glaser & Kiecolt-Glaser, 2005; Gouin et al., 2008; Lavretsky & Newhouse, 2012). There is also a growing body of literature examining the relationship between depression and increased inflammation in older adults (Alexopoulos & Morimoto, 2011; Bell, Kivimäki, & Bullmore, 2017; Kop, Gottdiener, & Tangen, 2002; Murri, Pariante, & Mondelli, 2014), but few studies examine the role of stress in this relationship. Nevertheless, stress-related immune dysregulation may be one such mechanism that increases risk of these adverse outcomes in stressed older adults.

Neuroimaging and stress in later life

Structural neuroimaging studies have also provided evidence for an association between stress and brain integrity. Studies have found that both perceived stress and stressful life events are associated with smaller hippocampal volume in older adults with and without depression (Gianaros et al., 2007; Zannas, McQuoid, & Payne, 2013; Zimmerman, Ezzati, & Katz, 2016). Furthermore, a study by Zimmerman et al. (2016) in older adults suggests that stress may be particularly associated with certain subfields of the hippocampus such as the dentate gyrus (Zimmerman et al., 2016). Less is known about the relationship between stress and other brain structures in older adults; however, Moreno, Bruss, and Denburg (2017) and Gianaros et al. (2007) reported that increased self-reported perceived stress was associated with smaller prefrontal structures (Moreno et al., 2017). Additionally, studies have shown that greater stress is positively associated with white matter hyperintensities in the brain, which are indicative of cerebrovascular disease (Aggarwal, Clark, & Beck, 2014; Johnson et al., 2017; Johansson, Skoog, & Gustafson, 2012). While there is little longitudinal research on stress and brain integrity to establish causality, Lupien and colleagues (1998) found that elevated cortisol, a stress-related hormone, over 5–6 years was related to smaller hippocampal volumes (Lupien et al., 1998). Nevertheless, more research is needed to further understand the complex relationship between the neurotoxic effect of stress and brain health.

Genetics, stress, and aging

Recent research has begun examining the multifaceted interaction between genetics, stress, and health-related outcomes in older adults. One gene of interest is *5-HTTLPR* which is a serotonin-transporter polymorphism that can result in either long or short alleles, with the short allele being associated with greater risk of depression (Zannas, 2018). Cross-sectional findings on the *5-HTTLPR* allele and stressful life events interaction on risk of depression in older adults are mixed (Arpawong et al., 2016; Goldman, Glei, Lin, & Weinstein, 2010; Kim, Stewart, & Kim, 2007; Power et al., 2010; Ritchie, Jaussent, & Stewart, 2009). However, one study found that the *5-HTTLPR* allele mediated the relationship between stressful life events and future depression remission in depressed older adults. This study found that short allele carriers with greater number of stressful life events were more likely to recover from depression at 12 months than long/long homozygotes (Zannas, McQuoid, Steffens, Chrousos, & Taylor, 2012). Additionally, younger adults with a short allele have been found to have reduced resilience to stress. This relationship is much less studied in older adults; however, one study did not find a significant relationship between *5-HTTLPR* allele and resilience to stress indicating that the relationship between short allele status and resilience may weaken with age (O'Hara, Marcus, & Thompson, 2012).

While the *5-HTTLPR* allele has been the most well studied in relation to stress, other genetic markers have also garnered interest. The gene that encodes brain-derived neurotrophic factor (BDNF) has also been studied, with findings suggesting that the *BDNF* met allele moderates the relationship between stressful life events and risk of depression in older adults (Kim et al., 2007; Rawson, Dixon, & Nowotny, 2015). Additionally, centenarians who are *APOE* ε4 carriers, a genetic risk factor for AD, were found to have greater negative affect with greater number of stressful life events in their life compared to noncarriers (Martin, Jazwinski, & Davey, 2014). Lastly, Musliner et al. (2015) examined a polygenic risk score for depression in relation to recent stressful life events in older age and found that polygenic risk of depression and stressful life events were both associated with depressive symptoms in older adults, but stressful life events did not significantly moderate this relationship (Musliner et al., 2015). We are just beginning to understand gene by environment interactions, but these insights could help to lead to more individualized interventions and preventative strategies.

Stress on cognitive health in older adults

There is ample evidence that acute and chronic stress can negatively affect cognitive functioning across the lifespan. Theorists suggest that stress activates the HPA axis leading to an increase in glucocorticoid hormones (e.g., cortisol) which has been shown to lead to brain atrophy, thus affecting cognitive abilities (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007).

Stress and objective cognitive functioning

Both cross-sectional and longitudinal research studies have reported that perceived stress is related to worse cognitive functioning in multiple populations of older adults. These findings have generally held even after adjusting for demographic factors, comorbidities, and other related constructs such as depression. Cross-sectional studies have consistently found that current perceived stress is associated with worse performance on tests of global cognition and several individual domains of cognitive functioning. Of these cognitive domains, greater perceived stress and worse episodic memory are consistently observed (Aggarwal, Wilson, & Beck, 2014; Korten, Comijs, Penninx, & Deeg, 2017; Peavy, Lange, & Salmon, 2007; Wilson et al., 2007). Additionally, this association seems to be stronger in carriers of *APOE* ε4 than noncarriers (Comijs, van den Kommer, Minnaar, Penninx, & Deeg, 2011; Peavy et al., 2007; Sheffler & Moxley, 2014). Of note, Peavy et al. (2007) observed an *APOE* by stress interaction, demonstrating that *APOE* ε4 carriers with greater stress had worse memory and greater cortisol levels than *APOE* ε4 carriers with lower levels of stress. This relationship was not observed in *APOE* ε4 noncarriers (Peavy et al., 2007). Furthermore, Wilson, Fleischman, and Myers (2004) found that premorbid proneness to distress was associated with worse baseline cognitive functioning but not associated with accelerated decline (Wilson et al., 2004). Numerous longitudinal studies also provide evidence that stress is associated with increased risk for future cognitive decline, mild cognitive impairment, and dementia (Aggarwal, Wilson et al., 2014; Katz, Derby, & Wang, 2016; Peavy, Jacobson, & Salmon, 2012; Turner, James, Capuano, Aggarwal, & Barnes, 2017; Wilson et al., 2007). Nevertheless, it should be noted that the association between stress and future decline is not necessarily causal; greater reaction to a stressful event relative to peers (i.e., rating an

event as more stressful than others) rather than stress itself may be associated with cognitive functioning or an early sign of future decline.

Results from these studies suggest that stress reduction interventions may improve cognitive functioning in older adults. However, results from mindfulness-based stress reduction studies are mixed. Some studies report minorimprovement on cognitive tests, but the largest study with an active control group did not find any significant findings with respect to cognitive functioning (Berk, van Boxtel, & van Os, 2017).

Day-to-day stress fluctuations and cognition

While the majority of studies have utilized retrospective questionnaires that capture recent global stress, a few studies have utilized daily diaries to examine how fluctuations in day-to-day stress affect cognitive functioning. Studies using daily diaries have found that on days in which people are experiencing more stress they also report more memory failures (Neupert, Almeida, Mroczek, & Spiro, 2006; Rickenbach, Almeida, Seeman, & Lachman, 2014). More recently, studies have been utilizing ecological momentary assessment (EMA) to measure daily experiences. EMA is a data collection method involving frequent, repeated assessment of thoughts, feelings, experiences, and behaviors in the naturalistic environment (Shiffman, Stone, & Hufford, 2008). For example, Hyun and colleagues (2018) utilized EMA and found that increased stress in the morning negatively affected working memory later in the day. Interestingly, older adults and younger adults demonstrated similar associations between stress on working memory (Hyun et al., 2018). These studies suggest fluctuations in cognitive abilities are associated with fluctuation in stress, but more research is needed to further understand this complex relationship.

Stress and subjective cognitive complaints

Subjective cognitive complaints, particularly related to memory, are common among older adults but are not always related to current cognitive functioning. However, depression, anxiety, and traits such as neuroticism have been found to be consistently associated with subjective cognitive complaints (Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014; Reid & MacLullich, 2006). Less is known about the relationship between stress and subjective cognitive complaints. However, available research in both middle-aged and older adults suggests that greater stress is related to more subjective cognitive complaints independent of depression and anxiety (Potter, Hartman, & Ward, 2009; Ronnlund, Sundstrom, Sorman, & Nilsson, 2013; Zuniga, Mackenzie, Kramer, & McAuley, 2016).

Early and midlife stress on late-life cognitive functioning

Much less is known about the effect of childhood and midlife stress on cognitive functioning in later life. Adverse childhood events (e.g., loss of a parent, separation from family) have found to be associated with both increased risk for dementia and worse cognitive functioning (Persson & Skoog, 1996; Radford, Delbaere, & Draper, 2017; Ritchie, Jaussent, & Stewart, 2011). A large longitudinal population-based study of females found that psychological stress in midlife was associated with greater risk for dementia in later life (Johansson, Guo, & Waern, 2010). Additionally, Wang, Wahlberg, Karp, Winblad, and Fratiglioni (2012) and Sindi, Hagman, and Hakansson (2017) found that greater work-related stress in midlife was associated with greater risk of cognitive impairment (i.e., mild cognitive impairment, AD, dementia) in later life (Sindi et al., 2017; Wang et al., 2012). While these studies suggest a possible association between prior stress and worse cognition in later life, establishing causality is extremely difficult as many of these studies have to rely on past adverse events thought to cause stress as a proxy for stress. Further, results may be affected by recall bias and several other confounding factors that affect late-life cognition.

Dementia worry

Dementia worry, and similar constructs known as dementia anxiety, anticipatory dementia, or fear of AD, is a type of aging anxiety or health worry that is a relatively unexplored health stressor for the aging population (Kessler, Bowen, Baer, Froelich, & Wahl, 2012). Kessler et al. (2012) defined dementia worry as "the perceived threat of developing dementia" and proposed perceived risk of dementia, perception of consequences, and lack of coping strategies as possible antecedents. Dementia worry is quite prevalent, with percentages ranging from 26% to 49%; furthermore, a large percentage of older adults (i.e., 26%–39%) have been found to fear AD more than any other disease or condition (Kessler et al., 2012).

Multiple studies have examined variables relatedto dementia worry and found that exposure to dementia (e.g., dementia caregiver, knowing someone with dementia) (Alberts, Hadjistavropoulos, Pugh, & Jones, 2011; Cutler, 2015; Kessler, Tempel, & Wahl, 2014; Kinzer & Suhr, 2016), depression (Kinzer & Suhr, 2016; Ostergren, Heeringa, Leon, Connell, & Roberts, 2017), general worry (French, Floyd, Wilkins, & Osato, 2012; Kinzer & Suhr, 2016), and perceived changes in memory (Cutler, 2015; Kinzer & Suhr, 2016; Ostergren et al., 2017) are related to increased dementia worry. However, the relationship between increased dementia worry and family history of dementia is mixed, with some studies reporting a significant relationship (Cutler, 2015; Ostergren et al., 2017) whereas others do not (French et al., 2012; Scerri & Scerri, 2016). Interestingly, several studies have found dementia worry is greater in middle-aged and "younger" older adults (i.e., ages 65−75) compared to those in their late 70s and beyond, even though actual risk of dementia increases with age (Cutler, 2015; French et al., 2012; Ostergren et al., 2017; Roberts, McLaughlin, & Connell, 2014; Sun, Gao, & Coon, 2013). Additionally, Molden and Maxfield (2017) found that priming participants with negative stereotypical aging words was associated with greater dementia worry, indicating that addressing aging stereotypes may help to relieve some dementia worry (Molden & Maxfield, 2017). Dementia educational programs have become more common in recent years, yet few studies have examined their impact on dementia worry. Scerri and Scerri (2016) found that baseline knowledge of AD was positively correlated with dementia worry and the educational training program intervention increased amount of knowledge about AD; however, fear of dementia did not increase (Scerri & Scerri, 2016). These studies highlight the need for additional research, particularly longitudinal studies, to understand if dementia worry is associated with future risk of dementia.

With increasing genetic and biomarker testing for AD, there are ethical considerations surrounding the risks and benefits of test result disclosure as neither genetic risk factors nor biomarkers in the brain are deterministic and could lead to undue stress and worry (Kim, Karlawish, & Berkman, 2015). Although they did not measure dementia worry, per se, Lineweaver, Bondi, Galasko, and Salmon (2014) conducted a case-controlled study where older adults who had a genetic risk factor for AD (*APOE* ε4 positive) were either informed or uninformed of their *APOE* ε4 status. Older adults who were informed of their *APOE* ε4 status had significantly more memory complaints and did worse on objective memory tests than the *APOE* ε4 positive older adults who did not know their status. Participants chose which group they would be in, which may have confounded results, but these results could also indicate that worry about dementia risk may negatively impact subjective views of cognitive functioning and objective cognitive performance (Lineweaver et al., 2014). Future research is needed to better understand how genetic and biological tests may contribute to or alleviate dementia worry and how stress related to poor results may influence clinical outcomes.

Impact on everyday functioning

Stress can also impact older adults' everyday functioning abilities such as ability to carry out basic self-care tasks (e.g., personal hygiene, activities of daily living), complete more complex tasks (e.g., financial and medication management, instrumental activities of daily living), and maintain employment and social relationships. As highlighted in the previous section, stress impacts cognition through the HPA axis by way of cortisol, and cognitive impairment is a well-established risk factor for everyday functioning impairment. The real-world demands and pressures of everyday life can also affect cortisol regulation.

Employment is one of the most demanding real-world stressors. Approximately 16% of US men and women aged 65 years and older are still employed (Kromer & Howard, 2013). A majority of the scientific literature examining the relationship between employment and work stress has been conducted in middle-aged adults. Limited research has been conducted examining the relationship between employment and work stress in older adults, nor the association between retirement and daily stressors. The transition to retirement, in and of itself, may lead to increased stress. Wong and Shobo (2016) examined the relationships between daily stressors and stress reactivity (measured via cortisol) among 182 employed versus 253 retired older adults (Wong & Shobo, 2016). Their findings indicated that older adults who were employed *and* had high levels of nonwork-related daily stressors had significantly higher cortisol levels and responsivity compared to retirees with the same level of daily stressors. These findings indicate the compounding effect of work-related stress plus nonwork-related stress in daily life may have a negative effect on physiological functioning.

The relationship between stress and cognitive functioning also has an impact on everyday functioning. When a situation in a person's life is viewed as stressful, instead of allocating attentional resources to the task at hand, these resources become assigned to coping with the current demands. For example, when a person's thoughts are preoccupied with awaiting results from a medical test, they have a reduced ability to pay attention to what they are doing during a nonstressed time, whether it be paying bills, cooking dinner, shopping, driving, or having a conversation. One study in middle-aged and older adults (mean age 60 years) found that greater longitudinal decline in cognition was associated

with more everyday memory problems during times of added daily stress (Rickenbach et al., 2014). Despite these findings, there is still much to learn about the relationship between stress and everyday functioning in late life. Longitudinal studies utilizing *in vivo* data collection (e.g., EMA or experience sampling method) and taking into account individual differences in stress responsivity and life circumstances (e.g., economic hardship, trauma history) could help further elucidate the real-time concurrent and temporal relationships between daily stressors and difficulties in everyday life.

The impact of stress on quality of life in older adults

Quality of life (QoL) is a multifaceted concept that has been broadly defined as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns"(World Health Organization, 1995). The research on QoL in older adults has been advanced by the development of QoL measures, including the World Health Organization's WHOQOL-100 and the abbreviated WHOQOL-BREF (WHOQOL Group, 1995, 1998) (World Health Organization, 1995, 1998). Although measures vary in their operationalization of QoL (Post, 2014), the WHOQOL assesses QoL across the domains of physical health (e.g., activities of daily living, pain, and discomfort), psychological health (e.g., self-esteem, negative feelings), social relationships (e.g., personal relationships, sexual activity), and environment (e.g., financial resources, home environment). Undoubtedly, stress and the associated adverse consequences of stress can negatively impact a person's QoL.

Chronic health conditions and quality of life

Up to 60% of older adults live with two or more chronic health conditions (Ward, Schiller, & Goodman, 2014) and over a third of individuals aged 65 and older in the United States live with a physical disability (Administration on Aging, Administration for Community Living, 2017). The relationship between physical health status and QoL has been demonstrated across diverse older adult samples, including those living with multiple sclerosis, HIV, cognitive impairment, sensory deficits, and cancer (Balderson et al., 2013; Cichy, Bishop, Roessler, Jian, & Rumrill, 2016; Dalton et al., 2003; Dunn, Ng, & Breitbart, 2013; Goulia, Voulgari, Tsifetaki, Drosos, & Hyphantis, 2010; Hyams, Hay-McCutcheon, & Scogin, 2018; Stites, Karlawish, Harkins, Rubright, & Wolk, 2017; Tseng, Liu, Lou, & Huang, 2018). Findings from these studies suggest that chronic health conditions can impact QoL across both physical and mental health domains.

The psychological and physical stress associated with chronic health conditions appears to be a driving force of reduced QoL amongst older adult patient populations. For instance, in a large sample of older adults living with multiple sclerosis, perceived stress was negatively associated with QoL (Cichy et al., 2016). Moreover, studies suggest that lower psychological resources, such as resilience and social support, likely contribute to reduced QoL amongst older adults living with chronic health conditions (Dunn et al., 2013; Matzka, Mayer, & Köck-Hódi, 2016; Moser, Luxenberger, & Freidl, 2017). Given the relationship between psychological resources and QoL in older adults living with chronic stress, researchers have noted that it will be critical to develop interventions aimed at enhancing stress management techniques (Chen, Hu, McCoy, Letvak, & Ivanov, 2018; Cichy et al., 2016).

Mental health and quality of life

While the majority of research on older adults and well-being has focused on the presence and severity of mental health diagnoses, a growing body of research has focused on the impact of mental health conditions on QoL in older adults (Atkins, Naismith, Luscombe, & Hickie, 2013; Brown & Roose, 2011; Chopra, Zhang, & Pless Kaiser, 2014; Sarma & Byrne, 2014). A number of mental health diagnoses have been associated with reduced QoL amongst older adults, including anxiety, PTSD, schizophrenia, and depression (Bourland, Stanley, & Snyder, 2000; Cohen, Vengassery, & Garcia Aracena, 2017; Lamoureux-Lamarche, Vasiliadis, Préville, & Berbiche, 2016; Sarma & Byrne, 2014; Sivertsen, Bjorklof, Engedal, Selbaek, & Helvik, 2015). Although multiple factors likely contribute to this relationship, converging evidence suggests that stress and related factors may play an important role. For instance, amongst adults aged 60 and over, greater psychological distress has been associated with lower QoL in comparison to those with lower reported distress (Atkins et al., 2013). Further, emerging evidence has demonstrated that stress is negatively associated with mental health QoL amongst older adults (de Frias & Whyne, 2015).

The relationship between stress and QoL in older adults has been further evidenced by studies demonstratingthe association between traumatic events and QoL in older adults. In one study of community-dwelling older adults,

lifetime exposure to traumatic events (i.e., acts of violence, natural disasters, life-threatening diseases, and sexual abuse) was associated with lower QoL in women, although not in men (Lamoureux-Lamarche et al., 2016). PTSD also appears to have a particularly detrimental effect on QoL. For instance, one study found that older adults with PTSD had worse mental health QoL than older adults with either no trauma exposure or trauma exposure without a PTSD diagnosis (Chopra et al., 2014). Interestingly, when comorbid disorders were accounted for, PTSD continued to be related to worse mental health QoL, particularly in men. Together, these findings underscore the impact that trauma and PTSD can have on QoL in older adults. Further, they highlight the importance of examining sociodemographic factors which may moderate this association.

Indeed, researchers have begun to examine whether mental health interventions designed to reduce symptom distress also improve QoL in older adults (Forsman, Nordmyr, & Wahlbeck, 2011). A number of studies suggest cognitive behavioral treatment is associated with gains in QoL for older adults with mental health diagnoses, such as generalized anxiety disorder (Brenes et al., 2012; Scogin et al., 2007; Shrestha, Stanley, & Wilson, 2015). Moreover, preliminary evidence suggests that enhancing protective factors may also contribute to improvements in QoL amongst older adults. For example, de Frias and Whyne (2015) found the impact of stress on QoL in middle-aged and older adults was attenuated in individuals with higher levels of mindfulness. Taken together, these findings suggest mental health interventions may effectively target QoL in older adults.

Although a growing body of research has demonstrated the relationship between stressors and QoL and potential interventions to improve well-being in older adults, it is important to note the current limitations in the literature. First, the operationalization of QoL and well-being varies across studies, which limits the ability to generalize study findings (Eack & Newhill, 2007). Second, further longitudinal research is needed to clarify the temporal relationship between stress and QoL in older adults. Lastly, it will be critical to examine moderating factors that influence the relationship between stress and QoL in older adults. For instance, the identification of additional modifiable factors (e.g., psychological resources) which reduce the strength of the relationship between stress and reduced QoL may advance preventative and intervention efforts for older adults at risk of stress-related conditions.

Alzheimer's disease caregivers—a use-case example of how stress directly impacts mental health in older adults

Alzheimer's disease (AD) is the most common form of dementia, affecting an estimated 5.7 million Americans in 2018. A majority of persons living with AD are cared for by informal family (primarily spousal) caregivers. The chronic stress of caring for a loved one with AD is associated with increased risk for psychological and physical morbidity. Caregivers are particularly at increased risk for depression and anxiety (Dura, Stukenberg, & Kiecolt-Glaser, 1991; Schulz, O'Brien, Bookwala, & Fleissner, 1995). Other psychological symptoms commonly reported by caregivers include anger/frustration and feeling overwhelmed by their caregiving duties (Coon, Rubert, & Solano, 2004). A number of family caregivers are also balancing work with caregiving, and caregiving can pose additional stresses due to economic hardships incurred through lost wages from reduced work hours, time out of the workforce, family leave, or early retirement. The psychological consequences of caregiving have been found to be associated with physiologic outcomes, and the growing population of AD caregivers are often studied in research focused on the mechanisms by which chronic stress affects negative health outcomes.

Chronic stress promotes dysregulation of immune system functioning, leading to enhanced inflammatory signaling associated with depressive symptomatology, so it is not surprising depressive symptoms are common among AD caregivers. In the general population, it is estimated that between 10% and 25% of women and 5% and 12% of men have at least one period of depression in their lives. For caregivers, these estimated prevalence rates are more than double, with 44% of women and 27% of men experiencing clinical symptoms of depression. Depression in caregivers is closely linked to the stress associated with their loved one's dementia. Research indicates depression may be associated with physiological changes which can lead to physical health problems, including increased risk of cardiovascular disease. Indeed, in a longitudinal study of over 54,000 US women without coronary heart disease, stroke, or cancer at baseline, spousal caregivers with high levels of caregiver burden were at nearly twice the risk for developing coronary heart disease relative to noncaregivers or caregivers of parents or nonspousal others over a 4-year period (Lee, Colditz, Berkman, & Kawachi, 2003). Older male caregivers also appear to be at higher risk than noncaregivers for developing cardiovascular disease. In a theoretical stress model testing the relationship between chronic stress, psychophysiology, and coronary heart disease in 47 caregiver men, Vitaliano and colleagues found that chronic stress led to distress (composite variable including depressive symptoms, daily hassles, caregiver burden, and sleep problems), which led to

metabolic syndrome, which in turn predicted coronary heart disease (Vitaliano et al., 2002). The longitudinal University of California San Diego (UCSD) Alzheimer's Caregiver Study has demonstrated caregiver distress, including depression (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007), caregiver burden (Mausbach, Mills, & Patterson, 2007), sleep disturbance (von Kanel, Ancoli-Israel, & Dimsdale, 2010), and behavioral and cognitive impairment of the AD patient are related to vascular risk factors such as dysregulation in blood pressure (Aschbacher, von Kanel, & Dimsdale, 2006), catecholamine levels (Mills, Ziegler, & Patterson, 1997), procoagulant shift and inflammation (von Kanel, Dimsdale, & Mills, 2006), endothelial dysfunction (Mausbach, Roepke, & Ziegler, 2010), and the prevalence of carotid plaque (Roepke, Chattillion, & von Kanel, 2011). Given this connection between chronic stress, distress, and cardiovascular disease risk markers, it is important to promote psychological and lifestyle factors that may diminish the effects of stress on caregivers' well-being.

Anxiety is also common in caregivers, with one out of three caregivers experience significant symptoms of anxiety. Research indicates AD caregivers are five times more likely than noncaregivers to have general anxiety due to the stress associated with their caregiving responsibilities and worry about the future. In a model examining the mechanism by which stress predicts anxiety in 256 spousal AD caregivers, Romero-Moreno and colleagues found high levels of rumination, high levels of experiential avoidance, and low levels of leisure satisfaction (i.e., engagement in pleasant events) mediate the relationship between stress and anxiety (Romero-Moreno, Losada, Marquez-Gonzalez, & Mausbach, 2016). While these data were cross-sectional and inferences of causality cannot be made, interventions focused on reducing rumination and experiential avoidance and increasing engagement in leisure satisfaction may have a positive impact on reducing stress-related anxiety in AD caregivers.

Other psychological factors that may play an important role in understanding how caregiving stress translates to increased risk for depression and anxiety and poor health outcomes include poor self-efficacy, reduced personal mastery, maladaptive or negative coping (e.g., escape-avoidant coping), and activity restriction. One study from the UCSD Alzheimer's Caregiver Study found that when spousal AD caregivers have low self-efficacy, caregiving stress is significantly related to a proinflammatory cytokine (interleukin-6) known to be associated with cardiovascular disease risk, but when self-efficacy is high, this relationship is attenuated (Mausbach, von Kanel, & Roepke, 2011). In another study by the same group of researchers which built upon Lewinsohn's model of depression (MacPhillamy & Lewinsohn, 1974) and the Activity Restriction Model (Williamson, 2000), caregivers who had a combination of low engagement in pleasant events and high activity restriction had significantly more depressive symptoms, negative affect, and lower positive affect when compared to caregivers in one of the three following groups: high engagement in pleasant events and low activity restriction, high engagement in pleasant events, and high activity restriction, or low engagement in pleasant events but low activity restriction (Mausbach et al., 2011). These findings imply that examining the behavioral constructs of engagement in pleasant events and activity restriction, together, provide useful information on factors predictive of caregiver well-being. Several studies have found personal mastery to have a protective effect on caregiver outcomes, including psychological distress, depressive symptoms, and allostatic load (e.g., Roepke, Mausbach, & Patterson, 2011). For instance, in a longitudinal study of older adult caregivers of individuals with AD, those who placed their spouses in long-term care facilities experienced a reduction in depressive symptoms as a result of increased personal mastery and less activity restriction (Mausbach, Chattillion, & Ho, 2014). Further, findings have shown spousal caregivers may reduce their risk of adverse psychological and physical health conditions when they transition away from their caregiving duties (Mausbach, Aschbacher, & Patterson, 2007; Mausbach et al., 2010). These findings suggest the negative outcomes associated with caregiving duties are not static and that interventions aimed at enhancing protective factors (e.g., personal mastery) or alleviating caregiver burden may improve well-being in older adult caregivers.

In summary, strong evidence exists for the efficacy of several caregiver-focused psychoeducational and behavioral interventions targeting stress reduction (Piersol et al., 2017). While one of the main challenges with clinical research is translating effective interventions into practice, advances in mobile health technologies provide opportunities to help facilitate this process and reach people, such as caregivers, who experience high levels of activity restriction and caregiver burden and thus struggle with the ability to participate in psychological interventions.

Stress-related anxiety disorders in older adults

Although most epidemiological studies on stress-related disorders have largely focused on younger and middle-aged cohorts, the changing demographics in the United States have prompted researchers to examine the prevalence of stress exposure and related disorders in older adults. Studies utilizing large community and nonclinical samples of US adults have found that up to 90% older adults have been exposed to at least one traumatic event over the course of their lifetime (Norris, 1992; Ogle, Rubin, Berntsen, & Siegler, 2013). Similarly, high rates of trauma exposure have been

found across diverse samples. For instance, in a community sample of Austrian older adults, over three-quarters of the participants endorsed one or more traumatic events over their lifetime (Spitzer et al., 2008). However, the prevalence of past-year trauma exposure is significantly lower amongst older adults. Norris (1992) found that while almost 70% of community-dwelling older adults endorsed lifetime trauma, only 20% of the sample reported exposure over the past year.

Despite the relatively high prevalence of lifetime and past-year trauma exposure in older adult samples, older adults in the community endorse significantly fewer traumatic events when compared to younger cohorts. Amongst a nationally representative sample of US adults (Reynolds, Pietrzak, Mackenzie, Chou, & Sareen, 2016), older adults endorsed an average of 5.2 lifetime traumatic experiences, which was significantly lower than younger (mean = 5.7) and middle-aged adults (mean = 6.4). Although older adults endorse fewer traumas over their lifetime, they may be more likely to face certain forms of trauma. Indeed, findings suggest that while certain traumas are more frequently experienced during childhood or young adulthood (i.e., sexual assault), other events are more likely to occur with advancing age (e.g., unexpected death of loved one, serious or life-threatening accident) (Ogle et al., 2013).

Older adults are also at risk for experiencing a range of other stressors, including financial difficulties, acting as caregivers to loved ones, and being diagnosed with serious illnesses (Garlo, O'Leary, Van Ness, & Fried, 2010; Vasunilashorn, Lynch, Glei, Weinstein, & Goldman, 2015). In a large community sample of Austrian older adults, over half of the sample endorsed experiencing a stressful life event (e.g., severe illness, financial problems, divorce) over the past 2 years (Maercker, Forstmeier, & Enzler, 2008). Further, the likelihood of experiencing certain stressors may increase over the lifespan. For instance, being diagnosed with multiple chronic health conditions, a potentially significant source of stress occurs more frequently in older adults. While only 18% of adults 18−44 live with multiple chronic health conditions, this number increases to approximately 49% in adults aged 45−65, and to over 80% in individuals over the age of 65 (Gerteis et al., 2014). These results underscore the significant stressors that older adults may face in their everyday life at greater rates than younger and middle-aged adults.

Posttraumatic stress disorder in older adults

Although the majority of older adults have been exposed to trauma and other stressors over the course of their lifetimes, only a minority will go on to develop stress-related disorders such as PTSD. In fact, in a nationally representative sample of older adults in the United States, the lifetime prevalence of PTSD was 4.5% (Pietrzak, Goldstein, Southwick, & Grant, 2012) and past-year prevalence of PTSD was 2.6% (Reynolds et al., 2016). Similar prevalence rates have also been found in European samples (Glaesmer, Kaiser, Braehler, Freyberger, & Kuwert, 2012). Interestingly, these rates are significantly lower than the lifetime and past-year prevalence of PTSD in younger and middle-aged adults (Averill & Beck, 2000; Frans, Rimmo, Aberg, & Fredrikson, 2005; Reynolds et al., 2016). Relatedly, studies have suggested older adults endorse fewer and less severe PTSD symptoms than younger age groups (Reynolds et al., 2016). Of note, however, older adults may underreport their symptoms and treating clinicians may attribute their symptoms of distress to health problems (Averill & Beck, 2000). Nonetheless, the research to date suggests there is a significant difference in the prevalence and features of PTSD in older adults.

Generalized anxiety disorder in older adults

Stress exposure has also been linked to anxiety disorders in older adults. In a systematic review of anxiety disorders in older adults across predominately Western nations, prevalence rates ranged from approximately 1% to 14% in community samples and from 1% to 28% in clinical samples (Bryant, Mohlman, & Gum, 2013). The authors noted that significant variations are likely a result of methodical differences across studies. In another systematic review of older adults living in long-term care facilities, the prevalence of anxiety disorders amongst higher quality studies ranged between 5% and 5.7% (Creighton, Davison, & Kissane, 2016). Rates also differ when examining anxiety disorders in nationally representative samples. Findings from US samples suggest that 1.2% of adults aged 65 and older meet criteria for generalized anxiety disorder (GAD) (Gum, King-Kallimanis, & Kohn, 2009), while 2.8% of older adults in a nationally representative sample of Australians met for GAD (Gonçalves, Pachana, & Byrne, 2011). Despite this variability, it is clear that anxiety disorders are a concern across diverse older adult samples. However, these rates are significantly lower than estimates of anxiety disorders across younger and middle-aged cohorts. For instance, in a nationally representative sample of US adults, the past-year prevalence of any anxiety disorder was estimated to be 9.0% in adults aged 60 and over and as high as 22.7% in adults aged 30−44 and 20.6% in individuals aged 45−59 (Harvard Medical School, 2007).

The special case of the veteran population

The US veteran population is aging at a fast rate, with over 40% of veterans aged 65 or older (U.S. Census Bureau, 2016). Older adult veterans may have been exposed to a number of military-related stressors, including combat, which may place them at increased risk for developing stress-related disorders over their lifetime. Indeed, while findings suggest 4.5% of older US adults meet criteria for PTSD, rates amongst Vietnam-era veterans with combat exposure are as high as 16.9% (Goldberg, Magruder, & Forsberg, 2016). Estimates of PTSD vary significantly across studies, however, with one systematic review reporting a range between 1.0% and 22.0% in older adult veterans (Williamson, Stevelink, Greenberg, & Greenberg, 2018).

The high rates of PTSD amongst some older veteran samples may be in part due to the long-term effects of combat exposure. Studies have confirmed that combat exposure during early adulthood contributes to the development or re-emergence of PTSD in later life (Franz, Lyons, & Kremen, 2018; Sachs-Ericsson, Joiner, Cougle, Stanley, & Sheffler, 2016). For instance, in a longitudinal study of veterans and civilians, combat status at baseline predicted PTSD at 10-year follow-up, even when controlling baseline mental health symptoms (Sachs-Ericsson et al., 2016). However, combat exposure only predicted PTSD in veterans with high levels of recent stress. The authors note that previous combat exposure may have sensitized or predisposed veterans to experience the negative effects of subsequent stress (Sachs-Ericsson et al., 2016). These results highlight the importance of evaluating current everyday stressors in addition to combat exposure in older adult veterans.

The effect of combat and trauma exposure extends beyond mental health functioning. PTSD has also been linked to a range of cognitive and physical health sequelae in older adult veterans. A number of studies suggest middle-aged and older adult veterans diagnosed with PTSD are more likely to be diagnosed with dementia, arthritis, gastrointestinal concerns, heart disease, and other cardiovascular problems (Roy, Foraker, Girton, & Mansfield, 2015; Schnurr, Spiro, & Paris, 2000; Yaffe, Vittinghoff, & Lindquist, 2010). Moreover, longitudinal research indicates that PTSD may impact brain functioning over time. In a large sample of Vietnam-era veterans, veterans with more severe PTSD symptoms at age 38 experienced greater hippocampal atrophy almost two decades later, while controlling for current risk factors (Franz et al., 2018). Importantly, the development of PTSD may also be influenced by genetic factors. For instance, in a sample of Vietnam veterans, *APOE* genotype moderated the association between level of combat trauma and PTSD symptoms. The findings suggested individuals with this genotype may be at greater risk of the negative sequelae associated with trauma exposure (Lyons, Genderson, & Grant, 2013). Given that older adults in the general population are already at heightened risk for developing chronic health conditions, these findings suggest older adult veterans with PTSD are a particularly vulnerable population.

Although combat exposure has been linked to negative mental health and physical health conditions, recent findings indicate it may also be associated with positive trajectories. Indeed, in a nationally representative sample of US veterans, Pietrzak and Cook (2013) found that 69.5% of older adult veterans with a high number of traumas were determined to be resilient (reported low current psychological distress despite high number of traumas). Moreover, other studies have suggested that combat exposure may contribute to the ability to withstand stress later in life. In a nationally representative sample of US veterans, older adult caregivers (20.4% of the sample) who endorsed combat exposure reported less emotional strain related to caregiving than veterans without combat exposure (Monin, Levy, & Pietrzak, 2014). It is important to note, however, that it is unlikely combat exposure itself contributes to later well-being. Lee, Aldwin, Choun, and Spiro (2017) found that amongst older adult veterans, combat exposure did not directly affect psychological well-being, but instead exerted its influence through positive perceptions regarding military service. Thus, older adult veterans who utilize certain coping strategies (e.g., positive appraisals) may experience enhanced well-being.

Protective role of positive psychological traits

Although older adults in the US have reported a greater increase in stress compared to younger generations in 2017 (American Psychological Association, 2017), most will not go on to develop stress-related conditions such as PTSD (Pietrzak et al., 2012). The fact that the majority of individuals are able to adapt and withstand daily and chronic stressors has led researchers to examine positive psychological factors that may confer protection in the aftermath of adverse or stressful events. Thus, rather than focusing solely on risk factors associated with worse adjustment to stress, researchers have increasingly examined factors that contribute to subjective well-being even in the presence of acute or chronic stress. Social support and resilience are two particularly well-documented protective factors related to less stress-related pathology in diverse older adult samples.

Stress and social support

Social support, broadly defined as the perceived or actual availability of aid from others, is inversely related to stress-related sequelae in older adult samples. Cross-sectional and longitudinal studies have indicated that greater social support is associated with better outcomes in the aftermath of stressors, including the illness of a spouse, relationship strain, chronic pain or disease, natural disasters, and adverse childhood experiences (Bei, Bryant, & Gilson, 2013; Lee, Kahana, & Kahana, 2016; Ryan, Wan, & Smith, 2014; Schnittger, Wherton, Prendergast, & Lawlor, 2012). Qualitative work has also highlighted the importance of social support when facing stressors (Casey & Stone, 2010; Dilorenzo, Becker-Feigeles, Halper, & Picone, 2008). For instance, in a small sample of older adults living with MS, social support emerged as an important contributor to adaptation to MS (Dilorenzo et al., 2008). Cumulatively, findings from these studies suggest that amongst older adults exposed to stress, social support may lower the likelihood of developing mental and physical health conditions including depression, PTSD, loneliness, fatigue, cardiovascular problems, and chronic health conditions (Chao, 2014; Cherry et al., 2015; Howard, Creaven, Hughes, O'Leary, & James, 2017; Kwag, Martin, Russell, Franke, & Kohut, 2011; Lee et al., 2016; Pietrzak & Cook, 2013; Schnittger et al., 2012; Tsai, Sippel, Mota, Southwick, & Pietrzak, 2016). Despite a number of studies highlighting the relationship between stress and social support, it is important to note that social support has been operationalized differently across studies, thus limiting the generalizability of findings.

Indeed, mixed findings have emerged when studies have examined different forms of social support and related constructs, such as community integration. For instance, in a study comparing younger and older male veterans, greater perceived social support was associated with reduced mental health problems in younger veterans, but not in older veterans, whereas community integration was associated with less mental health problems in older veterans, but not in younger veterans (Weiner, Monin, Mota, & Pietrzak, 2016). Further, in an Israeli sample of older adults admitted to a tertiary care medical center, psychological support from informal caregivers was related to reduced depressive symptoms, while instrumental support was associated with increased depressive symptoms in those who had greater independence prior to their hospitalization (Gur-Yaish, Zisberg, Sinoff, & Shadmi, 2013). These studies highlight the complex relationship between social support, culture, and mental health in older adults. Future research is needed to continue to investigate the impact of different forms of social support on well-being amongst older adults.

Despite the well-documented link between stress and social support, few studies have investigated the mechanisms that underlie this relationship in older adults. Emerging evidence suggests that regardless of stress level, social support is associated with greater structural integrity of brain regions associated with social processing (Sherman, Cheng, Fingerman, & Schnyer, 2016). For instance, while amygdala volume has been positively associated with stress, social support has demonstrated an inverse relationship with amygdala volume in older adults (Ehlers, Daugherty, & Burzynska, 2017; Sherman et al., 2016). Although preliminary, these studies suggest targeting social support may lead to well-being by protecting against structural abnormalities in stress-exposed older adults.

Stress and resilience

Psychological resilience (hereinafter referred to as resilience) refers to a range of individual (e.g., optimism, adaptive coping skills) and environmental level resources (e.g., social support, community integration) that are associated with adaptation, or the ability to "bounce back" or quickly recover after adverse or stressful events (Bonanno, 2004; Campbell-Sills & Stein, 2007). Although the operationalization of resilience has proved to be difficult given the multidimensional nature of the construct, resilience has most recently been conceptualized as a process that may vary based on context or over the developmental lifespan. In the context of aging, resilience has been defined as both the ability to recover and the capacity to maintain functioning in the aftermath of adversity (Ryff, Singer, Love, & Essex, 1998). Such responses stand in contrast to the concept of vulnerability, which is broadly defined as the reduced ability to cope with stressors. Although early work on resilience primarily focused on adverse events during early childhood (Cicchetti, 2010), a burgeoning body of literature has focused on resilience in older adult populations.

Converging evidence suggests resilience may be related to better psychiatric and physiological outcomes in stress-exposed older adults. Indeed, a number of cross-sectional findings have demonstrated that composite measures of resilience and measures of individual resilience factors (e.g., mindfulness, perceived control, optimism) are associated with better adjustment to daily and chronic stress (Bretherton & McLean, 2015; de Frias & Whyne, 2015; Fang, Vincent, & Calabrese, 2015; Pietrzak & Cook, 2013; Puig-Perez, Hackett, Salvador, & Steptoe, 2017). For instance, in a sample of older adults living with HIV/AIDS, resilience factors (i.e., coping self-efficacy, hope/optimism, active coping, and social support) explained the relationship between stress and physical, emotional, and functional well-being

(Fang et al., 2015). However, most of the research on stress, resilience, and well-being is cross-sectional, and thus longitudinal studies are needed to explore this relationship across the lifespan.

Factors associated with resilience have also been implicated in the relationship between stress and well-being in older adults. For instance, in recent years, optimism, long thought to confer protection against stress in younger adults, has been investigated in older adult cohorts. Several studies suggest optimism contributes to well-being in older adults exposed to stress. In a study of older adults with type 2 diabetes, lower levels of self-reported optimism (Scheier, Carver, & Bridges, 1994) were associated with a reduced cardiovascular response in response to a laboratory stress condition, whereas individuals with higher levels of optimism had a cardiovascular response similar to healthy adults (Puig-Perez et al., 2017). Importantly, higher levels of optimism have also been related to greater reported mental and physical health in healthy older adults and those with chronic health conditions (Bretherton & McLean, 2015; Kepka, Baumann, & Anota, 2013; Puig-Perez et al., 2017). Other factors have also been linked to resilience in older adults. In a review on resilience in older adults in Brazilian and international samples, psychological resources (e.g., self-esteem, sense of meaning, flexibility, social support) and emotional regulation (e.g., positive emotions regarding aging, self-control) emerged as common components of resilience (Fontes & Neri, 2015). Taken together, these findings suggest a range of individual and environmental factors may contribute to well-being in diverse older adult populations.

Additional resilience factors may also explain differences in well-being amongst older adults living with chronic health conditions (Fang et al., 2015) or acting as caregivers for relatives with chronic illnesses (Mausbach, Aschbacher, & Patterson, 2006; Mausbach et al., 2010). In particular, adaptive coping strategies (e.g., actively working to solve problems) appear to relate to better outcomes in comparison to escape avoidance coping (e.g., hoping that problems disappear) amongst older adults exposed to stress. For instance, in spousal caregivers of individuals with AD, avoidance coping was related to greater depressive symptoms (Mausbach, Roepke, & Chattillion, 2012). Alternatively, problem-focused or approach coping strategies have been associated with better outcomes, including increased levels of QoL and lower mood symptoms, in older adult caregivers (Roche, Croot, MacCann, Cramer, & Diehl-Schmid, 2015). These findings suggest that enhancing adaptive coping strategies may enhance well-being and protect against stress-related disorders in older adults facing chronic stressors.

Although fewer studies have investigated the temporal relationship between resilience factors and exposure to stress, a number of preliminary findings suggest resilience factors (e.g., mastery, positive coping strategies, planning ahead) may reduce the likelihood of stress-related health conditions (Bei et al., 2013; Bookwala, 2014; Kahana, Kelley-Moore, & Kahana, 2012). Findings from these studies lend support to ongoing research on interventions to promote resilience in stress-exposed aging adults (Alschuler, Arewasikporn, Nelson, Molton, & Ehde, 2018; Fullen & Gorby, 2016; Smith & Hanni, 2017).

Interventions to improve mental health and stress

Older adults experiencing chronic stress and associated mental health problems have psychological and psychosocial needs that require more than standard health care service providers can provide. Comprehensive mental health assessments in the context of primary care visits are the first step toward identifying those in need of further services. However, the mental health care needs of the rapidly growing older adult population in the United States will soon overwhelm the geriatric mental health care workforce, and there is a need to offer treatments that can be implemented remotely, in the context of team-based care and/or by nonlicensed providers. While hundreds of psychosocial mental health interventions for older adults exist, we chose a handful to discuss here based on their relevance to stress, mental health, and aging. Additionally, psychopharmacological treatments for mental health problems in older adults are widely used; however, a review of these treatments is beyond the scope of this chapter.

First, it is imperative to train all health care providers in working with issues and disorders related to aging. Simplest to implement in standard health care settings are programs or strategies to promote healthy lifestyle factors in older adults, which can in turn reduce stress and improve mental health. Research supports the old adage, "What is good for the heart is good for the brain," including mental health and overall well-being. Providing education, training, and avenues for social support can help ensure that older adults have the necessary resources to meet their needs.

Among older adults with chronic stress, such as spousal AD caregivers, there is a need for efficacious interventions for reducing caregiver distress and depression. More than 80 intervention studies for improving caregiver's mental well-being have been published. Overall, these interventions have been effective for reducing caregiver distress, with cognitive behavioral therapies (CBT) having the strongest effect of depressive symptoms (Gallagher-Thompson & Coon, 2007). Previous work has shown that brief behavioral activation (BA), a component of CBT, can significantly reduce depressive symptoms in distressed spousal AD caregivers when compared to supportive

psychotherapy (Moore, Chattillion, & Ceglowski, 2013). Stressors associated with caregiving, such as patient problem behaviors and increased time spent in caregiving tasks, reduce caregivers' engagement in positive, healthy activities they might otherwise enjoy. As a result of this reduced engagement in reinforcing environmental stimuli, caregivers begin to feel emotionally distressed, experiencing increased depression or anxiety. The primary goals of BA are to increase engagement in pleasurable events, regardless of current affective symptoms, which can in turn decrease negative affect. One advantage of BA is that it can be administered by nonlicensed providers. However, there continue to be challenges with the implementation of evidence-based treatments into the community. Studies are currently underway to test the efficacy of mobile interventions (including a mobile adaptation of our evidenced-based BA intervention) among caregivers, with the hope of eliminating some of the challenges with implementation and reaching a broader range of caregivers.

Research has also examined the effect of mindfulness-based stress reduction (MBSR) on reducing mental health symptoms among older adults with stress disorders. The results of one clinical trial found that participants randomized to the MBSR condition (vs health education control condition) improved on measures of worry, depression, and anxiety (Wetherell, Hershey, & Hickman, 2017). Another study examined the moderating roles of age and baseline depressive symptoms on MBSR's ability to improve positive affect among older adults (Gallegos, Hoerger, Talbot, Moynihan, & Duberstein, 2013). Results of this study indicated greater baseline depressive severity was associated with less improvement in positive affect post-study. They also found an age by depressive symptom severity interaction, such that MBSR participants aged 70 years and older who had lower baseline depressive symptoms had the greatest improvements in positive affect. While more work is needed, data suggesting positive effects for MBSR in reducing distress/improving positive affect among older adults are encouraging.

Lastly, although the research on evidence-based treatments for PTSD has largely focused on younger cohorts of veterans, recent studies have examined their effectiveness in older adults. In a sample of older adult veterans engaged in prolonged exposure (PE) therapy, a gold-standard treatment for PTSD, findings revealed large effect sizes (1.13−1.90) and low dropout rates amongst veterans aged 60 or older (Yoder et al., 2013). However, in another study examining cognitive processing therapy (CPT), another gold-standard treatment for PTSD, Vietnam era veterans had greater PTSD severity posttreatment in comparison to younger veterans after controlling for sessions attended and other covariates (Chard, Schumm, Owens, & Cottingham, 2010). The authors suggested this finding may be explained by the stronger relationship between pre and posttreatment PTSD symptom severity in Vietnam-era veterans and that individuals with more sessions attended had greater PTSD symptom distress. Moreover, the potential chronicity of symptom distress in Vietnam veterans may contribute to the higher severity of symptom distress at posttreatment. Nonetheless, despite concerns that have been raised regarding the potential for cognitive or health problems interfering in exposure and cognitive treatments for older adults with PTSD, older adults appear to benefit from these approaches. Further research is needed, however, to continue to examine these treatments in larger samples of older adult veterans.

Future directions for research and conclusions

There is a sufficient body of research focusing on the impact of stress on physiological and cognitive aging, and some studies have started to examine the complex interplay between stress, inflammation, immune activation, and mental health problems. However, as detailed throughout this chapter, significant work remains. In addition, it is difficult to study the impact of traumatic and/or stressful experiences across the lifespan and how the cumulative effect of multiple stressors [i.e., early adversity, chronic stress, major life events, daily stressors, and life circumstances (e.g., economic hardship, low socioeconomic status)], together with biological mechanisms and psychological mediators (e.g., resilience, social support), impact overall mental health and everyday functioning. Future studies that aim to fill in these gaps in the literature may lead to more precise and individualized interventions. While there is evidence that interventions targeting stress reduction can improve symptoms of depression and anxiety in older adults, gaps in the literature remain, particularly with regard to underserved (and often the most vulnerable) populations. Moreover, the majority of studies have been done in the United States or other Western cultures, so it is unclear how applicable these findings are to other cultural groups. Clinicians would benefit from being particularly sensitive to the high base rates of stress in older adults and the damaging effect this stress can have on physical, mental, cognitive, and everyday functioning. Leveraging technology, such as mobile health devices and sensors, can advance our understanding of stress. Technology has the potential for optimizing mental health care to improve diagnostic abilities, monitoring, and treatment of stress and mental health problems in older adults.

References

Aggarwal, N. T., Clark, C. J., Beck, T. L., Mendes de Leon, C. F., DeCarli, C., Evans, D. A., et al. (2014). Perceived stress is associated with subclinical cerebrovascular disease in older adults. *The American Journal of Geriatric Psychiatry*, *22*(1), 53–62.

Aggarwal, N. T., Wilson, R. S., Beck, T. L., Rajan, K. B., Mendes de Leon, C. F., Evans, D. A., & Everson-Rose, S. A. (2014). Perceived stress and change in cognitive function among adults 65 years and older. *Psychosomatic Medicine*, *76*(1), 80–85.

Alberts, N. M., Hadjistavropoulos, H. D., Pugh, N. E., & Jones, S. L. (2011). Dementia anxiety among older adult caregivers: An exploratory study of older adult caregivers in Canada. *International Psychogeriatrics*, *23*(6), 880–886.

Alexopoulos, G. S., & Morimoto, S. S. (2011). The inflammation hypothesis in geriatric depression. *International Journal of Geriatric Psychiatry*, *26*(11), 1109–1118.

Alschuler, K. N., Arewasikporn, A., Nelson, I. K., Molton, I. R., & Ehde, D. M. (2018). Promoting resilience in individuals aging with multiple sclerosis: Results from a pilot randomized controlled trial. *Rehabilitation Psychology*, *63*(3), 338–348.

American Psychological Association. (2017). Stress in America: The State of Our Nation. Stress in America TM Survey.

Administration on Aging, Administration for Community Living. (2018). 2017 profile of older Americans.

Arpawong, T. E., Lee, J., Phillips, D. F., Crimmins, E. M., Levine, M. E., & Prescott, C. A. (2016). Effects of recent stress and variation in the serotonin transporter polymorphism (5-HTTLPR) on depressive symptoms: A repeated-measures study of adults age 50 and older. *Behavior Genetics*, *46*(1), 72–88.

Aschbacher, K., von Känel, R., Dimsdale, J. E., Patterson, T. L., Mills, P. J., Mausbach, B. T., & Grant, I. (2006). Dementia severity of the care receiver predicts procoagulant response in Alzheimer caregivers. *The American Journal of Geriatric Psychiatry*, *14*(8), 694–703.

Atkins, J., Naismith, S. L., Luscombe, G. M., & Hickie, I. B. (2013). Psychological distress and quality of life in older persons: Relative contributions of fixed and modifiable risk factors. *BMC Psychiatry*, *13*, 249.

Averill, P. M., & Beck, J. G. (2000). Posttraumatic stress disorder in older adults: A conceptual review. *Journal of Anxiety Disorders*, *14*(2), 133–156.

Balderson, B. H., Grothaus, L., Harrison, R. G., McCoy, K., Mahoney, C., & Catz, S. (2013). Chronic illness burden and quality of life in an aging HIV population. *AIDS Care*, *25*(4), 451–458.

Bei, B., Bryant, C., Gilson, K. M., Koh, J., Gibson, P., Komiti, A., & Judd, F. (2013). A prospective study of the impact of floods on the mental and physical health of older adults. *Aging & Mental Health*, *17*(8), 992–1002.

Bell, J. A., Kivimäki, M., Bullmore, E. T., Steptoe, A., MRC ImmunoPsychiatry Consortium., & Carvalho, L. A. (2017). Repeated exposure to systemic inflammation and risk of new depressive symptoms among older adults. *Translational Psychiatry*, *7*(8), e1208.

Belvederi Murri, M., Pariante, C., Mondelli, V., Masotti, M., Atti, A. R., Mellacqua, Z., et al. (2014). HPA axis and aging in depression: Systematic review and meta-analysis. *Psychoneuroendocrinology*, *41*, 46–62.

Berk, L., van Boxtel, M., & van Os, J. (2017). Can mindfulness-based interventions influence cognitive functioning in older adults? A review and considerations for future research. *Aging & Mental Health*, *21*(11), 1113–1120.

Bonanno, G. A. (2004). Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? *American Psychologist*, *59*(1), 20–28.

Bookwala, J. (2014). Spouse health status, depressed affect, and resilience in mid and late life: A longitudinal study. *Developmental Psychology*, *50*(4), 1241–1249.

Bourland, S. L., Stanley, M. A., Snyder, A. G., Novy, D. M., Beck, J. G., Averill, P. M., et al. (2000). Quality of life in older adults with generalized anxiety disorder. *Aging & Mental Health*, *4*(4), 315–323.

Brenes, G. A., Miller, M. E., Williamson, J. D., McCall, W. V., Knudson, M., & Stanley, M. A. (2012). A randomized controlled trial of telephone-delivered cognitive-behavioral therapy for late-life anxiety disorders. *The American Journal of Geriatric Psychiatry*, *20*(8), 707–716.

Bretherton, S. J., & McLean, L. A. (2015). Interrelations of stress, optimism and control in older people's psychological adjustment. *Australasian Journal of Ageing*, *34*(2), 103–108.

Brown, P. J., & Roose, S. P. (2011). Age and anxiety and depressive symptoms: The effect on domains of quality of life. *International Journal of Geriatr Psychiatry*, *26*(12), 1260–1266.

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: does cortisol play a role? *Biological Psychiatry*, *55*(1), 1–9.

Bryant, C., Mohlman, J., Gum, A., Stanley, M., Beekman, A. T., Wetherell, J. L., et al. (2013). Anxiety disorders in older adults: Looking to DSM5 and beyond. *The American Journal of Geriatric Psychiatry*, *21*(9), 872–876.

Campbell-Sills, L., & Stein, M. B. (2007). Psychometric analysis and refinement of the Connor-Davidson Resilience Scale (CD-RISC): Validation of a 10-item measure of resilience. *Journal of Traumatic Stress*, *20*(6), 1019–1028.

Casaletto, K. B., Staffaroni, A. M., Elahi, F., Fox, E., Crittenden, P. A., You, M., et al. (2018). Perceived stress is associated with accelerated monocyte/macrophage aging trajectories in clinically normal adults. *The American Journal of Geriatric Psychiatry*, *26*(9), 952–963.

Casey, R., & Stone, S. D. (2010). Aging with long-term physical impairments: The significance of social support. *Canadian Journal of Aging*, *29*(3), 349–359.

Chao, S. F. (2014). Functional disability and depressive symptoms: Longitudinal effects of activity restriction, perceived stress, and social support. *Aging & Mental Health*, *18*(6), 767–776.

Chard, K. M., Schumm, J. A., Owens, G. P., & Cottingham, S. M. (2010). A comparison of OEF and OIF veterans and Vietnam veterans receiving cognitive processing therapy. *Journal of Traumatic Stress*, *23*(1), 25–32.

Chen, M. L., Hu, J., McCoy, T. P., Letvak, S., & Ivanov, L. (2018). Effect of a lifestyle-based intervention on health-related quality of life in older adults with hypertension. *Journal of Aging Research*, *2018*, 6059560.

Cherry, K. E., Sampson, L., Nezat, P. F., Cacamo, A., Marks, L. D., & Galea, S. (2015). Long-term psychological outcomes in older adults after disaster: Relationships to religiosity and social support. *Aging & Mental Health*, *19*(5), 430−443.

Chopra, M. P., Zhang, H., Pless Kaiser, A., Moye, J. A., Llorente, M. D., Oslin, D. W., et al. (2014). PTSD is a chronic, fluctuating disorder affecting the mental quality of life in older adults. *The American Journal of Geriatric Psychiatry*, *22*(1), 86−97.

Cicchetti, D. (2010). Resilience under conditions of extreme stress: A multilevel perspective. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *9*(3), 145−154.

Cichy, K. E., Bishop, M., Roessler, R. T., Jian, L., & Rumrill, P. D., Jr. (2016). Non-vocational health-related correlates of quality of life for older adults living with multiple sclerosis. *Journal of Rehabilitation*, *82*(3), 36−44.

Cohen, C. I., Vengassery, A., & Garcia Aracena, E. F. (2017). A longitudinal analysis of quality of life and associated factors in older adults with schizophrenia spectrum disorder. *The American Journal of Geriatric Psychiatry*, *25*(7), 755−765.

Comijs, H. C., van den Kommer, T. N., Minnaar, R. W., Penninx, B. W., & Deeg, D. J. (2011). Accumulated and differential effects of life events on cognitive decline in older persons: depending on depression, baseline cognition, or ApoE epsilon4 status? *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *66B*(Suppl. 1), i111−i120.

Coon, D. W., Rubert, M., Solano, N., Mausbach, B., Kraemer, H., Arguëlles, T., et al. (2004). Well-being, appraisal, and coping in Latina and Caucasian female dementia caregivers: Findings from the REACH study. *Aging & Mental Health*, *8*(4), 330−345.

Creighton, A. S., Davison, T. E., & Kissane, D. W. (2016). The prevalence of anxiety among older adults in nursing homes and other residential aged care facilities: A systematic review. *International Journal of Geriatr Psychiatry*, *31*(6), 555−566.

Cutler, S. J. (2015). Worries about getting Alzheimer's: Who's concerned? *American Journal of Alzheimer's Disease & Other Dementias*, *30*(6), 591−598.

Dalton, D. S., Cruickshanks, K. J., Klein, B. E., Klein, R., Wiley, T. L., & Nondahl, D. M. (2003). The impact of hearing loss on quality of life in older adults. *The Gerontologist*, *43*(5), 661−668.

Damjanovic, A. K., Yang, Y., Glaser, R., Kiecolt-Glaser, J. K., Nguyen, H., Laskowski, B., et al. (2007). Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *Journal of Immunology*, *179*(6), 4249−4254.

de Frias, C. M., & Whyne, E. (2015). Stress on health-related quality of life in older adults: The protective nature of mindfulness. *Aging & Mental Health*, *19*(3), 201−206.

Dilorenzo, T. A., Becker-Feigeles, J., Halper, J., & Picone, M. A. (2008). A qualitative investigation of adaptation in older individuals with multiple sclerosis. *Disability and Rehabilitation*, *30*(15), 1088−1097.

D'Mello, M. J., Ross, S. A., Briel, M., Anand, S. S., Gerstein, H., & Pare, G. (2015). Association between shortened leukocyte telomere length and cardiometabolic outcomes: Systematic review and meta-analysis. *Circulation: Cardiovascular Genetics*, *8*(1), 82−90.

Dunn, J., Ng, S. K., Breitbart, W., Aitken, J., Youl, P., Baade, P. D., et al. (2013). Health-related quality of life and life satisfaction in colorectal cancer survivors: trajectories of adjustment. *Health and Quality of Life Outcomes*, *11*(1), 46.

Dura, J., Stukenberg, K., & Kiecolt-Glaser, J. (1991). Anxiety and depressive disorders in adult children caring for demented parents. *Psychology and Aging*, *6*(3), 467−473.

Eack, S. M., & Newhill, C. E. (2007). Psychiatric symptoms and quality of life in schizophrenia: A meta-analysis. *Schizophrenia Bulletin*, *33*(5), 1225−1237.

Ehlers, D. K., Daugherty, A. M., Burzynska, A. Z., Fanning, J., Awick, E. A., Chaddock-Heyman, L., et al. (2017). Regional brain volumes moderate, but do not mediate, the effects of group-based exercise training on reductions in loneliness in older adults. *Frontiers in Aging Neuroscience*, *9*, 110, -110.

Epel, E. S., & Prather, A. A. (2018). Stress, telomeres, and psychopathology: Toward a deeper understanding of a triad of early aging. *Annual Review of Clinical Psychology*, *14*, 371−397.

Fang, X., Vincent, W., Calabrese, S. K., Heckman, T. G., Sikkema, K. J., Humphries, D. L., et al. (2015). Resilience, stress, and life quality in older adults living with HIV/AIDS. *Aging & Mental Health*, *19*(11), 1015−1021.

Fontes, A. P., & Neri, A. L. (2015). Resilience in aging: Literature review. *Ciencia & Saude Coletiva*, *20*(5), 1475−1495.

Forsman, A. K., Nordmyr, J., & Wahlbeck, K. (2011). Psychosocial interventions for the promotion of mental health and the prevention of depression among older adults. *Health Promotion International*, *26*(Suppl. 1), i85−i107.

Frans, O., Rimmo, P. A., Aberg, L., & Fredrikson, M. (2005). Trauma exposure and post-traumatic stress disorder in the general population. *Acta Psychiatrica Scandinavica*, *111*(4), 291−299.

Franz, C. E., Lyons, M. J., & Kremen, W. S. (2018). Long-term influences of combat exposure and posttraumatic stress symptoms on brain structure, health, and functioning: The Vietnam Era Twin Study of Aging. In: *Long-term outcomes of military service: The health and well-being of aging veteran*s (pp. 225−243).

French, S. L., Floyd, M., Wilkins, S., & Osato, S. (2012). The fear of Alzheimer's disease scale: A new measure designed to assess anticipatory dementia in older adults. *International Journal of Geriatric Psychiatry*, *27*(5), 521−528.

Fullen, M. C., & Gorby, S. R. (2016). Reframing resilience: Pilot evaluation of a program to promote resilience in marginalized older adults. *Educational Gerontology*, *42*(9), 660−671.

Gaffey, A. E., Bergeman, C. S., Clark, L. A., & Wirth, M. M. (2016). Aging and the HPA axis: Stress and resilience in older adults. *Neuroscience & Biobehavioral Reviews*, *68*, 928−945.

Gallagher-Thompson, D., & Coon, D. W. (2007). Evidence-based psychological treatments for distress in family caregivers of older adults. *Psychology and Aging*, *22*(1), 37–51.

Gallegos, A. M., Hoerger, M., Talbot, N. L., Moynihan, J. A., & Duberstein, P. R. (2013). Emotional benefits of mindfulness-based stress reduction in older adults: The moderating roles of age and depressive symptom severity. *Aging & Mental Health*, *17*(7), 823–829.

Garlo, K., O'Leary, J. R., Van Ness, P. H., & Fried, T. R. (2010). Burden in caregivers of older adults with advanced illness. *Journal of the American Geriatrics Society*, *58*(12), 2315–2322.

Gerteis, J., Izrael, D., Deitz, D., LeRoy, L., Ricciardi, R., Miller, T., & Basu, J. (2014). AHRQ Publications No, Q14-0038 *Multiple chronic conditions chartbook: 2010 Medical Expenditure Panel Survey data*. Rockville, MD: Agency for Healthcare Research and Quality.

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Greer, P. J., Kuller, L. H., & Matthews, K. A. (2007). Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage*, *35*(2), 795–803.

Glaesmer, H., Kaiser, M., Braehler, E., Freyberger, H. J., & Kuwert, P. (2012). Posttraumatic stress disorder and its comorbidity with depression and somatisation in the elderly–A German community-based study. *Aging & Mental Health*, *16*(4), 403–412.

Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology*, *5*(3), 243–251.

Goldberg, J., Magruder, K. M., Forsberg, C. W., Friedman, M. J., Litz, B. T., Vaccarino, V., et al. (2016). Prevalence of post-traumatic stress disorder in aging Vietnam-era veterans: Veterans Administration Cooperative Study 569: Course and consequences of post-traumatic stress disorder in Vietnam-era veteran twins. *The American Journal of Geriatric Psychiatry*, *24*(3), 181–191.

Goldman, N., Glei, D. A., Lin, Y. H., & Weinstein, M. (2010). The serotonin transporter polymorphism (5-HTTLPR): Allelic variation and links with depressive symptoms. *Depression and Anxiety*, *27*(3), 260–269.

Gonçalves, D. C., Pachana, N. A., & Byrne, G. J. (2011). Prevalence and correlates of generalized anxiety disorder among older adults in the Australian National Survey of Mental Health and Well-Being. *Journal of Affective Disorders*, *132*(1-2), 223–230.

Gouin, J. P., Glaser, R., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. (2012). Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*, *31*(2), 264–268.

Gouin, J. P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: A review. *Neuroimmunomodulation*, *15*(4-6), 251–259.

Goulia, P., Voulgari, P. V., Tsifetaki, N., Drosos, A. A., & Hyphantis, T. (2010). Comparison of health-related quality of life and associated psychological factors between younger and older patients with established rheumatic disorders. *Aging & Mental Health*, *14*(7), 819–827.

Graham, J. E., Christian, L. M., & Kiecolt-Glaser, J. K. (2006). Stress, age, and immune function: Toward a lifespan approach. *Journal of Behavioral Medicine*, *29*(4), 389–400.

Gum, A. M., King-Kallimanis, B., & Kohn, R. (2009). Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. *The American Journal of Geriatric Psychiatry*, *17*(9), 769–781.

Gur-Yaish, N., Zisberg, A., Sinoff, G., & Shadmi, E. (2013). Effects of instrumental and psychological support on levels of depressive symptoms for hospitalized older adults. *Aging & Mental Health*, *17*(5), 646–653.

Harvard Medical School. (2007). National Comorbidity Survey (NCS).

Howard, S., Creaven, A. M., Hughes, B. M., O'Leary, E. D., & James, J. E. (2017). Perceived social support predicts lower cardiovascular reactivity to stress in older adults. *Biological Psychology*, *125*, 70–75.

Hyams, A. V., Hay-McCutcheon, M., & Scogin, F. (2018). Hearing and quality of life in older adults. *Journal of Clinical Psychology*, *74*(10), 1874–1883.

Hyun, J., Sliwinski, M. J., & Smyth, J. M. (2019). Waking up on the wrong side of the bed: The effects of stress anticipation on working memory in daily life. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *74*, 38–46.

Johansson, L., Guo, X., Waern, M., Ostling, S., Gustafson, D., Bengtsson, C., et al. (2010). Midlife psychological stress and risk of dementia: A 35-year longitudinal population study. *Brain*, *133*(Pt 8), 2217–2224.

Johansson, L., Skoog, I., Gustafson, D. R., Olesen, P. J., Waern, M., Bengtsson, C., et al. (2012). Midlife psychological distress associated with late-life brain atrophy and white matter lesions: A 32-year population study of women. *Psychosomatic Medicine*, *74*(2), 120–125.

Johnson, A. D., McQuoid, D. R., Steffens, D. C., Payne, M. E., Beyer, J. L., & Taylor, W. D. (2017). Effects of stressful life events on cerebral white matter hyperintensity progression. *International Journal of Geriatric Psychiatry*, *32*(12), e10–e17.

Jones, H. J., Janson, S. L., & Lee, K. A. (2017). Leukocyte telomere length in postmenopausal women. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, *46*(4), 567–575.

Juruena, M. (2013). Early-life stress and HPA axis trigger recurrent adulthood depression. *Epilepsy & Behavior*, *38*, 149–159.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews*, *35*(1), 2–16.

Kahana, E., Kelley-Moore, J., & Kahana, B. (2012). Proactive aging: A longitudinal study of stress, resources, agency, and well-being in late life. *Aging & Mental Health*, *16*(4), 438–451.

Katz, M. J., Derby, C. A., Wang, C., Sliwinski, M. J., Ezzati, A., Zimmerman, M. E., et al. (2016). Influence of perceived stress on incident amnestic mild cognitive impairment: Results from the Einstein Aging Study. *Alzheimer Disease and Associated Disorders*, *30*(2), 93–98.

Kepka, S., Baumann, C., Anota, A., Buron, G., Spitz, E., Auquier, P., et al. (2013). The relationship between traits optimism and anxiety and health-related quality of life in patients hospitalized for chronic diseases: data from the SATISQOL study. *Health and Quality of Life Outcomes*, *11*, 134.

Kessler, E. M., Bowen, C. E., Baer, M., Froelich, L., & Wahl, H. W. (2012). Dementia worry: A psychological examination of an unexplored phenomenon. *European Journal of Ageing*, *9*(4), 275–284.

Kessler, E.-M., Tempel, J., & Wahl, H.-W. (2014). Concerns about one's aging. *GeroPsych*, *27*(2), 81–86.
Kiecolt-Glaser, J. K., Preacher, K. J., MacCallum, R. C., Atkinson, C., Malarkey, W. B., & Glaser, R. (2003). Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(15), 9090–9095.
Kim, S. Y., Karlawish, J., & Berkman, B. E. (2015). Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. *Neurology*, *84*(14), 1488–1494.
Kim, J. M., Stewart, R., Kim, S. W., Yang, S. J., Shin, I. S., Kim, Y. H., et al. (2007). Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. *Biological Psychiatry*, *62*(5), 423–428.
Kinzer, A., & Suhr, J. A. (2016). Dementia worry and its relationship to dementia exposure, psychological factors, and subjective memory concerns. *Applied Neuropsychology: Adult*, *23*(3), 196–204.
Kop, W. J., Gottdiener, J. S., Tangen, C. M., Fried, L. P., McBurnie, M. A., Walston, J., et al. (2002). Inflammation and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. *The American Journal of Cardiology*, *89*(4), 419–424.
Korten, N. C., Comijs, H. C., Penninx, B. W., & Deeg, D. J. (2017). Perceived stress and cognitive function in older adults: Which aspect of perceived stress is important? *International Journal of Geriatric Psychiatry*, *32*(4), 439–445.
Kromer B., & Howard D. (2013). Labor force participation and work status of people 65 years and older <http://www.census.gov/content/dam/Census/library/publications/2013/acs/acsbr11-09.pdf>.
Kwag, K. H., Martin, P., Russell, D., Franke, W., & Kohut, M. (2011). The impact of perceived stress, social support, and home-based physical activity on mental health among older adults. *The International Journal of Aging and Human Development*, *72*(2), 137–154.
Lamoureux-Lamarche, C., Vasiliadis, H.-M., Préville, M., & Berbiche, D. (2016). Post-traumatic stress syndrome in a large sample of older adults: Determinants and quality of life. *Aging & Mental Health*, *20*(4), 401–406.
Lavretsky, H., & Newhouse, P. A. (2012). Stress, inflammation, and aging. *The American Journal of Geriatric Psychiatry*, *20*(9), 729–733.
Lee, H., Aldwin, C. M., Choun, S., & Spiro, A. (2017). Does combat exposure affect well-being in later life? The VA Normative Aging Study. *Psychological Trauma: Theory, Research, Practice and Policy*, *9*(6), 672–678.
Lee, S., Colditz, G. A., Berkman, L. F., & Kawachi, I. (2003). Caregiving and risk of coronary heart disease in U.S. women: A prospective study. *American Journal of Preventive Medicine*, *24*(2), 113–119.
Lee, J. E., Kahana, B., & Kahana, E. (2016). Social support and cognitive functioning as resources for elderly persons with chronic arthritis pain. *Aging & Mental Health*, *20*(4), 370–379.
Lineweaver, T. T., Bondi, M. W., Galasko, D., & Salmon, D. P. (2014). Effect of knowledge of APOE genotype on subjective and objective memory performance in healthy older adults. *The American Journal of Psychiatry*, *171*(2), 201–208.
Lupien, S. J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N. P., et al. (1998). Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nature Neuroscience*, *1*(1), 69–73.
Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209–237.
Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445.
Lyons, M. J., Genderson, M., Grant, M. D., Logue, M., Zink, T., McKenzie, R., et al. (2013). Gene-environment interaction of ApoE genotype and combat exposure on PTSD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162*(7), 762–769.
MacPhillamy, D. J., & Lewinsohn, P. M. (1974). Depression as a function of levels of desired and obtained pleasure. *Journal of Abnormal Psychology*, *83*(6), 651–657.
Maercker, A., Forstmeier, S., Enzler, A., Krüsi, G., Hörler, E., Maier, C., et al. (2008). Adjustment disorders, posttraumatic stress disorder, and depressive disorders in old age: Findings from a community survey. *Comprehensive Psychiatry*, *49*(2), 113–120.
Martin, P., Jazwinski, S. M., Davey, A., Green, R. C., Macdonald, M., Margrett, J. A., et al. (2014). APOE 4, rated life experiences, and affect among centenarians. *Aging & Mental Health*, *18*(2), 240–247.
Mathur, M. B., Epel, E., Kind, S., Desai, M., Parks, C. G., Sandler, D. P., et al. (2016). Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain, Behavior, and Immunity*, *54*, 158–169.
Matzka, M., Mayer, H., Köck-Hódi, S., Moses-Passini, C., Dubey, C., Jahn, P., et al. (2016). Relationship between resilience, psychological distress and physical activity in cancer patients: A cross-sectional observation study. *PLoS One*, *11*(4), e0154496.
Mausbach, B. T., Aschbacher, K., Patterson, T. L., Ancoli-Israel, S., von Känel, R., Mills, P. J., et al. (2006). Avoidant coping partially mediates the relationship between patient problem behaviors and depressive symptoms in spousal Alzheimer's caregivers. *The American Journal of Geriatric Psychiatry*, *14*(4), 299–306.
Mausbach, B. T., Aschbacher, K., Patterson, T. L., von Känel, R., Dimsdale, J. E., Mills, P. J., et al. (2007). Effects of placement and bereavement on psychological well-being and cardiovascular risk in Alzheimer's caregivers: A longitudinal analysis. *Journal of Psychosomatic Research*, *62*(4), 439–445.
Mausbach, B. T., Chattillion, E. A., Ho, J., Flynn, L. M., Tiznado, D., von Känel, R., et al. (2014). Why does placement of persons with Alzheimer's disease into long-term care improve caregivers' well-being? Examination of psychological mediators. *Psychology and Aging*, *29*(4), 776–786.
Mausbach, B. T., Mills, P. J., Patterson, T. L., Aschbacher, K., Dimsdale, J. E., Ancoli-Israel, S., et al. (2007). Stress-related reduction in personal mastery is associated with reduced immune cell beta2-adrenergic receptor sensitivity. *International Psychogeriatrics*, *19*(5), 935–946.

Mausbach, B. T., Patterson, T. L., Rabinowitz, Y. G., Grant, I., & Schulz, R. (2007). Depression and distress predict time to cardiovascular disease in dementia caregivers. *Health Psychology*, *26*(5), 539–544.

Mausbach, B. T., Roepke, S. K., Chattillion, E. A., Harmell, A. L., Moore, R. C., Romero-Moreno, R., et al. (2012). Multiple mediators of the relations between caregiving stress and depressive symptoms. *Aging & Mental Health*, *16*(1), 27–38.

Mausbach, B. T., Roepke, S. K., Depp, C. A., Moore, R., Patterson, T. L., & Grant, I. (2011). Integration of the pleasant events and activity restriction models: development and validation of a "PEAR" model of negative outcomes in Alzheimer's caregivers. *Behavior Therapy*, *42*(1), 78–88.

Mausbach, B. T., Roepke, S. K., Ziegler, M. G., Milic, M., von Känel, R., Dimsdale, J. E., et al. (2010). Association between chronic caregiving stress and impaired endothelial function in the elderly. *Journal of the American College of Cardiology*, *55*(23), 2599–2606.

Mausbach, B. T., von Känel, R., Roepke, S. K., Moore, R. C., Patterson, T. L., Mills, P. J., et al. (2011). Self-efficacy buffers the relationship between dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. *The American Journal of Geriatric Psychiatry*, *19*(1), 64–71.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33–44.

Mills, P. J., Ziegler, M. G., Patterson, T., Dimsdale, J. E., Hauger, R., Irwin, M., et al. (1997). Plasma catecholamine and lymphocyte beta 2-adrenergic receptor alterations in elderly Alzheimer caregivers under stress. *Psychosomatic Medicine*, *59*(3), 251–256.

Mitchell, A. J., Beaumont, H., Ferguson, D., Yadegarfar, M., & Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: Meta-analysis. *Acta Psychiatrica Scandinavica*, *130*(6), 439–451.

Molden, J., & Maxfield, M. (2017). The impact of aging stereotypes on dementia worry. *European Journal of Ageing*, *14*(1), 29–37.

Monin, J. K., Levy, B. R., & Pietrzak, R. H. (2014). From serving in the military to serving loved ones: Unique experiences of older veteran caregivers. *The American Journal of Geriatric Psychiatry*, *22*(6), 570–579.

Moore, R. C., Chattillion, E. A., Ceglowski, J., Ho, J., von Känel, R., Mills, P. J., et al. (2013). A randomized clinical trial of behavioral activation (BA) therapy for improving psychological and physical health in dementia caregivers: Results of the Pleasant Events Program (PEP). *Behaviour Research and Therapy*, *51*(10), 623–632.

Moreno, G. L., Bruss, J., & Denburg, N. L. (2017). Increased perceived stress is related to decreased prefrontal cortex volumes among older adults. *Journal of Clinical and Experimental Neuropsychology*, *39*(4), 313–325.

Moser, S., Luxenberger, W., & Freidl, W. (2017). The influence of social support and coping on quality of life among elderly with age-related hearing loss. *American Journal of Audiology*, *26*(2), 170–179.

Musliner, K. L., Seifuddin, F., Judy, J. A., Pirooznia, M., Goes, F. S., & Zandi, P. P. (2015). Polygenic risk, stressful life events and depressive symptoms in older adults: A polygenic score analysis. *Psychological Medicine*, *45*(8), 1709–1720.

Neupert, S. D., Almeida, D. M., Mroczek, D. K., & Spiro, A., 3rd (2006). Daily stressors and memory failures in a naturalistic setting: Findings from the VA Normative Aging Study. *Psychology and Aging*, *21*(2), 424–429.

Norris, F. H. (1992). Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. *Journal of Consulting and Clinical Psychology*, *60*(3), 409–418.

Ogle, C. M., Rubin, D. C., Berntsen, D., & Siegler, I. C. (2013). The frequency and impact of exposure to potentially traumatic events over the life course. *Clinical Psychological Science*, *1*(4), 426–434.

O'Hara, R. (2006). Stress, aging, and mental health. *The American Journal of Geriatric Psychiatry*, *14*(4), 295–298.

O'Hara, R., Marcus, P., Thompson, W. K., Flournoy, J., Vahia, I., Lin, X., et al. (2012). 5-HTTLPR short allele, resilience, and successful aging in older adults. *The American Journal of Geriatric Psychiatry*, *20*(5), 452–456.

Oliveira, B. S., Zunzunegui, M. V., Quinlan, J., Fahmi, H., Tu, M. T., & Guerra, R. O. (2016). Systematic review of the association between chronic social stress and telomere length: A life course perspective. *Ageing Research Reviews*, *26*, 37–52.

Ostergren, J. E., Heeringa, S. G., Leon, C. F. M., Connell, C. M., & Roberts, J. S. (2017). The influence of psychosocial and cognitive factors on perceived threat of Alzheimer's disease. *American Journal of Alzheimer's Disease and Other Dementias*, *32*(5), 289–299.

Peavy, G. M., Jacobson, M. W., Salmon, D. P., Gamst, A. C., Patterson, T. L., Goldman, S., et al. (2012). The influence of chronic stress on dementia-related diagnostic change in older adults. *Alzheimer Disease and Associated Disorders*, *26*(3), 260–266.

Peavy, G. M., Lange, K. L., Salmon, D. P., Patterson, T. L., Goldman, S., Gamst, A. C., et al. (2007). The effects of prolonged stress and APOE genotype on memory and cortisol in older adults. *Biological Psychiatry*, *62*(5), 472–478.

Persson, G., & Skoog, I. (1996). A prospective population study of psychosocial risk factors for late onset dementia. *International Journal of Geriatric Psychiatry*, *11*(1), 15–22.

Piersol, C. V., Canton, K., Connor, S. E., Giller, I., Lipman, S., & Sager, S. (2017). Effectiveness of interventions for caregivers of people with Alzheimer's disease and related major neurocognitive disorders: A systematic review. *The American Journal of Occupational Therapy*, *71*(5), 7105180020p7105180021-7105180020p7105180010.

Pietrzak, R. H., & Cook, J. M. (2013). Psychological resilience in older U.S. veterans: Results from the national health and resilience in veterans study. *Depression and Anxiety*, *30*(5), 432–443.

Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2012). Psychiatric comorbidity of full and partial posttraumatic stress disorder among older adults in the United States: Results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *American Journal of Geriatric Psychiatry*, *20*(5), 380–390.

Post, M. W. M. (2014). Definitions of quality of life: What has happened and how to move on. *Topics in Spinal Cord Injury Rehabilitation*, *20*(3), 167–180.

Potter, G. G., Hartman, M., & Ward, T. (2009). Perceived stress and everyday memory complaints among older adult women. *Anxiety, Stress, and Coping*, *22*(4), 475–481.

Power, T., Stewart, R., Ancelin, M. L., Jaussent, I., Malafosse, A., & Ritchie, K. (2010). 5-HTTLPR genotype, stressful life events and late-life depression: No evidence of interaction in a French population. *Neurobiology of Aging*, *31*(5), 886–887.

Puig-Perez, S., Hackett, R. A., Salvador, A., & Steptoe, A. (2017). Optimism moderates psychophysiological responses to stress in older people with Type 2 diabetes. *Psychophysiology*, *54*(4), 536–543.

Puterman, E., Lin, J., Blackburn, E., O'Donovan, A., Adler, N., & Epel, E. (2010). The power of exercise: Buffering the effect of chronic stress on telomere length. *PLoS One*, *5*(5), e10837.

Puterman, E., Lin, J., Krauss, J., Blackburn, E. H., & Epel, E. S. (2015). Determinants of telomere attrition over 1 year in healthy older women: Stress and health behaviors matter. *Molecular Psychiatry*, *20*(4), 529–535.

Radford, K., Delbaere, K., Draper, B., Mack, H. A., Daylight, G., Cumming, R., et al. (2017). Childhood stress and adversity is associated with late-life dementia in aboriginal Australians. *The American Journal of Geriatric Psychiatry*, *25*(10), 1097–1106.

Rawson, K. S., Dixon, D., Nowotny, P., Ricci, W. M., Binder, E. F., Rodebaugh, T. L., et al. (2015). Association of functional polymorphisms from brain-derived neurotrophic factor and serotonin-related genes with depressive symptoms after a medical stressor in older adults. *PLoS One*, *10*(3), e0120685.

Reid, L. M., & MacLullich, A. M. (2006). Subjective memory complaints and cognitive impairment in older people. *Dementia and Geriatric Cognitive Disorders*, *22*(5-6), 471–485.

Reynolds, K., Pietrzak, R. H., Mackenzie, C. S., Chou, K. L., & Sareen, J. (2016). Post-traumatic stress disorder across the adult lifespan: Findings from a nationally representative survey. *The American Journal of Geriatric Psychiatry*, *24*(1), 81–93.

Rickenbach, E. H., Almeida, D. M., Seeman, T. E., & Lachman, M. E. (2014). Daily stress magnifies the association between cognitive decline and everyday memory problems: An integration of longitudinal and diary methods. *Psychology and Aging*, *29*(4), 852–862.

Ritchie, K., Jaussent, I., Stewart, R., Dupuy, A. M., Courtet, P., Ancelin, M. L., et al. (2009). Association of adverse childhood environment and 5-HTTLPR genotype with late-life depression. *Journal of Clinical Psychiatry*, *70*(9), 1281–1288.

Ritchie, K., Jaussent, I., Stewart, R., Dupuy, A. M., Courtet, P., Malafosse, A., et al. (2011). Adverse childhood environment and late-life cognitive functioning. *International Journal of Geriatric Psychiatry*, *26*(5), 503–510.

Roberts, J. S., McLaughlin, S. J., & Connell, C. M. (2014). Public beliefs and knowledge about risk and protective factors for Alzheimer's disease. *Alzheimer's & Dementia*, *10*(5), S381–S389.

Roche, D. L., Croot, K., MacCann, C., Cramer, B., & Diehl-Schmid, J. (2015). The role of coping strategies in psychological outcomes for frontotemporal dementia caregivers. *Journal of Geriatric Psychiatry and Neurology*, *28*(3), 218–228.

Roepke, S. K., Chattillion, E. A., von Känel, R., Allison, M., Ziegler, M. G., Dimsdale, J. E., et al. (2011). Carotid plaque in Alzheimer caregivers and the role of sympathoadrenal arousal. *Psychosomatic Medicine*, *73*(2), 206–213.

Roepke, S. K., Mausbach, B. T., Patterson, T. L., Von Känel, R., Ancoli-Israel, S., Harmell, A. L., et al. (2011). Effects of Alzheimer caregiving on allostatic load. *Journal of Health Psychology*, *16*(1), 58–69.

Romero-Moreno, R., Losada, A., Marquez-Gonzalez, M., & Mausbach, B. T. (2016). Stressors and anxiety in dementia caregiving: Multiple mediation analysis of rumination, experiential avoidance, and leisure. *International Psychogeriatrics*, *28*(11), 1835–1844.

Ronnlund, M., Sundstrom, A., Sorman, D. E., & Nilsson, L. G. (2013). Effects of perceived long-term stress on subjective and objective aspects of memory and cognitive functioning in a middle-aged population-based sample. *The Journal of Genetic Psychology*, *174*(1), 25–41.

Roy, S. S., Foraker, R. E., Girton, R. A., & Mansfield, A. J. (2015). Posttraumatic stress disorder and incident heart failure among a community-based sample of US veterans. *American Journal of Public Health*, *105*(4), 757–763.

Ryan, L. H., Wan, W. H., & Smith, J. (2014). Spousal social support and strain: Impacts on health in older couples. *Journal of Behavioral Medicine*, *37*(6), 1108–1117.

Ryff, C. D., Singer, B., Love, G. D., & Essex, M. J. (1998). *Resilience in adulthood and later life: Defining features and dynamic processes*. *Handbook of aging and mental health: An integrative approach* (pp. 69–96). New York: Plenum Press.

Sachs-Ericsson, N., Joiner, T. E., Cougle, J. R., Stanley, I. H., & Sheffler, J. L. (2016). Combat exposure in early adulthood interacts with recent stressors to predict PTSD in aging male veterans. *The Gerontologist*, *56*(1), 82–91.

Sarma, S. I., & Byrne, G. J. (2014). Relationship between anxiety and quality of life in older mental health patients. *Australasian Journal of Ageing*, *33*(3), 201–204.

Savolainen, K., Eriksson, J. G., Kananen, L., Kajantie, E., Pesonen, A. K., Heinonen, K., et al. (2014). Associations between early life stress, self-reported traumatic experiences across the lifespan and leukocyte telomere length in elderly adults. *Biological Psychology*, *97*, 35–42.

Scerri, A., & Scerri, C. (2016). Training older adults about Alzheimer's disease—Impact on knowledge and fear. *Educational Gerontology*, *43*(3), 117–127.

Schaakxs, R., Wielaard, I., Verhoeven, J. E., Beekman, A. T., Penninx, B. W., & Comijs, H. C. (2016). Early and recent psychosocial stress and telomere length in older adults. *International Psychogeriatrics*, *28*(3), 405–413.

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the life orientation test. *Journal of Personality and Social Psychology*, *67*(6), 1063–1078.

Schnittger, R. I. B., Wherton, J., Prendergast, D., & Lawlor, B. A. (2012). Risk factors and mediating pathways of loneliness and social support in community-dwelling older adults. *Aging & Mental Health*, *16*(3), 335–346.

Schnurr, P. P., Spiro, A., 3rd, & Paris, A. H. (2000). Physician-diagnosed medical disorders in relation to PTSD symptoms in older male military veterans. *Health Psychology*, *19*(1), 91–97.

Schulz, R., O'Brien, A., Bookwala, J., & Fleissner, K. (1995). Psychiatric and physical morbidity effects of dementia caregiving: Prevalence, correlates, and causes. *The Gerontologist*, *35*(6), 771–791.

Schutte, N. S., & Malouff, J. M. (2016). The relationship between perceived stress and telomere length: A meta-analysis. *Stress and Health*, *32*(4), 313–319.

Scogin, F., Morthland, M., Kaufman, A., Burgio, L., Chaplin, W., & Kong, G. (2007). Improving quality of life in diverse rural older adults: A randomized trial of a psychological treatment. *Psychology and Aging*, *22*(4), 657–665.

Sheffler, J., Moxley, J., & Sachs-Ericsson, N. (2014). Stress, race, and APOE: Understanding the interplay of risk factors for changes in cognitive functioning. *Aging & Mental Health*, *18*(6), 784–791.

Sherman, S. M., Cheng, Y.-P., Fingerman, K. L., & Schnyer, D. M. (2016). Social support, stress and the aging brain. *Social Cognitive and Affective Neuroscience*, *11*(7), 1050–1058.

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*, 1–32.

Shrestha, S., Stanley, M. A., Wilson, N. L., Cully, J. A., Kunik, M. E., Novy, D. M., et al. (2015). Predictors of change in quality of life in older adults with generalized anxiety disorder. *International Psychogeriatrics*, *27*(7), 1207–1215.

Sindi, S., Hagman, G., Håkansson, K., Kulmala, J., Nilsen, C., Kåreholt, I., et al. (2017). Midlife work-related stress increases dementia risk in later life: The CAIDE 30-year study. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *72*(6), 1044–1053.

Sivertsen, H., Bjorklof, G. H., Engedal, K., Selbaek, G., & Helvik, A. S. (2015). Depression and quality of life in older persons: A review. *Dementia and Geriatric Cognitive Disorders*, *40*(5–6), 311–339.

Smith, J. L., & Hanni, A. A. (2017). Effects of a savoring intervention on resilience and well-being of older adults. *Journal of Applied Gerontology*, 0733464817693375.

Spitzer, C., Barnow, S., Volzke, H., John, U., Freyberger, H. J., & Grabe, H. J. (2008). Trauma and posttraumatic stress disorder in the elderly: Findings from a German community study. *Journal of Clinical Psychiatry*, *69*(5), 693–700.

Steptoe, A., Hamer, M., Lin, J., Blackburn, E. H., & Erusalimsky, J. D. (2017). The longitudinal relationship between cortisol responses to mental stress and leukocyte telomere attrition. *The Journal of Clinical Endocrinology and Metabolism*, *102*(3), 962–969.

Stites, S. D., Karlawish, J., Harkins, K., Rubright, J. D., & Wolk, D. (2017). Awareness of mild cognitive impairment and mild Alzheimer's disease dementia diagnoses associated with lower self-ratings of quality of life in older adults. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *72*(6), 974–985.

Sun, F., Gao, X., & Coon, D. W. (2013). Perceived threat of Alzheimer's disease among Chinese American older adults: The role of Alzheimer's disease literacy. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *70*(2), 245–255.

Tsai, J., Sippel, L. M., Mota, N., Southwick, S. M., & Pietrzak, R. H. (2016). Longitudinal course of posttraumatic growth among U.S. military veterans: Results from the National Health and Resilience in Veterans Study. *Depression and Anxiety*, *33*(1), 9–18.

Tseng, Y.-C., Liu, S. H.-Y., Lou, M.-F., & Huang, G.-S. (2018). Quality of life in older adults with sensory impairments: A systematic review. *Quality of Life Research*, *27*(8), 1957–1971.

Turner, A. D., James, B. D., Capuano, A. W., Aggarwal, N. T., & Barnes, L. L. (2017). Perceived stress and cognitive decline in different cognitive domains in a cohort of older African Americans. *The American Journal of Geriatric Psychiatry*, *25*(1), 25–34.

U.S. Census Bureau. (2016). 2012–2016 American community survey 5-year estimates. Retrieved from: <https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid = ACS_16_5YR_S2101&prodType = table>.

Varghese, F. P., & Brown, E. S. (2001). The hypothalamic-pituitary-adrenal axis in major depressive disorder: A brief primer for primary care physicians. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(4), 151–155.

Vasunilashorn, S., Lynch, S. M., Glei, D. A., Weinstein, M., & Goldman, N. (2015). Exposure to stressors and trajectories of perceived stress among older adults. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, *70*(2), 329–337.

Verhoeven, J. E., van Oppen, P., Puterman, E., Elzinga, B., & Penninx, B. W. (2015). The association of early and recent psychosocial life stress with leukocyte telomere length. *Psychosomatic Medicine*, *77*(8), 882–891.

Vitaliano, P. P., Scanlan, J. M., Zhang, J., Savage, M. V., Hirsch, I. B., & Siegler, I. C. (2002). A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosomatic Medicine*, *64*(3), 418–435.

von Känel, R., Ancoli-Israel, S., Dimsdale, J. E., Mills, P. J., Mausbach, B. T., Ziegler, M. G., et al. (2010). Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls. *Gerontology*, *56*(1), 41–50.

von Känel, R., Dimsdale, J. E., Mills, P. J., Ancoli-Israel, S., Patterson, T. L., Mausbach, B. T., et al. (2006). Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, *61*(9), 963–969.

Wang, J., Dong, X., Cao, L., Sun, Y., Qiu, Y., Zhang, Y., et al. (2016). Association between telomere length and diabetes mellitus: A meta-analysis. *Journal of International Medical Research*, *44*(6), 1156–1173.

Wang, H. X., Wahlberg, M., Karp, A., Winblad, B., & Fratiglioni, L. (2012). Psychosocial stress at work is associated with increased dementia risk in late life. *Alzheimer's & Dementia*, *8*(2), 114–120.

Ward, B. W., Schiller, J. S., & Goodman, R. A. (2014). Multiple chronic conditions among US adults: A 2012 update. *Preventing Chronic Disease*, *11*, E62.

Weiner, M. R., Monin, J. K., Mota, N., & Pietrzak, R. H. (2016). Age differences in the association of social support and mental health in male U.S. veterans: Results from the National Health and Resilience in Veterans Study. *The American Journal of Geriatric Psychiatry*, *24*(4), 327−336.

Wentzensen, I. M., Mirabello, L., Pfeiffer, R. M., & Savage, S. A. (2011). The association of telomere length and cancer: A meta-analysis. *Cancer Epidemiology, Biomarkers, & Prevention*, *20*(6), 1238−1250.

Wetherell, J. L., Hershey, T., Hickman, S., Tate, S. R., Dixon, D., Bower, E. S., et al. (2017). Mindfulness-based stress reduction for older adults with stress disorders and neurocognitive difficulties: A randomized controlled trial. *The Journal of Clinical Psychiatry*, *78*(7), e734−e743.

Williamson, G. M. (2000). Extending the activity restriction model of depressed affect: Evidence from a sample of breast cancer patients. *Health Psychology*, *19*(4), 339−347.

Williamson, V., Stevelink, S. A. M., Greenberg, K., & Greenberg, N. (2018). Prevalence of mental health disorders in elderly U.S. military veterans: A meta-analysis and systematic review. *The American Journal of Geriatric Psychiatry*, *26*(5), 534−545.

Wilson, R. S., Fleischman, D. A., Myers, R. A., Bennett, D. A., Bienias, J. L., Gilley, D. W., et al. (2004). Premorbid proneness to distress and episodic memory impairment in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*(2), 191−195.

Wilson, R. S., Schneider, J. A., Boyle, P. A., Arnold, S. E., Tang, Y., & Bennett, D. A. (2007). Chronic distress and incidence of mild cognitive impairment. *Neurology*, *68*(24), 2085−2092.

Wolkowitz, O. M., Epel, E. S., Reus, V. I., & Mellon, S. H. (2010). Depression gets old fast: Do stress and depression accelerate cell aging? *Depression and Anxiety*, *27*(4), 327−338.

Wong, J. D., & Shobo, Y. (2016). The influences of employment status and daily stressors on physiological functioning in a sample of midlife and older adults. *The International Journal of Aging and Human Development*, *83*(1), 26−43.

World Health Organization. (1995). The World Health Organization Quality of Life Assessment (WHOQOL): Position paper from the World Health Organization. *Social Science & Medicine*, *41*(10), 1403−1409.

World Health Organization. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychological Medicine*, *28*(3), 551−558.

World Health Organization. (2015). World report on ageing and health.

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T., et al. (2010). Posttraumatic stress disorder and risk of dementia among US veterans. *Archives of General Psychiatry*, *67*(6), 608−613.

Yoder, M. S., Lozano, B., Center, K. B., Miller, A., Acierno, R., & Tuerk, P. W. (2013). Effectiveness of prolonged exposure for PTSD in older veterans. *The International Journal of Psychiatry in Medicine*, *45*(2), 111−124.

Zannas, A. S. (2018). Gene-environment interactions in late life: Linking psychosocial stress with brain aging. *Current Neuropharmacology*, *16*(3), 327−333.

Zannas, A. S., McQuoid, D. R., Payne, M. E., Steffens, D. C., MacFall, J. R., Ashley-Koch, A., et al. (2013). Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression. *Journal of Psychiatric Research*, *47*(6), 829−834.

Zannas, A. S., McQuoid, D. R., Steffens, D. C., Chrousos, G. P., & Taylor, W. D. (2012). Stressful life events, perceived stress, and 12-month course of geriatric depression: Direct effects and moderation by the 5-HTTLPR and COMT Val158Met polymorphisms. *Stress*, *15*(4), 425−434.

Zimmerman, M. E., Ezzati, A., Katz, M. J., Lipton, M. L., Brickman, A. M., Sliwinski, M. J., et al. (2016). Perceived stress Is differentially related to hippocampal subfield volumes among older adults. *PLoS One*, *11*(5), e0154530.

Zuniga, K. E., Mackenzie, M. J., Kramer, A., & McAuley, E. (2016). Subjective memory impairment and well-being in community-dwelling older adults. *Psychogeriatrics*, *16*(1), 20−26.

Chapter 5

Structural changes in the aging brain

Meghan Riddle[1,2] **and Warren D. Taylor**[1,3]

[1]Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, United States, [2]Department of Psychiatry, University of Kentucky College of Medicine, Lexington, KY, United States, [3]Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, United States

Introduction

As in other developed nations, the United States will see a substantial increase in the proportion of elderly adults in the population. Largely due to aging of the baby boomer cohort, the population of elderly adults will almost double from 43.1 million in 2012 to an estimated population of 83.7 million in 2050 (Ortman, Velkoff, & Hogan, 2014). This demographic shift has significant implications for many areas including health care, where even if medicine can reduce the prevalence of disease states, the increased numbers of older adults may still result in increased number of disease cases. Most relevant to brain health are rates of dementia. These changes highlight the need for a better understanding of structural changes in the aging brain, how pathological changes diverge from normal aging, and highlight the need for better tools to apply scientific findings to the individual level.

There are at least two compelling and interrelated reasons to study brain structure in aging (Fjell & Walhovd, 2010). First, such work allow us to better understand how aging of the brain underlies cognitive aging, or changes in cognitive function and performance. Whether the changes in cognition may reflect shifts seen in normal aging (Park & Reuter-Lorenz, 2009) or whether they represent underlying neuropathology, we can better elucidate structural-functional relationships. This may be particularly important in the context of longitudinal studies where trajectories of change, both in cognition and in measures of brain structure, can be examined.

Second, it is important to distinguish "normal" brain aging patterns from pathological aging patterns seen in aging-related disorders such as Alzheimer's disease (AD). Significant efforts have been made to distinguish expected changes in the healthy aging brain from "abnormal" patterns consistent with disease states. Highly sophisticated neuroimaging modalities and automated image processing tools have revolutionized the ability to study the aging brain. It is now well accepted that even normally aging brains undergo structural changes in the absence of neurodegenerative disease. The ability to study how structural changes relate to cognitive changes in normal aging allows for the identification of abnormal changes associated with underlying neuropathology.

Current models of AD propose that structural changes occur after the development of neuropathology but before obvious cognitive symptoms (Jack et al., 2013). A better understanding of how and when brain aging diverges in normal aging compared with pathological states provides an opportunity for early detection and ultimately early intervention upon the development of disease-modifying therapeutics. Although such treatments are not currently available, findings that inform longer-term prognosis and diagnosis can still be highly valuable.

As individuals age, they experience changes in their cognitive abilities even in the absence of neurodegeneration, particularly in domains of executive function, processing speed, and episodic memory, while verbal abilities and knowledge are typically preserved (Park & Reuter-Lorenz, 2009). These cognitive changes are considered part of normal aging and may arise from underlying changes in the aging brain. With the advent of magnetic resonance imaging (MRI), people began to study if changes in cognitive performance were directly related to underlying structural changes in distinct brain regions (Andrews-Hanna et al., 2007).

Similar to observations in cognitive aging, evidence supports expected structural brain changes in normal aging as well, specifically reductions in regional volumes, thinning of the gray matter cortex, and expansion of ventricles (Fig. 5.1) (Driscoll et al., 2009; Salat et al., 2004; Scahill et al., 2003). The age-related structural changes visible on

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00005-3

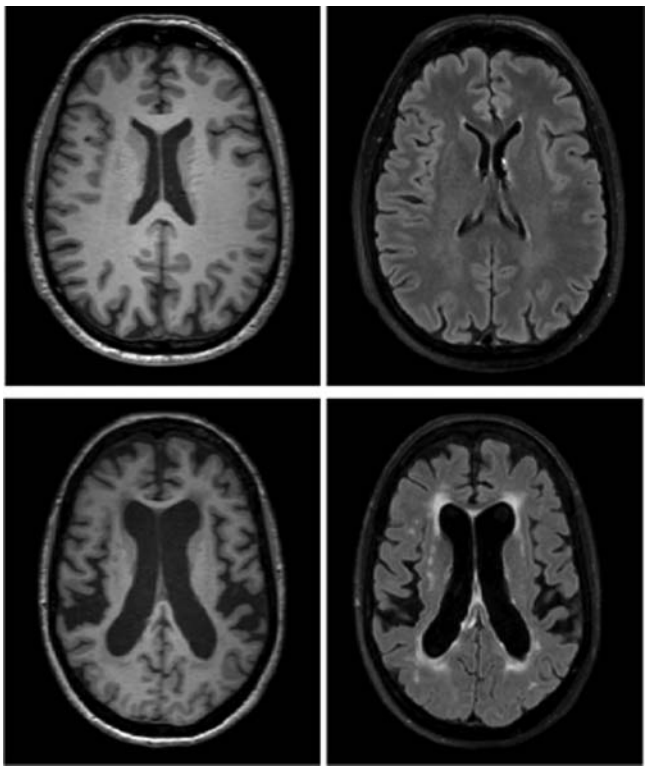


FIGURE 5.1 Examples of normal and accelerated brain aging. The MR images of older adults include a T1-weighted acquisition (left side) and a fluid-attenuated inversion recovery (FLAIR) acquisition (right side). The top images are of an individual with normal brain aging, while the bottom images are of an individual with accelerated brain aging. Specifically, the bottom image shows greater cortical atrophy and larger ventricles. The bottom image also shows greater severity of white matter hyperintensities, displayed as bright regions in the brain tissue on the FLAIR image.

MRI that occur with time may explain the cognitive decline seen in normal aging (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). There is additional evidence that volumetric changes of specific brain regions are related to decline in cognitive performance, so MRI-based volume measurements have been proposed as potential surrogate markers for disease diagnosis or progression. This may be particularly useful in early detection of dementia (Davatzikos, Fan, Wu, Shen, & Resnick, 2008; Driscoll et al., 2009).

When considering brain−cognition relationships, it is reasonable to start by examining cortical or subcortical gray matter regions. However, consideration should not be limited to gray matter regions, as early work proposed that cognitive decline in normal aging may be less related to significant neuronal loss in gray matter (Morrison & Hof, 1997), but rather changes in the white matter (Pakkenberg & Gundersen, 1997). In addition to aforementioned structural changes, disruptions in the structural and functional connections between coordinated brain systems have a prominent role in cognitive change. Known as the "disconnection hypothesis," damage to white matter tracts decreases white matter integrity, resulting in a reduction in connections and decreased efficiency of these systems, ultimately contributing to cognitive decline (O'Sullivan et al., 2001).

This chapter will review our understanding of normal brain aging in older adults, at times highlighting specific findings that may have diagnostic or prognostic value for neurodegenerative disorders. Over the last decade, our understanding of brain aging has improved in parallel with advances in neuroimaging and advanced automated tools for image analyses. While earlier approaches used time-intensive techniques to manually delineate brain regions to measure volumes, newer techniques utilize fully or partially automated processes to assess a wide range of metrics measuring brain structure. These techniques tend to be relatively distinct depending on whether the scientific focus is on either gray matter or white matter structure. Finally, we will briefly discuss new approaches and commercial software programs designed to translate neuroscience research into clinical neuroradiology.

Gray matter structure

Analyses of gray matter are clearly segregated into studies examining the cortex, subcortical gray matter structures such as hippocampus, amygdala, basal ganglia, and thalamus, or both. Early neuroimaging studies focused on regional volumes, typically examining specific *a priori* defined regions due to the time burden required to accurately and reproducibly identify each region. More recent studies mostly utilize automated processes that are faster and reliable, but are

dependent on clear demarcation of the boundary between white and gray matter. These approaches measure a wide range of brain regions and allow assessment of metrics beyond simple region volume, such as examining regional differences in cortical thickness. Such data are highly complementary and provide unique information.

Gray matter volumetry

Initial approaches utilizing MRI to examine structural changes in the aging brain focused on volumetric differences of brain regions. Early longitudinal brain imaging studies, including results from the Baltimore Longitudinal Study of Aging, found substantial decline in both gray and white matter volume with aging (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Gray matter volume begins to decrease early in life, although these changes are initially small and the rate of decline accelerates after the age of 50 years (DeCarli et al., 2005; Raz & Rodrigue, 2006). Chronological age has a powerful effect, accounting for approximately 50% of variation in total brain volume (DeCarli et al., 2005). However, there is substantial variability in the rate of volumetric change in different brain areas, with some brain structures exhibiting greater atrophy with age than others (Raz & Kennedy, 2009). Aging tends to overall result in greater gray matter loss in the cortex than in subcortical gray matter structures (Walhovd et al., 2005), with the hippocampus being an important exception.

There are a substantial number of both cross-sectional and longitudinal studies examining brain aging (Fjell & Walhovd, 2010). Most studies show that the largest gray matter volume reductions with aging occur in frontal regions (Raz et al., 1997; Resnick et al., 2003). In a cross-sectional analysis looking at gray and white matter volume, the greatest age-related volume difference was in the lateral prefrontal cortex, which declined linearly with age at a nearly 3% volume loss per decade (Brickman et al., 2005). These findings support a "last in, first out" hypothesis, which suggests the final brain areas to develop are the first to experience atrophy even in healthy aging. Neuropsychological data support this hypothesis. Executive function, a cognitive domain that depends upon intact frontal lobe functioning, is one of the domains most affected in aging (Fjell & Walhovd, 2010; Schretlen, Pearlson, Anthony, & Aylward, 2000).

Age-related atrophy is not restricted to the frontal lobes. Medial temporal lobe structures are also vulnerable to aging, with annual rates of atrophy ranging from 0.79% to 2.0% for the hippocampus and 0.3% to 2.4% for the entorhinal cortex (ERC, Fig. 5.2) (Du et al., 2006; Fjell et al., 2009; Raz et al., 2005). Both cross-sectional and longitudinal studies of brain structure volume across the life span show notable volume reduction in regions beyond the frontotemporal axis, including the caudate and cerebellum, with relative sparing of parietal, temporal, and occipital regions (Raz et al., 2005). Importantly, the literature is not always consistent across studies and may reflect differences in MRI acquisition or the methodology used to identify or define each region. However, such patterns are important as they can be used to distinguish normal brain aging from pathological neurodegenerative processes.

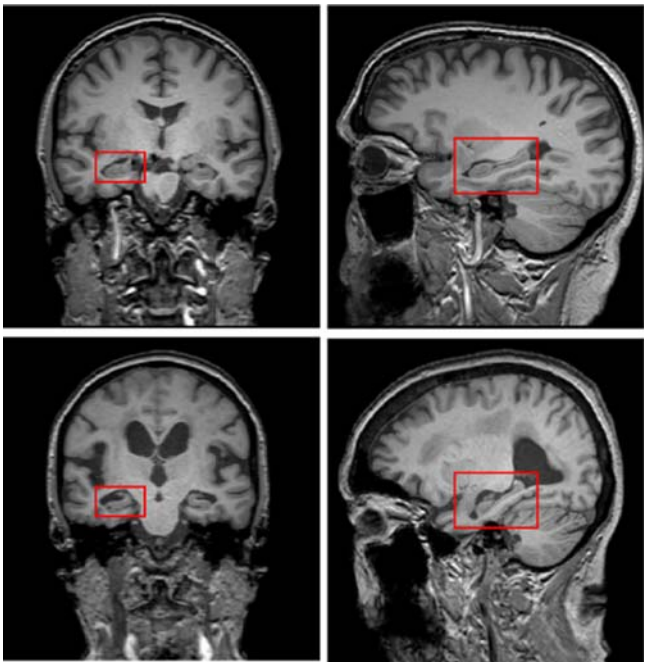


FIGURE 5.2 Examples of normal and accelerated hippocampal aging. These images show T1-weighted MRI, displaying both coronal orientation (left images) and sagittal orientation (right images). The hippocampus (boxed in all images) is larger in the top images. There is less cerebrospinal fluid (CSF), displayed as darker black regions, surrounding the hippocampus on the top images, supporting only slight atrophy. In contrast, in the bottom images, the hippocampus is more atrophic and there is more CSF surrounding the hippocampus. Notably, the bottom images also display enlarged ventricles.

Beyond the effects of age itself, age-related medical disorders also adversely affect brain aging. The best studied are vascular risk factors, including hypertension, cardiac disease, and diabetes. These conditions strongly affect cerebral volumes and rates of atrophy. Elevated blood pressure, even at the high end of the normal range, is associated with smaller regional brain volumes (Seshadri et al., 2004), and differences related to hypertension can be seen early in adulthood (Maillard et al., 2012). In cognitively normal populations, the effects of vascular risk factors on cerebral atrophy may be more common than atrophy due to developing AD (Nettiksimmons et al., 2013).

It is important to acknowledge that brain areas affected in normal aging are also some of the same areas affected early in neurodegenerative illnesses such as AD. However, the difference relies less on the location of atrophy and more on the degree and extent of atrophy. Atrophy is not a binary consideration and slight atrophy does not necessarily signify impending dementia, but the magnitude of atrophy in specific brain areas can be used to distinguish normal aging from AD. Even in precursor states to AD, such as mild cognitive impairment (MCI), rates of annual brain atrophy are several times higher than in normal aging, with further increases in atrophy associated with progression to an AD diagnosis (Fotenos, Snyder, Girton, Morris, & Buckner, 2005). Thus longitudinal assessment of change in brain structure may be more informative for prognosis than a cross-sectional assessment. In this context, significant work has identified the hippocampus as experiencing early and more extensive atrophy in individuals who ultimately progress to AD. These changes may occur after amyloid deposition but precede clinically evident changes in cognitive performance (Jack et al., 2013). Hippocampal atrophy has been identified as a biomarker for AD and often used for diagnosis and monitoring disease progression, as hippocampal volume has been found to correlate with severity of cognitive disorders (McDonald et al., 2012). It is important to recognize that the hippocampus does shrink with normal aging (Taylor et al., 2014), although not to the extent seen in dementia.

As proposed by Buckner (2004), normal aging may broadly be associated with frontal changes, while individuals exhibiting more severe declines in hippocampal and entorhinal volume with age are more likely to progress to dementia. MRI studies comparing hippocampal volume in patients with cognitive impairment to those with normal aging showed reduction in hippocampal volume by 15%−30% at the mild dementia stage of AD (van der Flier et al., 2005), and by 10%−15% in amnestic MCI (Shi, Liu, Zhou, Yu, & Jiang, 2009). Expanding on this work, a meta-analysis of hippocampal atrophy rates in AD versus healthy controls found the mean difference to be 3.33% (annual hippocampal atrophy rate 4.66% for AD subjects and 1.41% for healthy controls) (Barnes et al., 2009). One longitudinal study examined atrophy of the ERC between cognitively normal elders and those who progressed to AD, finding a greater rate of ERC atrophy in AD than in normal aging, but also reporting that ERC volumes shrink even in the cognitively normal group (Du et al., 2006). Such entorhinal and hippocampal volume decreases are clinically relevant and associated with clinical decline in memory performance (Rodrigue & Raz, 2004; Rosen, Prull, Gabrieli, Stoub, & O'Hara, 2003). Identifying spatial patterns of brain atrophy longitudinally can distinguish cognitively normal adults from those who go on to develop MCI or AD. In this light, structural neuroimaging can be used as a diagnostic tool for early diagnosis (Davatzikos et al., 2008).

Gray matter cortical thickness

A complementary approach to measures of regional volumes is to examine regional differences in the thickness of the cortical gray matter. This analytic approach measures the distance between the cortical surface and the boundary between gray and white matter, testing for differences on a voxel-by-voxel basis. As this depends on the quality of segmentation of white and gray matter, study results can vary due to methodological differences including variability in MRI acquisition. This approach has the advantage of not being confined to specific brain labeling atlases and can identify differences in cortical thickness cutting across traditional anatomic boundaries. As differences in cortical thickness are typically calculated in a voxel-by-voxel basis, statistical analysis tools are built into the image analysis software and can adjust for multiple comparisons.

Studies examining cortical thickness across the life span show global thinning by middle age, including thinning in the same regions where early volumetric changes are reported (Salat et al., 2004; van Velsen et al., 2013). Similar to volumetric studies, frontal and temporal lobes exhibit the most prominent reductions in cortical thickness with advanced age, although negative correlations between cortical thickness and age have been reported in all brain regions (Fjell et al., 2014). Thinning is particularly noticeable in superior and inferior frontal areas and medial and superior temporal areas, while relatively preserved in the anterior medial cortex, along with anterior cingulate cortex and inferior frontal regions (Fjell & Walhovd, 2010). The Alzheimer's Disease Neuroimaging Initiative found a roughly 0.5% annual change in cortical thickness of healthy elderly participants without a diagnosis of MCI or AD (Fjell et al., 2009). This rate of change is comparable to the approximately 0.5% annualized brain volume loss seen in healthy aging (Fotenos et al., 2005; Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012).

Although changes in regional brain volumes and cortical thickness are seen both in healthy aging and during the development of AD, changes in thickness are also more rapid and of a greater magnitude in neurodegenerative disorders. AD has a distinct pattern of thinning in the parietal cortex, hippocampus, and ERC. Particular attention has been paid to the temporal cortex as temporal lobe thinning is thought to be a surrogate marker for underlying hippocampal atrophy. Recent work has proposed that different patterns of cortical thickness loss may identify subpopulations of individuals with AD but with different clinical and neuropathological characteristics (Hwang et al., 2015; Möller et al., 2016).

Ventricular changes

While gray matter measures exhibit volume reductions and atrophy with aging, the ventricles enlarge with aging (Figs. 5.1 and 5.2). Such changes can be significant, with increases of 20% per decade (Kaye, DeCarli, Luxenberg, & Rapoport, 1992), a rate more rapid than the rate of brain tissue loss (Drachman, 2006). Although increasing ventricular volume is associated with aging and vascular disease, including frank infarcts, neuropathological studies demonstrate that greater changes in ventricular volume are also associated with greater severity of neurofibrillary tangles and neuritic plaques and a diagnosis of dementia (Erten-Lyons et al., 2013). However, others have found that in AD populations, greater ventricular expansion is less related to classical patterns of cortical and hippocampal volume loss, but more related to measures of white matter damage (Coutu, Goldblatt, Rosas, & Salat, 2016).

White matter structure

Although gray matter regions clearly play a critical role in brain function and cognitive processes, damage to or alterations in white matter also play a prominent role in brain aging and can negatively affect cognitive function. White matter is mostly occupied by glia cells and myelinated axons involved in the transmission of electrical signals to varying brain regions. Any damage to white matter integrity can lead to neurobehavioral and cognitive impairments (Bennett and Madden, 2014). Initial studies examining white matter structure focused primarily on white matter "lesions" or white matter hyperintensities (WMHs). With subsequent MRI technological advances, later work examined measures of white matter microstructure using diffusion tensor imaging (DTI).

White matter hyperintensities

With the advent and widespread application of MR neuroimaging, radiologists and clinicians had to deal with observations of incidental findings in the white matter. Initial reports described these as WMHs or "leukoencephalopathy" when more severe (Fig. 5.1). WMHs are areas of increased signal intensity appearing bright on T2-weighted or fluid-attenuated inversion recovery MRI images. They are believed to be indicative of white matter damage and thought to represent a neural insult, possibly from hypoperfusion or vascular pathology, trauma, inflammatory disease or demyelination, among other possibilities. In the elderly population, the presence of WMH is common in normal aging (Gunning-Dixon et al., 2009) but not static, as WMH volumes tend to increase over time (Taylor, Macfall, et al., 2003; Taylor, Steffens, et al., 2003). WMHs are not evenly distributed across brain regions and the majority of WMHs are typically located in the frontal and occipital lobes (Wen & Sachdev, 2004). Many studies further distinguish the location of WMH, distinguishing between WMHs that are periventricular and adjacent to the lateral ventricles or located in the deep white matter.

Assessment of WMH severity is an area that has clearly benefited from automated image processing tools. Early approaches to grading WMH severity either counted the number of WMH visible on MRI or visually graded severity of WMH based on classification systems, such as the Fazekas severity scale (Fazekas et al., 1988). More recent work has used the inherent difference in tissue contrast and WMH appearance across MR acquisitions to segment WMHs separately from gray or white matter, allowing for quantification of WMH volume. Although volumetric measures are more accurate, visual rating scales may have clinical utility in terms of classifying individuals as having higher or lower burdens of WMH disease.

As WMHs progress over time, increases in WMH severity are associated with and more common in advanced age (Awad, Spetzler, Hodak, Awad, & Carey, 1986). They are strongly associated with cerebrovascular risk factors including diabetes, cardiac disease, and hypertension (Longstreth et al., 1996; Taylor et al., 2005; Taylor, Macfall, et al., 2003; Taylor, Steffens, et al., 2003). Vascular processes often appear to play a significant role in their development, as white matter is sensitive to transient ischemia (Pantoni, Garcia, & Gutierrez, 1996) and many larger WMHs are ischemic in origin (Thomas, Perry, Barber, Kalaria, & O'Brien, 2002). Hypertension and blood pressure variability also

contributes to WMH development (Puisieux et al., 2001), particularly when accompanied by impaired cerebral vasomotor reactivity and altered autoregulatory processes (Bakker et al., 1999).

Greater WMH severity has functional consequences. Beyond an association with increased mortality (Debette & Markus, 2010; Ikram, Vernooij, Vrooman, Hofman, & Breteler, 2009) and functional decline (Salat, 2014), greater WMH severity is also associated with increased risk of stroke (Debette & Markus, 2010) and a range of cognitive, motor, and neuropsychiatric symptoms. Greater WMH severity in older adults is associated with poorer cognitive performance, particularly in domains of executive function, episodic memory, and processing speed (De Groot et al., 2002; Gunning-Dixon & Raz, 2000; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). Such cross-sectional findings are further supported by longitudinal reports of WMH progression paralleling cognitive decline (Longstreth et al., 2005; Marquine et al., 2010). WHMs are further associated with altered gait and balance (Baezner et al., 2008; Starr et al., 2003), and urinary incontinence and urgency (Kuchel et al., 2009). In geriatric psychiatry, WMHs are most closely associated with late-life depression and are a key radiological hallmark of vascular depression (Krishnan et al., 2004; Taylor, Aizenstein, & Alexopoulos, 2013). WMHs are more common and severe in older adults (Park et al., 2015; Taylor et al., 2005), associated with poor acute antidepressant responses (Sheline, Price, Yan, & Mintun, 2010), and greater long-term progression of WMH volumes are associated with poorer long-term depression course (Taylor, Macfall, et al., 2003; Taylor, Steffens, et al., 2003).

Other white matter vascular pathology

Beyond WMHs, clinical MRIs can reveal other measures of brain pathology located in the white matter. MRI infarcts, often referred to as "lacunar infarcts," are lesions in the brain parenchyma that have MRI characteristics of tissue infarction but are not associated with signs or symptoms of a stroke (Hachinski et al., 2006). Despite varying definitions of how they are defined, studies confirm age-related increases in the prevalence of MRI infarcts. These silent infarcts commonly cooccur with symptomatic and often larger infarcts and have the same vascular risk factors (Debette et al., 2010). Individuals with MRI infarcts tend to exhibit greater cerebral atrophy and their presence is a marker of increased risk for future stroke and dementia (Debette et al., 2010).

Cerebral microbleeds are small, punctate lesions with low signal intensity on T2-weighted MRI, appearing as small, dark regions. In neuropathology studies, these regions correspond to hemosiderin-laden macrophages in the perivascular tissue, a finding consistent with blood cell leakage (Fazekas et al., 1999). Their frequency increases from approximately 10% in health community samples, rising to 50% in individuals with a history of ischemic stroke (Takashima et al., 2011). Although their full clinical significance remains unclear, they may best be viewed as another measure of microvascular disease (Werring, Gregoire, & Cipolotti, 2010).

White matter structure—volumetric measures and diffusion tensor imaging

The earliest work examining the relationship between age and white matter focused on volumetric changes. Substantial work suggests that there is greater age-related loss of white matter volume than gray matter volume, and some individuals exhibit white matter volume loss in the absence of gray matter atrophy (Bartzokis et al., 2003; Guttmann et al., 1998; Resnick et al., 2003). For example, one group reported a 14% reduction in gray matter volume with aging across the adult life span, but a 26% reduction in white matter volume (Jernigan et al., 2001). However, others report the opposite (Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004) and propose that white matter loss may occur after gray matter volume loss. It is unclear how differences in image analysis methodologies may contribute to this apparent conflict.

Structural changes in white matter and the loss of integrity of white matter tracts are thought to contribute to age-related changes in cognitive performance, as the decrease in neuronal connectivity interferes with transmission of information and resultant cognitive decline (Albert, 1993). The development of DTI provided a way to assess such relationships by measuring white matter structural integrity using the magnitude and direction of water diffusion (Taylor, Hsu, Krishnan, & Macfall, 2004). Without the presence of structural barriers, diffusion is isotropic, or occurs equally in all directions. In contrast, when barriers are present, diffusion is anisotropic, or occurs in some directions preferentially to other directions, specifically following the long axis of those barriers. Thus this imaging modality is particularly useful for assessing the highly organized white matter structure that consists of axonal membranes, myelin sheaths, and discrete white matter fiber tracts. Several DTI-based metrics can be calculated. Fractional anisotropy (FA) is a commonly used measure that is a scalar value between zero and one and represents the degree of anisotropy in a region, with a measure of zero being perfectly isotropic and unrestricted diffusion. A higher FA value indicates greater diffusion along the primary axis. Several other DTI measures are also utilized, most notably radial diffusion, a measure of diffusion in

directions other than the main direction of diffusion. This has been proposed to represent the degree of myelination in white matter regions (Song et al., 2005). DTI data, when analyzed using advanced software techniques, can be used to reconstruct white matter fiber tracts and conduct tractography, or mapping structural connections between brain regions.

DTI has been widely used to examine which white matter regions are most susceptible to aging (Gunning-Dixon et al., 2009). One of the most consistent findings supports that frontal white matter is particularly sensitive to aging effects. Numerous aging studies report lower FA values in frontal white matter regions than in posterior white matter regions. This has been interpreted as an anterior-to-posterior gradient of vulnerability to disruption of the white matter microstructure or greater susceptibility of frontal (anterior) white matter to the effects of aging (O'Sullivan et al., 2001; Grieve, Williams, & Paul, 2007; Head et al., 2004; Salat, 2014). Similar findings are observed in the corpus callosum, the major commissure for cross-hemisphere communication, where injury or deficits may contribute to cognitive aging. Like findings in lobar studies, the corpus callosum also exhibits a gradient across anterior-to-posterior regions, where the genu and rostral body exhibit lower FA with aging, while posterior regions exhibit more stable FA values (Sullivan, Rohlfing, & Pfefferbaum, 2010). FA may be a sensitive marker of aging that precedes obvious atrophy (Hugenschmidt et al., 2008).

Such age-related changes in white matter microstructure may be greater or magnified in pathological aging and AD. Individuals with AD exhibit widespread differences in DTI measures not only across lobar regions but also in the cingulate gyrus and corpus callosum (Bozzali et al., 2002; Teipel, Walter, Likitjaroen, Schönknecht, & Gruber, 2014; Zhang et al., 2007). More subtle differences can be similarly observed in patients with MCI or cognitively healthy subjects at risk for AD, such as individuals who carry the primary genetic risk for AD, the apolipoprotein E epsilon 4 allele (Nierenberg et al., 2005; Zhang et al., 2007). Similarly, greater WMH severity is associated with altered DTI measures in the areas of hyperintensity itself and is also associated with lower FA in normal-appearing white matter (Taylor et al., 2001, 2007). This supports the observation that DTI measures detect white matter structural changes beyond what is observed with WMH volume alone.

Clinical translation and utility of neuroimaging data

Traditionally, data acquired from analyses of research scans inform us about the underlying disorders being studied, but are not easily applied to the clinic. In part, this is due to the complexity, time, and effort required to extract quantifiable data from MRI scans. It is further complicated by the challenges in how to interpret such data. There are currently efforts to simplify and automate these processes and, by utilizing large normative databases, provide useful interpretations of the quantified data. Such an approach, termed "Preventive Neuroradiology," aims to use quantifiable clinical neuroimaging data to provide critical prognostic information and ultimately guide treatment decisions (Raji et al., 2015).

Several groups are developing and marketing validated commercial software packages for clinical use, such as Neuroreader (Brainreader, Denmark) and NeuroQuant (CorTechs Labs, San Diego, California, United States). These packages are designed to conduct quick and focused analyses of clinical MRI data and provide quantitative results presented in context of normative data. For aging, given the relationship with dementia there is currently a focus on hippocampal volumes and ventricular volumes. Such tools provide information beyond what is offered in typical radiologist reports and so may provide novel information that can guide clinical diagnoses (Ross, Ochs, Seabaugh, & Shrader, 2013). Such approaches have the potential to improve clinical assessments and prognosis and have significant implications for AD clinical trial design. For example, use of such computational tools and a focus on biomarker assessment during screening could allow for more efficient identification and enrollment of at-risk populations into AD clinical trials (Yu et al., 2014). It is likely that in the next decade further software platforms will be developed and marketed, likely moving beyond isolated volumetric measures to also include more complex algorithms assessing volume loss, DTI, or resting-state functional MRI data.

References

Albert, M. (1993). Neuropsychological and neurophysiological changes in healthy adult humans across the age range. *Neurobiology of Aging*, *14*, 623–625.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924–935.

Awad, I. A., Spetzler, R. F., Hodak, J. A., Awad, C. A., & Carey, R. (1986). Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. *Stroke*, *17*, 1084–1089.

Baezner, H., Blahak, C., Poggesi, A., Pantoni, L., Inzitari, D., Chabriat, H., … Group, L. S. (2008). Association of gait and balance disorders with age-related white matter changes: The LADIS study. *Neurology*, *70*, 935–942.

Bakker, S. L., de Leeuw, F. E., de Groot, J. C., Hofman, A., Koudstaal, P. J., & Breteler, M. M. (1999). Cerebral vasomotor reactivity and cerebral white matter lesions in the elderly. *Neurology*, *52*, 578–583.

Barnes, J., Bartlett, J. W., van de Pol, L. A., Loy, C. T., Scahill, R. I., Frost, C., … Fox, N. C. (2009). A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiology of Aging*, *30*, 1711–1723.

Bartzokis, G., Cummings, J. L., Sultzer, D., Henderson, V. W., Nuechterlein, K. H., & Mintz, J. (2003). White matter structural integrity in healthy aging adults and patients with Alzheimer disease: A magnetic resonance imaging study. *Archives of Neurology*, *60*, 393–398. Available from https://doi.org/10.1001/archneur.60.3.393.

Bennett, I.J., & Madden, D.J. (2014). Disconnected aging: cerebral white matter integrity and age-related differences in cognition. *Neuroscience*, *276*, 187–205.

Bozzali, M., Falini, A., Franceschi, M., Cercignani, M., Zuffi, M., Scotti, G., … Filippi, M. (2002). White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. *Journal of Neurology, Neurosurgery and Psychiatry*, *72*, 742–746. Available from https://doi.org/10.1136/jnnp.72.6.742.

Brickman, A. M., Paul, R. H., Cohen, R. A., Williams, L. M., MacGregor, K. L., Jefferson, A. L., … Gordon, E. (2005). Category and letter verbal fluency across the adult lifespan: Relationship to EEG theta power. *Archives of Clinical Neuropsychology*, *20*, 561–573.

Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*(1), 195–208.

Coutu, J.-P., Goldblatt, A., Rosas, H. D., & Salat, D. H. (2016). White matter changes are associated with ventricular expansion in aging, mild cognitive impairment, and Alzheimer's disease. *Journal of Alzheimer's Disease*, *49*, 329–342. Available from https://doi.org/10.3233/JAD-150306.

Davatzikos, C., Fan, Y., Wu, X., Shen, D., & Resnick, S. M. (2008). Detection of prodromal Alzheimer's disease via pattern classification of MRI. *Neurobiology of Aging*, *29*, 514–523.

Debette, S., Beiser, A., Decarli, C., Au, R., Himali, J. J., Kelly-Hayes, M., … Seshadri, S. (2010). Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: The Framingham offspring study. *Stroke*, *41*, 600–606. Available from https://doi.org/10.1161/STROKEAHA.109.570044.

Debette, S., & Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *British Medical Journal*, *341*, 1–9. Available from https://doi.org/10.1136/bmj.c3666.

DeCarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., … Wolf, P. A. (2005). Measures of brain morphology and infarction in the Framingham heart study: Establishing what is normal. *Neurobiology of Aging*, *26*, 491–510. Available from https://doi.org/10.1016/j.neurobiolaging.2004.05.004.

De Groot, J. C., De Leeuw, F.-E., Oudkerk, M., Van Gijn, J., Hofman, A., Jolles, J., & Breteler, M. M. B. (2002). Periventricular cerebral white matter lesions predict rate of cognitive decline. *Annals of Neurology*, *52*, 335–341. Available from https://doi.org/10.1002/ana.10294.

Drachman, D. A. (2006). Aging of the brain, entropy, and Alzheimer disease. *Neurology*, *67*(8), 1340–1352. Available from https://doi.org/10.1212/01.wnl.0000240127.89601.83.

Driscoll, I., Davatzikos, C., An, Y., Wu, X., Shen, D., Kraut, M., & Resnick, S. M. (2009). Longitudinal pattern of regional brain volume change differentiates normal aging form MCI. *Neurology*, *72*, 1906–1913.

Du, A. T., Schuff, N., Chao, L. L., Kornak, J., Jagust, W. J., Kramer, J. H., … Weiner, M. W. (2006). Age effects on atrophy rates of entorhinal cortex and hippocampus. *Neurobiology of Aging*, *27*, 733–740.

Erten-Lyons, D., Dodge, H. H., Woltjer, R., Silbert, L. C., Howieson, D. B., Kramer, P., & Kaye, J. A. (2013). Neuropathologic basis of age-associated brain atrophy. *JAMA Neurology*, *70*, 616. Available from https://doi.org/10.1001/jamaneurol.2013.1957.

Fazekas, F., Kleinert, R., Roob, G., Kleinert, G., Kapeller, P., Schmidt, R., & Hartung, H. P. (1999). Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy-related microbleeds. *American Journal of Neuroradiology*, *20*, 637–642. Available from https://doi.org/10.1016/S1471-4906(01)02051-8.

Fazekas, F., Niederkor, K., Schmidt, R., Offenbacher, H., Honner, S., Bertha, G., et al. (1988). White matter signal abnormalities in normal individuals: Correlation with carotid ultrasonagraphy, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke*, *19*, 1285–1288.

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, *21*, 187–221.

Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., … Dale, A. M. (2009). One-year brain atrophy evident in healthy aging. *Journal of Neuroscience*, *29*, 15223–15231. Available from https://doi.org/10.1523/JNEUROSCI.3252-09.2009.

Fjell, A. M., Westlye, L. T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I., … Walhovd, K. B. (2014). Accelerating cortical thinning: Unique to dementia or universal in aging? *Cerebral Cortex*, *24*, 919–934.

Fotenos, A. F., Snyder, A. Z., Girton, L. E., Morris, J. C., & Buckner, R. L. (2005). Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. *Neurology*, *64*, 1032–1039. Available from https://doi.org/10.1212/01.WNL.0000154530.72969.11.

Grieve, S. M., Williams, L. M., & Paul, R. H. (2007). Cognitive aging, executive function, and fractional anisotropy: A diffusion tensor MR imaging study. *American Journal of Neuroradiology*, *28*, 226–235.

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: A review of MRI findings. *International Journal of Geriatric Psychiatry*, *24*, 109–117. Available from https://doi.org/10.1002/gps.2087.

Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, *14*, 224–232.

Guttmann, C. R. G., Jolesz, F. A., Kikinis, R., Killiany, R. J., Moss, M. B., Sandor, T., & Albert, M. S. (1998). White matter changes with normal aging. *Neurology*, *50*, 972–978. Available from https://doi.org/10.1212/WNL.50.4.972.

Hachinski, V., Iadecola, C., Petersen, R. C., Breteler, M. M., Nyenhuis, D. L., Black, S. E., … Leblanc, G. G. (2006). National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke*, *37*, 2220–2241. Available from https://doi.org/10.1161/01.STR.0000237236.88823.47.

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., … Snyder, A. Z. (2004). Differential vulnerability of anterior white matter in non-demented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex*, *14*(4), 410–423.

Hedman, A. M., van Haren, N. E. M., Schnack, H. G., Kahn, R. S., & Hulshoff Pol, H. E. (2012). Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Human Brain Mapping*, *33*, 1987–2002. Available from https://doi.org/10.1002/hbm.21334.

Hugenschmidt, C. E., Peiffer, A. M., Kraft, R. A., Casanova, R., Deibler, A. R., Burdette, J. H., … Laurienti, P. J. (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cerebral Cortex*, *18*, 433–442. Available from https://doi.org/10.1093/cercor/bhm080.

Hwang, J., Kim, C. M., Jeon, S., Lee, J. M., Hong, Y. J., Roh, J. H., … Alzheimer's Disease Neuroimaging Initiative. (2015). Prediction of Alzheimer's disease pathophysiology based on cortical thickness patterns. *Alzheimers Dementia (Amsterdam, Netherlands)*, *2*, 58–67.

Ikram, M. A., Vernooij, M. W., Vrooman, H. A., Hofman, A., & Breteler, M. M. (2009). Brain tissue volumes and small vessel disease in relation to the risk of mortality. *Neurobiology of Aging*, *30*, 450–456.

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., … Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurology*, *12*, 207–216. Available from https://doi.org/10.1016/S1474-4422(12)70291-0.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., & Hesselink, J. R. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging*, *22*, 581–594. Available from https://doi.org/10.1016/S0197-4580(01)00217-2.

Kaye, J., DeCarli, C., Luxenberg, J., & Rapoport, S. (1992). The significance of age-related enlargement of the cerebral ventricles in healthy men and women measured by quantitative computed X-ray tomography. *Journal of American Geriatric Society*, *40*, 225–231.

Krishnan, K. R. R., Taylor, W. D., Mcquoid, D. R., Macfall, J. R., Payne, M. E., Provenzale, J. M., & Steffens, D. C. (2004). Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biological Psychiatry*, *55*, 390–397. Available from https://doi.org/10.1016/j.biopsych.2003.08.014.

Kuchel, G. A., Moscufo, N., Guttmann, C. R., Zeevi, N., Wakefield, D., Schmidt, J., … Wofson, L. (2009). Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. *Journal of Gerontology and Biological Sciences*, *64*, 902–909.

Longstreth, W. T., Arnold, A. M., Beauchamp, N. J., Manolio, T. A., Lefkowitz, D., Jungreis, C., … Furberg, C. D. (2005). Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The Cardiovascular Health Study. *Stroke*, *36*, 56–61. Available from https://doi.org/10.1161/01.STR.0000149625.99732.69.

Longstreth, W. T., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., & Jungreis, C. A. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The cardiovascular health study. *Stroke*, *27*, 1274–1282.

Maillard, P., Seshadri, S., Beiser, A., Himali, J. J., Au, R., Fletcher, E., … DeCarli, C. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: A cross-sectional study. *Lancet Neurology*, *11*, 1039–1047. Available from https://doi.org/10.1016/S1474-4422(12)70241-7.

Marquine, M. J., Attix, D. K., Goldstein, L. B., Samsa, G. P., Payne, E., Chelune, G. J., & Steffens, D. C. (2010). Differential patterns of cognitive decline in anterior and posterior white matter hyperintensity progression. *Stroke*, *41*, 1946–1950. Available from https://doi.org/10.1161/STROKEAHA.110.587717.

McDonald, C. R., Gharapetian, L., McEvoy, L. K., Fennema-Notestine, C., Hagler, D. J., Holland, D., … Alzheimer's Disease Neuroimaging Initiative. (2012). Relationship between regional atrophy rates and cognitive decline in mild cognitive impairment. *Neurobiology of Aging*, *33*, 242–253.

Möller, C., Hafkemeijer, A., Pijnenburg, Y. A., Rombouts, S. A., van der Grond, J., Dopper, E., … van der Flier, W. M. (2016). Different patterns of cortical gray matter loss over time in behavioral variant frontotemporal dementia and Alzheimer's disease. *Neurobiology of Aging*, *38*, 21–31.

Morrison, J. H., & Hof, P. R. (1997). Life and death of neurons in the aging brain. *Science*, *278*, 412–419.

Nettiksimmons, J., Beckett, L., Schwarz, C., Carmichael, O., Fletcher, E., & Decarli, C. (2013). Subgroup of ADNI normal controls characterized by atrophy and cognitive decline associated with vascular damage. *Psychology and Aging*, *28*, 191–201. Available from https://doi.org/10.1037/a0031063.

Nierenberg, J., Pomara, N., Hoptman, M. J., Sidtis, J. J., Ardekani, B. A., & Lim, K. O. (2005). Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. *Neuroreport*, *16*, 1369–1372. Available from https://doi.org/00001756-200508220-00022.

Ortman, J. M., Velkoff, V. A., & Hogan, H. (2014). *An aging nation: The older population in the United States. Population estimates and projections* (pp. P25–1140). Washington, DC: US Census Bureau.

O'Sullivan, M., Summers, P. E., Jones, D. K., Jarosz, J. M., Williams, S. C., & Markus, H. S. (2001). Normal-appearing white matter in ischemic leukoaraiosis: A diffusion tensor MRI study. *Neurology*, *57*, 2307–2310.

Pakkenberg, B., & Gundersen, H. J. (1997). Neocortical neuron number in humans: Effect of sex and age. *Journal of Comparative Neurology*, *384*, 312–320.

Pantoni, L., Garcia, J. H., & Gutierrez, J. A. (1996). Cerebral white matter is highly vulnerable to ischemia. *Stroke*, *27*, 1641–1646.

Park, J. H., Lee, S. B., Lee, J. J., Yoon, J. C., Han, J. W., Kim, T. H., … Kim, K. W. (2015). Epidemiology of MRI-defined vascular depression: A longitudinal, community-based study in Korean elders. *Journal of Affective Disorders*, *180*, 200–206. Available from https://doi.org/10.1016/j.jad.2015.04.008.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. Available from https://doi.org/10.1146/annurev.psych.59.103006.093656.

Puisieux, F., Monaca, P., Deplanque, D., Delmaire, C., di Pompeo, C., & Monaca, C. (2001). Relationship between leuko-araiosis and blood pressure variability in the elderly. *European Neurology*, *46*, 115–120.

Raji, C. A., Eyre, H., Wei, S. H., Bredesen, D. E., Moylan, S., Law, M., … Vernooij, M. W. (2015). Hot topics in research: Preventive neuroradiology in brain aging and cognitive decline. *American Journal of Neuroradiology*, *36*, 1803–1809. Available from https://doi.org/10.3174/ajnr.A4409.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., … Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*, *7*, 268–282.

Raz, N., & Kennedy, K. (2009). *A systems approach to age-related change: Neuroanatomical changes, their modifiers, and cognitive correlates. Imaging the aging brain.* (pp. 43–70). New York, NY: Oxford University Press.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*, 1676–1689.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews*, *30*, 730–748.

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *Journal of Neuroscience*, *23*(8), 3295–3301.

Rodrigue, K. M., & Raz, N. (2004). Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *Journal of Neuroscience*, *24*(4), 956–963.

Rosen, A. C., Prull, M. W., Gabrieli, J. D., Stoub, T., & O'Hara, R. (2003). Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. *Behavioral Neuroscience*, *117*(6), 1150–1160.

Ross, D. E., Ochs, A. L., Seabaugh, J. M., & Shrader, C. R. (2013). Man versus machine: Comparison of radiologists' interpretations and NeuroQuant® volumetric analyses of brain MRIs in patients with traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*, 32–39. Available from https://doi.org/10.1176/appi.neuropsych.11120377.

Salat, D. H. (2014). Imaging small vessel-associated white matter changes in aging. *Neuroscience*, 174–186.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., … Fischl, B. (2004). Thinning of cerebral cortex in aging. *Cerebral Cortex*, *14*, 721–730.

Scahill, C., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., & Fox, N. C. (2003). A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archives of Neurology*, *60*, 989–994.

Schretlen, D., Pearlson, G. D., Anthony, J. C., & Aylward, E. H. (2000). Elucidating the contributions of processing speed, executive ability, and frontal lobe volume to normal age-related differences in fluid intelligence. *Journal of the International Neuropsychological Society*, *6*, 52–61.

Seshadri, S., Wolf, P. A., Beiser, A., Elias, M. F., Au, R., Kase, C. S., … DeCarli, C. (2004). Stroke risk profile, brain volume, and cognitive function: The Framingham Offspring Study. *Neurology*, *63*, 1591–1599. Available from https://doi.org/10.1212/01.WNL.0000142968.22691.70.

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 11020–11025. Available from https://doi.org/10.1073/pnas.1000446107.

Shi, F., Liu, B., Zhou, Y., Yu, C., & Jiang, T. (2009). Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus*, *19*, 1055–1064.

Song, S. K., Yushino, J., Le, T. Q., Lin, S. J., Sun, S. W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, *26*(1), 132–140.

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., & Whalley, L. J. (2003). Brain white matter lesions detected by magnetic resonance [correction of resonance] imaging are associated with balance and gait speed. *Journal of Neurology, Neurosurgery and Psychiatry*, *74*, 94–98.

Sullivan, E. V., Rohlfing, T., & Pfefferbaum, A. (2010). Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Developmental Neuropsychology*, *35*, 233–256. Available from https://doi.org/10.1080/87565641003689556.

Sullivan, E. V., Rosenbloom, M., Serventi, K. L., & Pfefferbaum, A. (2004). Effects of age and sex on volumes of the thalamus, pons, and cortex. *Neurobiology of Aging*, *25*, 185–192. Available from https://doi.org/10.1016/S0197-4580(03)00044-7.

Takashima, Y., Mori, T., Hashimoto, M., Kinukawa, N., Uchino, A., Yuzuriha, T., & Yao, H. (2011). Clinical correlating factors and cognitive function in community-dwelling healthy subjects with cerebral microbleeds. *Journal of Stroke & Cerebrovascular Disease*, *20*, 105–110. Available from https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.11.007.

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*, 963–974. Available from https://doi.org/10.1038/mp.2013.20.

Taylor, W. D., Bae, J. N., MacFall, J. R., Payne, M. E., Provenzale, J. M., Steffens, D. C., & Krishnan, K. R. R. (2007). Widespread effects of hyperintense lesions on cerebral white matter structure. *American Journal of Roentgenology*, *188*, 1695–1704. Available from https://doi.org/10.2214/AJR.06.1163.

Taylor, W. D., Hsu, E., Krishnan, K. R. R., & Macfall, J. R. (2004). Diffusion tensor imaging: Background, potential, and utility in psychiatric research. *Biological Psychiatry*, *55*, 201–207. Available from https://doi.org/10.1016/S0006-3223(03)00813-8.

Taylor, W. D., MacFall, J. R., Payne, M. E., McQuoid, D. R., Steffens, D. C., Provenzale, J. M., & Krishnan, R. R. (2005). Greater MRI lesion volumes in elderly depressed subjects than in control subjects. *Psychiatry Research: Neuroimaging*, *139*, 1–7.

Taylor, W. D., Macfall, J. R., Provenzale, J. M., Payne, M. E., Mcquoid, D. R., Steffens, D. C., & Krishnan, K. R. R. (2003). Serial MR imaging of volumes of hyperintense white matter lesions in elderly patients : Correlation with vascular risk factors. *American Journal of Roentgenology*, *181*, 571–576.

Taylor, W. D., Payne, M. E., Krishnan, K., Wagner, H. R., Provenzale, J. M., Steffens, D. C., & MacFall, J. R. (2001). Evidence of white matter tract disruption in MRI hyperintensities. *Biological Psychiatry*, *50*, 179–183.

Taylor, J. L., Scanlon, B. K., Farrell, M., Hernandez, B., Adamson, M. M., Ashford, J. W., ... Weiner, M. W. (2014). APOE-epsilon4 and aging of medial temporal lobe gray matter in healthy adults older than 50 years. *Neurobiology of Aging*, *35*, 2479–2485. Available from https://doi.org/10.1016/j.neurobiolaging.2014.05.011.

Taylor, W. D., Steffens, D. C., MacFall, J., McQuoid, D., Payne, M. E., Provenzale, J. M., & Krishnan, R. R. (2003). White matter hyperintensity progression and late-life depression outcomes. *Archives of General Psychiatry*, *60*, 1090–1096.

Teipel, S. J., Walter, M., Likitjaroen, Y., Schönknecht, P., & Gruber, O. (2014). Diffusion tensor imaging in Alzheimer's disease and affective disorders. *European Archives of Psychiatry and Clinical Neuroscience*, *264*, 467–483. Available from https://doi.org/10.1007/s00406-014-0496-6.

Thomas, A., Perry, R., Barber, R., Kalaria, R. N., & O'Brien, J. T. (2002). Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Annals of the New York Academy of Sciences*, *977*, 333–339.

van der Flier, W. M., van Straaten, E. C., Barkhof, F., Ferro, J. M., Pantoni, L., Basile, A. M., ... LADIS study group. (2005). Medial temporal lobe atrophy and white matter hyperintensities are associated with mild cognitive deficits in nondisabled elderly people: The LADIS study. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*, 1497–1500.

Vannorsdall, T. D., Waldstein, S. R., Kraut, M., Pearlson, G. D., & Schretlen, D. J. (2009). White matter abnormalities and cognition in a community sample. *Archives of Clinical Neuropsychology*, *24*, 209–217. Available from https://doi.org/10.1093/arclin/acp037.

van Velsen, E. F. S., Vernooij, M. W., Vrooman, H. A., van der Lugt, A., Breteler, M. M. B., Hofman, A., ... Ikram, M. A. (2013). Brain cortical thickness in the general elderly population: The Rotterdam Scan Study. *Neuroscience Letters*, *550*, 189–194. Available from https://doi.org/10.1016/j.neulet.2013.06.063.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Dale, A. M., Eilertsen, D. E., ... Fischl, B. (2005). Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiology of Aging*, *26*, 1261–1270. Available from https://doi.org/10.1016/j.neurobiolaging.2005.05.020.

Wen, W., & Sachdev, P. (2004). The topography of white matter hyperintensities on brain MRI in healthy 60-to-64-year-old individuals. *NeuroImage*, *22*(1), 144–154.

Werring, D. J., Gregoire, S. M., & Cipolotti, L. (2010). Cerebral microbleeds and vascular cognitive impairment. *Journal of the Neurological Sciences*, *299*, 131–135. Available from https://doi.org/10.1016/j.jns.2010.08.034.

Yu, P., Sun, J., Wolz, R., Stephenson, D., Brewer, J., Fox, N. C., ... Schwarz, A. J. (2014). Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: Effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size. *Neurobiology of Aging*, *35*, 808–818. Available from https://doi.org/10.1016/j.neurobiolaging.2013.09.039.

Zhang, Y., Schuff, N., Jahng, G.-H., Bayne, W., Mori, S., Schad, L., ... einer, M. W. (2007). Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology*, *68*, 13–19. Available from https://doi.org/10.1212/01.wnl.0000250326.77323.

This page intentionally left blank

Chapter 6

Sleep-dependent cellular chemical changes in the aging brain

Gordon X. Wang[1,2] and Philippe Mourrain[1,2]

[1]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States,* [2]*Beckman Center, Stanford University School of Medicine, Stanford, CA, United States*

Introduction

Sleep quality appears to change dramatically from young to older adults. Sleep becomes more fragmented (i.e., frequent awakenings) (Bonnet & Rosa, 1987; Cabeza, Nyberg, & Park, 2016; Scullin & Bliwise, 2015), and there is a decline in the quantity and quality of the "deep" non-REM sleep (Kawai et al., 2016; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). However, the molecular framework underpinning the link of sleep to cognitive aging is currently unknown. Likely, aging and sleep impact the totality of the brain that included signaling and metabolism of neurons, glia, vasculature, glymphatic and immune systems. However, all those molecular systems, to affect cognition, must interrupt at some point the function of synaptic networks. Thus, synaptic function potentially represents the singular molecular framework that intersects the impact of sleep and aging across all nodes of brain function. Synaptic network function is fundamental to proper cognitive performance. Degradation of synaptic function can occur through direct molecular perturbation of specific synaptic systems through cellular or local micro-environmental changes (amyloid buildup, cellular stress) or through global brain level changes such as body metabolism or oxygenation (sleep-disturbed breathing).

Both local and global mechanisms likely act through changes in molecular mechanisms spread across neurons and glia that access molecular mechanisms within synapses. These changes in turn affect the fidelity, reliability, and timing of the synaptic networks and thus influence brain function. Robust timing and synchrony of neural networks are integral to the functional plasticity of the brain. Aging and sleep likely represent two parallel organismal processes that directly influence the efficiency and fidelity of the synaptic network through plasticity. Sleep, in this context, is a necessary neurological state that facilitates the modulation and homeostasis of molecular networks that prime information flow and retention through the optimization of synaptic activity. Aging, on the other hand, is a progressive, accumulative modification by environmental and genetic effectors of the molecular circuitry in the brain that can dysregulate necessary processes that facilitate optimal brain functioning. In this perspective, we will describe how during aging abnormal sleep may affect intra- and extracellular mechanisms critical for neuronal homeostasis and survival, as well as synaptic plasticity and maintenance of synaptic network efficiency.

Plasticity, synapses, aging, and sleep

Sleep and aging represent two parallel processes that influence the efficiency and fidelity of the synaptic network. Sleep, on the one hand, is a neurological state that facilitates the modulation and homeostasis of molecular networks. These molecular networks support information flow and retention by optimizing synaptic activity. Aging, on the other hand, is a progressive, cumulative modification of the molecular circuitry in the brain, which occurs via environmental and genetic influences. This modification of the brain's molecular circuitry can dysregulate processes necessary for optimal brain functioning. One way that age-related sleep abnormalities might affect brain function is by degrading intra- and extracellular mechanisms critical for synaptic plasticity. Plasticity, the functional modification of neural network, is fundamental to the operation of all aspects of cognitive function. From executive processes to attention to

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00006-5

memory, the fundamental synaptic processes are similar, but their context changes due to different engaged brain regions and varying connectivity statistics between varying neuronal cell types. Plasticity is not a unitary process, it can vary by synaptic type and the molecular effectors of this plasticity can vary depending on cell type and local environment. However, canonical understanding of all network plasticity follow the same arc, from short term (molecular state changes) to long term (structural changes). Short-term changes are initiated by dynamic molecular interactions that are both direct (phosphorylation) and indirect (modification of ionic driving force by the activation of multiple channels). These short-term changes can drive longer-term changes that range from changing receptor profiles or numbers in the synapse to the actual growth and rewiring of the neural network itself (e.g., through dendritic growth or pruning). Both sleep and aging have shown to affect both short- and long-term plasticity; however, the molecular mechanisms by which they drive these changes are only beginning to be illuminated.

Structural plasticity of synapses appears to be a critical aspect of sleep-mediated synaptic circuit optimization and is likely a contributor to age-mediated changes in the brain. Advances in in vivo live imaging have facilitated longitudinal analyses of neuronal projections and identified sleep-dependent structural synaptic changes. Imaging of fly, zebrafish, and mouse nervous systems has revealed a decrease in pre- and postsynaptic boutons during a full night of sleep (Wang, Grone, Colas, Appelbaum, & Mourrain, 2011). Furthermore, recent studies have identified nonrapid eye movement (NREM) sleep-specific changes in postsynaptic spines of the mouse motor cortex demonstrating that different features or stages of sleep architecture may differentially impact structural synaptic plasticity (Li, Ma, Yang, & Gan, 2017). Looking at dendritic spine formation of layer 5 pyramidal neurons in the motor cortex, it was observed that NREM sleep is involved in forming new synapses after motor learning. Normal aging does not appear to incur substantial loss of neurons in most brain regions studied in animals and humans (Hara, Rapp, & Morrison, 2012; Young, Ohm, Dumitriu, Rapp, & Morrison, 2014). However, synapse density shows variable vulnerability to aging that is region- and type-dependent. In monkeys, electron microscopy (EM) synapse measurements within the dorsal lateral prefrontal cortex showed a 30% decrease in excitatory and inhibitory synapses in layers II/III that correlates with decreased performance in cognitive tests (Peters, Sethares, & Luebke, 2008). Similarly, EM analysis of aging rats showed significant age-related losses of synapses in parts of the dentate gyrus and CA3 region that correlated with reduced memory performance, while synapse density does not change with aging in the CA1 regions (Hara et al., 2012; Petralia, Mattson, & Yao, 2014). Recent two-photon imaging studies reveal that dendritic spines are smaller and less stable in older (2-year-old) mice (Grillo et al., 2013; Mostany et al., 2013). Although this decrease in stability did not affect spine density on the apical dendrites of pyramidal neurons in the somatosensory cortex (Mostany et al., 2013).

Structural plasticity of synapses appears to be a critical aspect of sleep-mediated synaptic circuit optimization and is likely a contributor to age-mediated changes in the brain. However, the shared molecular actors in synaptic plasticity during sleep and aging remain mostly unknown. Defining these unknown actors will likely be the area of study that will generate the most impact in tackling cognitive issues arising from sleep loss and aging in the near future. While molecular screens should be carried out to identify novel molecular interlinks between sleep and aging, two well-known proteins amyloid beta (Aβ) and Fragile X mental retardation protein (FMRP) are known to be important in synaptic plasticity, sleep, and aging. They could represent starting points for a more targeted analysis of the synaptic interaction of sleep and aging. Moreover, these molecules could represent the most tractable near-term targets with immediate impact for understanding both the normal function and pathologies in both sleep and aging.

Amyloid beta and the Fragile X mental retardation protein

Aβ is a molecule with a storied history in aging and neurodegeneration research. While its function and mechanistic role in aging and neurodegeneration remains debated, current research into its role at synapses provide clear evidence that its production responds to neural activity and it plays a modulating role in synaptic plasticity (Hu et al., 2014; Li et al., 2009; Parihar & Brewer, 2010; Rowan, Klyubin, Wang, & Anwyl, 2005; Shankar et al., 2008; Snyder et al., 2005). Specifically, Aβ appears to block long-term potentiation (LTP) of synapses and facilitate long-term depression (LTD) of synapses (Li et al., 2009; Shankar et al., 2008). LTP and LTD work to strengthen and weaken synaptic linkages, respectively, during the course of normal brain function, and the synaptic strength changes they produce, if salient, lead to structural change and modifications of the network topography of the brain. Cortical Aβ levels also appear to increase during sleep deprivation (Shokri-Kojori et al., 2018) and sleep appears to decrease overall cortical Aβ levels through glymphatic flow (Xie et al., 2013) (as discussed further below). Furthermore, while Aβ buildup in the brain is well documented in normal aging (Fukumoto et al., 1996; Piccini et al., 2005), chronic sleep disturbance is often a precursor to clinical onset of Alzheimer's disease (AD) and increased Aβ plaque formation (Cardinali, Furio, & Brusco, 2010; Daulatzai, 2010; Musiek, Xiong, & Holtzman, 2015). This suggests that there is a link between neural

mechanisms of sleep and Aβ pathology. Whether Aβ plaques are symptomatic or causal of Alzheimer's remains uncertain, but the role of Aβ in synaptic plasticity cannot be ignored. Independent of plaque formation, increased Aβ load due to sleep disturbances could contribute to both neural circuit and behavioral changes that feed further degradation of sleep patterns and increased cognitive stress. This vicious circle could ultimately undo the homeostatic set points of the neural networks and drive the system toward atrophy and degeneration. Much work remains to be done to validate this hypothesis, but if it is Aβ itself and not the Aβ plaques that are indicative of neural degeneration, it would suggest that clearing the brain of Aβ, perhaps during sleep, when initial sleep disturbances arise could be a successful therapeutic intervention in neurodegeneration.

FMRP is a RNA regulator at the synapse (Ascano et al., 2012; Brown et al., 2001). The loss of FMRP is the hallmark of Fragile X syndrome, which is highly comorbid with sleep disturbances (Bechara et al., 2009; Won et al., 2017). The loss of Drosophila FMRP causes increased sleep and the loss of sleep rebound after sleep deprivation (Bushey, Tononi, & Cirelli, 2009). In mice, FMRP loss causes reduced free-running activity during wake (Zhang et al., 2008). Interestingly, FMRP is also a known regulator of Aβ (Westmark & Malter, 2007). The loss of FMRP causes the increased production of amyloid precursor protein (APP) and Aβ and reduces the activity dependence of APP production (Westmark & Malter, 2007). A recent study of the soluble product of APP (sAPP) provides a potential mechanistic link between increased APP production and increased sleep (Rice et al., 2019). The protease production of sAPP from APP by beta secretase is the first cleavage step that generates the substrate for gamma secretase to produce Aβ. In this recent report, the cognate receptor for sAPP was discovered to be a GABAb receptor (GABAb1a). GABAb receptors are g-protein coupled receptors that modulate synaptic transmission via binding of GABA neural transmitter. This particular GABAb receptor has a novel protein interaction domain called a sushi domain. Binding of sAPP to this domain of GABAb1a acts as an agonist and acts to reduce downstream excitatory synaptic transmission (Rice et al., 2019). GABAergic signaling is also a critical circuit element that facilitates the entering of the nervous system into the sleep state and acts to maintain synchronized oscillation of the brain (Cain et al., 2017; Llinás, Urbano, Leznik, Ramírez, & van Marle, 2005). Thus increasing APP production could directly lead to increased sleep and also Aβ production. In aging rats, it is shown that aging decreases FMRP levels in the brain (Smidak et al., 2017). Taken together, FMRP appears to be an important regulator of sleep, synaptic plasticity, and Aβ production. Perhaps, FMRP is part of the homeostatic fabric of the brain, and understanding its regulation during sleep and aging can help us resolve the connected regulatory mechanisms that drive the network set points of the brain. These set points are likely the foundations of the neurological impact of sleep and the difference between normal aging and neural degeneration. One *caveat* in mammals is that unlike drosophila, mammals have two paralogues of FMRP, the Fragile X-related proteins 1 and 2 (FXR1 & FXR2) (Schenck, Bardoni, Moro, Bagni, & Mandel, 2001). These proteins are highly related to FMRP structurally, and they are also expressed in the synapses (Wang, Smith, & Mourrain, 2014; Wang, Smith, & Mourrain, 2016). Although these proteins likely play important roles in regulating synaptic function in concert with FMRP, their synaptic function remains mostly unstudied. They likely play important roles in regulating synaptic function in concert with FMRP, and more work needs to be done on these interesting proteins.

Amyloid, astrocytes, and the glymphatic system

Synaptic activity and Aβ production are highly correlated (Shokri-Kojori et al., 2018). During wake, Aβ level in the brain is increased (Shokri-Kojori et al., 2018; Xie et al., 2013). This increase of Aβ requires the brain to effectively remove this Aβ on a daily basis. There are currently two major pathways that have been proposed to remove Aβ from the brain. One pathway is through the glymphatic system. The brain is separated into distinct fluid compartments (Jessen, Munk, Lundgaard, & Nedergaard, 2015). There is the cerebrospinal fluid (CSF), interstitial fluid, intracellular fluid, and the blood vasculature. The blood is kept separate from the brain parenchyma and CSF by the blood−brain and blood−CSF barriers. The blood and CSF barriers are essential in maintaining the extracellular environment of the brain because they regulate the ionic and biochemical composition of the interstitial fluid (Johanson et al., 2008). CSF comprises 10% of the total brain fluid volume in humans (Thrane, Rangroo Thrane, & Nedergaard, 2014). The CSF flows through the brain ventricles and channels in the subarachnoid space of the cortex and spinal cord; from there, the CSF penetrates the brain perivascularly before draining into the lymphatic system. The CNS vasculature within the brain is surrounded by astrocytic vascular endfeet. In the penetrating arterioles of the brain, the endothelial cells, pericytes, and astrocytes are separated by the basal lamina. The basal lamina is formed by laminin, fibronectin, and collagen into a porous extracellular matrix through which CSF readily flows into the brain (Thrane et al., 2014). This transport of CSF into the central brain matter is facilitated by aquaporin 4 (AQP4), a water channel expressed in the astrocytic endfeet that ensheathe the brain vasculature (Iliff et al., 2012). This CSF transport is supposed to be the

driving force that creates convective interstitial fluid fluxes within the brain toward the perivenous spaces in the brain where it drains out of the brain toward the cervical lymphatic system (Johnston, Zakharov, Papaiconomou, Salmasi, & Armstrong, 2004). This convective movement of fluid that exchanges the interstitial fluid with CSF fluid is known as the glymphatic system (Jessen et al., 2015).

The fluid flow of the glymphatic system was recently characterized in vivo using two-photon microscopy in mice (Iliff et al., 2012). The CSF was visualized by injected fluorescent tracers which showed that CSF and dye enter the brain via cortical pial arteries and along the penetrating arterioles (Iliff et al., 2012). This flow of fluid appears to facilitate the clearance of interstitial solutes to perivenous drainage pathways (Bradbury, Cserr, & Westrop, 1981). This macroscopic clearance of interstitial solutes may be important to brain beta amyloid metabolism as injection of fluorescent or radiolabeled amyloid β1−40 into the mouse striatum was cleared via glymphatic paravenous efflux (Iliff et al., 2012). Interestingly, using similar techniques, researchers were able to demonstrate that the rate of glymphatic flux appears to be correlated with sleep or anesthetic states (Xie et al., 2013). The CSF influx in the awake state was reduced by 90% in anesthetized mice and this correlated with a volume fraction increase of the interstitial space in sleep from 13% to 15% in wake from 22% to 24% during sleep (Xie et al., 2013). This observation indicates that the sleep state could be an important period during which major toxic metabolites are cleared from the brain, including Aβ. Furthermore, the glymphatic system, like the peripheral lymphatic system, appears to be important for lipid transport as lipophylic molecules are readily transported via glymphatic flow (Iliff et al., 2012). Apolipoprotein E (ApoE) is highly expressed in astrocytic processes around the blood vessels and areas of CSF production, such as the choroid plexus and cerebral tanycytes (Boyles, Pitas, Wilson, Mahley, & Taylor, 1985; Xu et al., 2006). ApoE allele 4 is a major genetic risk factor for Alzheimer's and is implicated in the clearance of Aβ (Strittmatter et al., 1993; Verghese et al., 2013). Finally, CSF tracer studies revealed in AQP4 knockout mice a ∼65% reduction in CSF fluid flux compared to wild-type control mice and a 55% reduction of Aβ clearance (Iliff et al., 2012); and interestingly, during aging AQP4 localization to the astrocytic endfeet appears to be disrupted (Kress et al., 2014). This results in a dramatic 80%−90% decrease in glymphatic flow of aged mice (Kress et al., 2014). This suggests a mechanistic link between aging, reduced glymphatic flow, and potential Aβ buildup and neural degeneration.

Another major pathway for Aβ clearance was recently reported to be the direct degradation of Aβ via astrocytic expression of a chymotrypsin-like protease called kallikrein 7 (KLK7) (Kidana et al., 2018). Previous research into KLK7 suggested that it cleaved the amyloidogenic core of Aβ (Shropshire et al., 2014). The current study suggests that Aβ levels directly influence the expression of KLK7 in astrocytes, but not microglia (Kidana et al., 2018). In cell culture, Aβ laden medium in neuron-astrocyte cocultures led to reduced Aβ levels that correlated with increases in astrocyte number. Furthermore, in vitro, microglial lines (MG6 or BV2) were not able to degrade Aβ, while astrocytoma cell line (CCF-STTG1) was (Kidana et al., 2018). This difference was confirmed by immunohistochemistry to be due to differential expression of KLK7. Moreover, Aβ in culture boosted the expression of KLK7 in astrocyte cultures, while glutamate, a known toxin in neurodegenerative conditions, inhibited the production of the protease. A more general inflammatory signal (lipopolysaccharide) did not affect KLK7 expression. This reduction of astrocytic KLK7 production by glutamate extended to NMDA a specific agonist of NMDA glutamate receptors, while NMDA receptor antagonist, memantin, which is used for treating mild cases of AD, increased KLK7 production eightfold (Kidana et al., 2018). However, it remains unknown how NMDA receptor activation leads to astrocytic reduction in KLK7 production. Interestingly, using postmortem brain samples from aged 60−90 years old Japanese people, the researchers found that there was less KLK7 in AD brains than in control brains (Kidana et al., 2018). Furthermore, crosses of KLK7 knockout mice with human APP knock-in mice created mice with more soluble Aβ in the brain and over three times as many Aβ plaques as control (Kidana et al., 2018). Phosphorylated tau also increased by 20% (Kidana et al., 2018). While more work is needed to fully characterize the pathways surrounding KLK7 function and response to Aβ, the constellation of proteins surrounding KLK7 represents potential novel drugable targets against AD.

Cellular metabolism and the astrocytes

The number of failed clinical drugs associated with reducing Aβ burden in the brain in the treatment of AD (Rosenblum, 2014) suggest the buildup of Aβ, while a clear indicator of neuronal dysfunction and neurodegeneration does not appear to be the causal mechanism of age-related neural degeneration. More likely, Aβ production and accumulation are the indicator of fundamental changes in brain function during aging, sleep, and disease that remains unknown to date. One tantalizing possibility is that changing brain metabolism and energy consumption during aging and sleep are the root cause of increased Aβ production (DiNuzzo & Nedergaard, 2017; Hoyer, 1990; Nofzinger et al., 2002; Smith, 1984). Interestingly like many of the processes we have discussed so far, brain metabolism in many ways

is governed by astrocytic function. This casts the astrocyte, which is so critical for glymphatic flow, Aβ breakdown, and brain energy metabolism in wake, sleep, and aging, as the locus of perturbation during aging and neural degeneration. Astrocytes play a major role in glucose metabolism in the brain through the control of glucose transport via glucose transporter 1 (Glut1) enriched in the astrocytic endfeet ensheathing the cerebral vasculature (Petit & Magistretti, 2016). During sleep, imported glucose is stored as glycogen by astrocytes (Bellesi, de Vivo, Koebe, Tononi, & Cirelli, 2018); this glycogen is the major energy reserve of the brain. A large portion of this astrocytic glucose is broken down via aerobic glycolysis into ATP and a majority of this lactate is transported via the monocarboxylate transporters out of the astrocyte and into neurons, where the lactate is converted to pyruvate and is either used for ATP generation or anabolic processes (Petit & Magistretti, 2016). During wake, lactate facilitates hippocampal memory formation (Suzuki et al., 2011) and dendritic spine formation (Margineanu, Mahmood, Fiumelli, & Magistretti, 2018). Lactate is also a major agonist of NMDA glutamate receptors (Jourdain et al., 2018), which potentially links this process to KLK7 protease function, and it is cleared via the glymphatic system during sleep (Xie et al., 2013). Aerobic glycolysis is the glycolytic breakdown of glucose even in the presence of abundant oxygen (Petit & Magistretti, 2016). Aerobic glycolysis produces only 6% of the ATP that is produced through oxidative phosphorylation via electron transport in the mitochondria (Dienel, 2019). While this appears inefficient, the downstream products from this process result in the foundational building blocks for nucleic acid synthesis, amino acid synthesis, lipid biosynthesis, and the production and cycling of glutamate and glutamine in the brain. In short, glycolysis leads to all of the material that is require for the constant plasticity and function of the brain. This is why, during wake, aerobic glycolysis is doubled compared to sleep (DiNuzzo & Nedergaard, 2017), and it is further elevated when brain is engaged in complex tasks (Harris et al., 2019; Shannon et al., 2016). In normal aging humans, it is well documented that glucose metabolism past the seventh decade decreases, and the bulk of that reduction is in aerobic glycolysis (Goyal et al., 2017; Hoyer, 1990; Smith, 1984). This reduction in aerobic glycolysis could reflect or contribute to the loss of plasticity during senescence. In the human brain, glycolysis is highest in the frontal and parietal cortices, which is lowest in regions such as the cerebellum (Vaishnavi et al., 2010). Interestingly, the frontal and parietal cortices are the regions that generally bear the biggest amyloid burden, and they are also the region with the highest astrocyte to neuron ratio (von Bartheld, Bahney, & Herculano-Houzel, 2016). These correlations are tantalizing, but direct evidence needs to be sought in relation to astrocyte function that connects brain metabolism, Aβ formation, and neural degeneration.

Sleep, chromosome dynamics, and DNA repair in neurons

In addition to a potential role for neuronal environment cleaning and energetic metabolism, sleep may also be important for cellular maintenance within neurons to counteract damages accumulated during wake. Recent works suggest that sleep is important for nuclear maintenance and genome integrity. During a cell life, the genome can accumulate DNA double-strand breaks (DSBs) that will affect its functions including gene expression. The causes of DSBs are diverse and include reactive oxygen species, ionizing radiation, and accidental action of nuclear enzymes (Lieber, 2010). Although such DNA damage may not be problematic for fast renewing cells, it can be a deleterious situation for long-lived neurons. The Tononi and Cirelli's lab first had found that sleep could contribute to faster repair of DSBs in fruit flies and mice (Bellesi, Bushey, Chini, Tononi, & Cirelli, 2016). These observations suggest a beneficial role of sleep at the chromosomal level, autonomously in single neurons or nonautonomously in synchronized neuronal networks (Fig. 6.1).

In a 2019 study, the Appelbaum Lab hypothesized that sleep behavior has evolved in order to regulate sleep bouts of functionally linked single neurons, thus enabling coordinated nuclear maintenance. Although across the sleep−wake cycle global gene expression in the brain is dynamically regulated, the expression of the majority of genes peaks during wakefulness (Bellesi et al., 2016; Mackiewicz et al., 2007), whereas chromosome dynamics may change during sleep. They used the transparent live zebrafish as a vertebrate model to image chromosome dynamics and DSBs during wake and sleep periods. They imaged single chromosome dynamics in live larvae by using telomere and centromere markers fused to enhanced green fluorescent protein. They focused on the fish cerebrum and brainstem. Remarkably, the time-lapse imaging showed that chromosome dynamics increased by approximately twofold during nighttime sleep in both brain regions. To differentiate between sleep and circadian effect, they repeated their experiments in free-running conditions as well as after sleep deprivation and sleep rebound. They found that sleep increases neuronal chromosome dynamics in a homeostatic-dependent manner but independently of the circadian clock suggesting a sleep-dependent process. To test whether these changes are also present in other cell types, they monitored chromosome dynamics in peripheral endothelial and Schwann cells. Interestingly, chromosome dynamics did not differ between day and night in both cell types supporting a specific function for sleep in neuron nuclei.

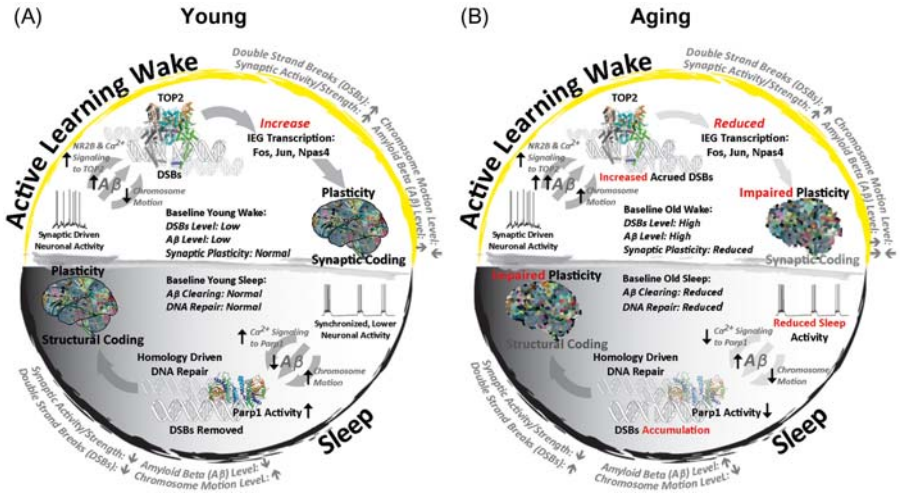


FIGURE 6.1 Sleep, DSBs repair, and hypothesized impact during neuronal aging. (A) During a normal daily cycle, active learning during wake increases synaptic strength, Ca^{2+} signaling, and amyloid beta (Aβ) load in the brain. This drives topoisomerase 2 (TOP2) mediated DSBs of the genome, which leads to the activation of immediate early genes (IEG) that facilitate the encoding of synaptic plasticity and learning. During sleep, neuronal activity is overall lower and synchronized, Aβ is removed via the glymphatic system, and chromosome motion is increased by twofold. Chomatin movement elevation leads to the repair of DSBs in the genome. This leads to renormalization of the synaptic network, encoding of memories through structural rewiring, and metabolic preparation of the nervous system for another period of wake. (B) During normal aging, sleep is less consolidated and shorter in duration. Basal level of Aβ is increased as clearing is less efficient. This all leads to reduced DNA repair, which causes the accumulation of DSBs in the genome, and reduced induction of IEGs, thus disrupting synaptic plasticity. This reduces memory encoding, synaptic renormalization, and optimization. Thus over a lifetime accumulation of DSBs in neuronal nuclei, reduced efficiency in clearing Aβ and reduced functional synaptic efficiency may lead to dementia and cell death/neurodegeneration eventually.

They next speculated that increased chromosome dynamics could enhance the efficiency of DSBs elimination during sleep. They used the γH2AX marker, which is activated as part of the DNA damage response system, to quantify DSBs during the day−night cycle. During the day, the number of DSBs consistently increased and peaked 1 hour before darkness. During the night, the number of DSBs dramatically decreased, reached the minimum levels in the middle of the 10-hour night, and remained low until the beginning of the day. In parallel, during the day, chromosome dynamics remained low but then following 1 hour of darkness, it increased by twofold and stayed high during the entire night. Chromosome dynamics thus correlated with efficient reduction of DSBs during the night. This correlation was substantiated by the observation that sleep deprivation prevented DSBs reduction in neuron chromosomes while sleep rebound facilitated it. In contrast to the day/night changes observed in neurons, the number of DSBs was consistently low during day and night in endothelial and Schwann cells, suggesting again that sleep has a specific influence on chromosome dynamics and DSBs repair in neurons. Zada and colleagues then showed that sleep-dependent chromosome dynamics are necessary to reduce DSBs by manipulating chromosome binding to the nuclear lamina and blocking chromosome dynamics (Zada, Bronshtein, Lerer-Goldshtein, Garini, & Appelbaum, 2019).

The emerging image of this very recent work is that during wake neurons accumulate DNA damage that can be repaired by sleep-dependent chromosome level mechanisms. This finding is consistent with the fact that in mammals and zebrafish, neuronal activity promotes the formation of DSBs (Madabhushi et al., 2015; Suberbielle et al., 2013; Zada et al., 2019) and overall brain neuronal activity is at its highest during wake and at its lowest during sleep. As often with sleep function(s), it may be hard to distinguish between a primary function of sleep and an opportunistic function taking advantage of this long period of body rest. To start answering this question, Zada and colleagues tested whether DSBs could actually cause changes in sleep. The authors used etoposide (ETO), which induces DSBs (Smart et al., 2008), and monitored the number of γH2AX foci, chromosome dynamics, and sleep time. One hour following ETO withdrawal, sleep time increased in ETO-treated larvae. After 2 hours of recovery from the ETO treatment, sleep time remained high, and chromosome dynamics increased by approximately twofold accompanied by a reduction in the number of DSBs. These results suggest that while chromosome dynamics are low during the formation of DSBs, the accumulation of DSBs during wakefulness triggers sleep, which increases chromosome dynamics and eventually reduces the number of DSBs.

This study requires validation in other contexts including aging. Still the finding that sleep can actually increase chromosome dynamics to repair DNA damage accumulated during wake in neurons is an appealing one. As DSBs

accumulation and repair were observed over a matter of hours in a single wake/day-sleep/night cycle, one can speculate of the impact of chronic insufficient sleep or sleep abnormalities over a lifetime. Sleep-dependent alterations in chromatin structure could affect a variety of nuclear processes, including genome stability, transcription, DNA repair, chromosome segregation, and condensation. Depending on the extent of DNA damage accumulated during the course of a lifetime, this could lead to abnormal neuronal firing physiology, accumulation of somatic mutations disrupting the normal neuronal function, or even cell death. One could hypothesize that chronic sleep-dependent DNA repair defects could generate over years abnormal or defective cognition as well as neuronal degeneration eventually.

Animal models for aging and neurochemical changes

The cause of cell death or abnormal circuit function/synaptic connections in the aging brain and in neurodegenerative disorders is still poorly understood. Thus the emergence of putative sleep functions responsible for recovery from toxic extracellular and intracellular neurochemical changes is attractive. From nematode to fly to zebrafish to mammals, similar neurochemical components have been found regulating sleep, including GABA, serotonin, dopamine, and acetylcholine. This body of work reminds us that it is critical to keep in mind that sleep is likely to have basic cellular functions as it is found in all invertebrates (cephalopods, arthropods, and nematodes) and vertebrates (from fishes to mammals) studied so far, suggesting the emergence of sleep at least 700 million years ago. It is hence tempting that despite the evolutionary distance, neuronal networks whether hosted in an invertebrate or a vertebrate face the same physiological, homeostatic, maintenance constraints. Such comparison should shed light on the fundamental, ancestral function(s) of sleep and how it may be involved in normal and pathological aging. Over the past 20 years, introduction of animal genetic models has at last occurred in the sleep field. Fortunately, some of them such as *Caenorhabditis elegans* and Drosophila are premiere models for aging research. While zebrafish is not a model for aging per se, its close relative killifish is also a powerful model to study the biology underpinning life span. With the discovery of sleep-dependent brain clearing by the glymphatic system in mice and DSBs repair by increased chromosome dynamics in zebrafish, new research avenues are opened to understand how the nervous system may maintain its integrity during sleep without replacing its cells as it is the norm for most of the rest of the body organs.

Conclusion

The nervous system is a complex framework of cells. It functions through the connectivity of the billions of neurons that compose the brain. Most of these cells, the neurons, will live as long as the animal that hosts them, in contrast to most cells composing the rest of the body that are replaced on a weekly/monthly basis. To sustain such an impressive cellular life span, neuronal tissue must efficiently deal with intracellular and extracellular stress, damage, and all types of chemical changes during normal aging. New evidence suggests that sleep may have a critical role in the homeostasis and integrity of the brain and its connections to maintain a long-lived and functionally harmonious brain. Aging is an accumulative process by which environmental stressors through the lens of genetics impact the molecular set points of nervous system: a system maintained in part by sleep. Over the past decade, new roles have emerged for sleep that are likely critical for the homeostatic regulation of synaptic plasticity, the maintenance of balanced excitatory and inhibitory synaptic tone, the energetic and metabolic equilibrium of the neural cells, the clearing of toxic waste in the brain, and nuclear DNA repair. Today, the molecular interlinks between sleep and aging are not fully understood, but these connections are likely critical to our understanding of neuropathology that ranges from neurodevelopmental disorders to neurodegenerative diseases. The molecular mechanisms that tie sleep and aging are complex and likely cross neurons, glia, vasculature, glymphatic and immune systems. Still, the emergence of new animal system models and tools to visualize and functionally investigate the cellular and extracellular neurochemical changes that occur with aging but are homeostatically counteracted or repaired during sleep brings new hopes in the development of strategies to alleviate pathological aging symptoms.

References

Ascano, M., et al. (2012). FMRP targets distinct mRNA sequence elements to regulate protein expression. *Nature*, *492*, 382–386.

Bechara, E. G., et al. (2009). A novel function for fragile X mental retardation protein in translational activation. *PLoS Biology*, *7*, e16.

Bellesi, M., Bushey, D., Chini, M., Tononi, G., & Cirelli, C. (2016). Contribution of sleep to the repair of neuronal DNA double-strand breaks: Evidence from flies and mice. *Scientific Reports*, *6*, 36804.

Bellesi, M., de Vivo, L., Koebe, S., Tononi, G., & Cirelli, C. (2018). Sleep and wake affect glycogen content and turnover at perisynaptic astrocytic processes. *Frontiers in Cellular Neuroscience*, *12*, 308.

Bonnet, M. H., & Rosa, R. R. (1987). Sleep and performance in young adults and older normals and insomniacs during acute sleep loss and recovery. *Biological Psychology*, *25*, 153−172.

Boyles, J. K., Pitas, R. E., Wilson, E., Mahley, R. W., & Taylor, J. M. (1985). Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. *Journal of Clinical Investigation*, *76*, 1501−1513.

Bradbury, M. W., Cserr, H. F., & Westrop, R. J. (1981). Drainage of cerebral interstitial fluid into deep cervical lymph of the rabbit. *American Journal of Physiology*, *240*, F329−F336.

Brown, V., et al. (2001). Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell*, *107*, 477−487.

Bushey, D., Tononi, G., & Cirelli, C. (2009). The Drosophila fragile X mental retardation gene regulates sleep need. *The Journal of Neuroscience*, *29*, 1948−1961.

Cain, S. M., et al. (2017). $GABA_B$ receptors suppress burst-firing in reticular thalamic neurons. *Channels*, *11*, 574−586.

Cabeza, R., Nyberg, L., & Park, D. C. (2016). *Cognitive neuroscience of aging*. Oxford University Press. Available from https://doi.org/10.1093/acprof:oso/9780199372935.001.0001.

Cardinali, D. P., Furio, A. M., & Brusco, L. I. (2010). Clinical aspects of melatonin intervention in Alzheimer's disease progression. *Current Neuropharmacology*, *8*, 218−227.

Daulatzai, M. A. (2010). Early stages of pathogenesis in memory impairment during normal senescence and Alzheimer's disease. *Journal of Alzheimer's Disease*, *20*, 355−367.

Dienel, G. A. (2019). Brain glucose metabolism: Integration of energetics with function. *Physiological Reviews*, *99*, 949−1045.

DiNuzzo, M., & Nedergaard, M. (2017). Brain energetics during the sleep-wake cycle. *Current Opinion in Neurobiology*, *47*, 65−72.

Fukumoto, H., et al. (1996). Amyloid beta protein deposition in normal aging has the same characteristics as that in Alzheimer's disease. Predominance of A beta 42(43) and association of A beta 40 with cored plaques. *The American Journal of Pathology*, *148*, 259−265.

Goyal, M. S., et al. (2017). Loss of brain aerobic glycolysis in normal human aging. *Cell Metabolism*, *26*, 353−360.e3.

Grillo, F. W., et al. (2013). Increased axonal bouton dynamics in the aging mouse cortex. *Proceedings of. National Academy of Science of United States of America*, *110*, E1514−E1523.

Hara, Y., Rapp, P. R., & Morrison, J. H. (2012). Neuronal and morphological bases of cognitive decline in aged rhesus monkeys. *Age (Dordrecht, Netherlands)*, *34*, 1051−1073.

Harris, R. A., et al. (2019). Aerobic glycolysis is required for spatial memory acquisition but not memory retrieval in mice. *eNeuro*, *6*, ENEURO.0389-18.2019.

Hoyer, S. (1990). Brain glucose and energy metabolism during normal aging. *Aging Clinical and Experimental Research*, *2*, 245−258.

Hu, N.-W., et al. (2014). mGlu5 receptors and cellular prion protein mediate amyloid-β-facilitated synaptic long-term depression in vivo. *Nature Communications*, *5*, 3374.

Iliff, J. J., et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid. *Science Translational Medicine*, *4*, 147ra111−147ra111.

Jessen, N. A., Munk, A. S. F., Lundgaard, I., & Nedergaard, M. (2015). The glymphatic system: A beginner's guide. *Neurochemical Research*, *40*, 2583−2599.

Johanson, C. E., et al. (2008). Multiplicity of cerebrospinal fluid functions: New challenges in health and disease. *Cerebrospinal Fluid Research*, *5*, 10.

Johnston, M., Zakharov, A., Papaiconomou, C., Salmasi, G., & Armstrong, D. (2004). Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. *Cerebrospinal Fluid Research*, *1*, 2.

Jourdain, P., et al. (2018). Dual action of L-lactate on the activity of NR2B-containing NMDA receptors: From potentiation to neuroprotection. *Scientific Reports*, *8*, 13472.

Kawai, M., et al. (2016). Delta activity at sleep onset and cognitive performance in community-dwelling Older Adults. *Sleep*, *39*, 907−914.

Kidana, K., et al. (2018). Loss of kallikrein-related peptidase 7 exacerbates amyloid pathology in Alzheimer's disease model mice. *EMBO Molecular Medicine*, *10*, e8184.

Kress, B. T., et al. (2014). Impairment of paravascular clearance pathways in the aging brain. *Annals of Neurology*, *76*, 845−861.

Li, S., et al. (2009). Soluble oligomers of amyloid β protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron*, *62*, 788−801.

Li, W., Ma, L., Yang, G., & Gan, W.-B. (2017). REM sleep selectively prunes and maintains new synapses in development and learning. *Nature Neuroscience*, *20*, 427−437.

Lieber, M. R. (2010). The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. *Annual Review of Biochemistry*, *79*, 181−211.

Llinás, R., Urbano, F. J., Leznik, E., Ramírez, R. R., & van Marle, H. J. F. (2005). Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends in Neuroscience*, *28*, 325−333.

Mackiewicz, M., et al. (2007). Macromolecule biosynthesis: A key function of sleep. *Physiological Genomics*, *31*, 441−457.

Madabhushi, R., et al. (2015). Activity-induced DNA breaks govern the expression of neuronal early-response genes. *Cell*, *161*, 1592−1605.

Margineanu, M. B., Mahmood, H., Fiumelli, H., & Magistretti, P. J. (2018). L-Lactate regulates the expression of synaptic plasticity and neuroprotection genes in cortical neurons: A transcriptome analysis. *Frontiers in Molecular. Neuroscience*, *11*, 375.

Mostany, R., et al. (2013). Altered synaptic dynamics during normal brain aging. *The Journal of Neuroscience*, *33*, 4094–4104.
Musiek, E. S., Xiong, D. D., & Holtzman, D. M. (2015). Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. *Experimental Mol. Med*, *47*, e148.
Nofzinger, E. A., et al. (2002). Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain*, *125*, 1105–1115.
Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, *27*, 1255–1273.
Parihar, M. S., & Brewer, G. J. (2010). Amyloid-β as a modulator of synaptic plasticity. *Journal of Alzheimer's Disease*, *22*, 741–763.
Peters, A., Sethares, C., & Luebke, J. I. (2008). Synapses are lost during aging in the primate prefrontal cortex. *Neuroscience*, *152*, 970–981.
Petit, J.-M., & Magistretti, P. J. (2016). Regulation of neuron–astrocyte metabolic coupling across the sleep–wake cycle. *Neuroscience*, *323*, 135–156.
Petralia, R. S., Mattson, M. P., & Yao, P. J. (2014). Communication breakdown: The impact of ageing on synapse structure. *Ageing Research Reviews*, *14*, 31–42.
Piccini, A., et al. (2005). β-Amyloid is different in normal aging and in Alzheimer disease. *The Journal of Biological Chemistry*, *280*, 34186–34192.
Rice, H. C., et al. (2019). Secreted amyloid-β precursor protein functions as a $GABA_B$ R1a ligand to modulate synaptic transmission. *Science*, *363*, eaao4827.
Rosenblum, W. I. (2014). Why Alzheimer trials fail: Removing soluble oligomeric beta amyloid is essential, inconsistent, and difficult. *Neurobiology of Aging*, *35*, 969–974.
Rowan, M. J., Klyubin, I., Wang, Q., & Anwyl, R. (2005). Synaptic plasticity disruption by amyloid β protein: Modulation by potential Alzheimer's disease modifying therapies. *Biochemical Society Transactions*, *33*, 563–567.
Schenck, A., Bardoni, B., Moro, A., Bagni, C., & Mandel, J. L. (2001). A highly conserved protein family interacting with the fragile X mental retardation protein (FMRP) and displaying selective interactions with FMRP-related proteins FXR1P and FXR2P. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 8844–8849.
Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science*, *10*, 97–137.
Shankar, G. M., et al. (2008). Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nature Medicine*, *14*, 837–842.
Shannon, B. J., et al. (2016). Brain aerobic glycolysis and motor adaptation learning. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, E3782–E3791.
Shokri-Kojori, E., et al. (2018). β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 4483–4488.
Shropshire, T. D., et al. (2014). Amyloid β peptide cleavage by kallikrein 7 attenuates fibril growth and rescues neurons from Aβ-mediated toxicity in vitro. *Biological Chemistry*, *395*, 109–118.
Smart, D. J., et al. (2008). Assessment of DNA double-strand breaks and γH2AX induced by the topoisomerase II poisons etoposide and mitoxantrone. *Mutation Research*, *641*, 43–47.
Smidak, R., et al. (2017). Reduced levels of the synaptic functional regulator FMRP in dentate gyrus of the aging Sprague-Dawley rat. *Frontiers in Aging Neuroscience*, *9*, 384.
Smith, C. B. (1984). Aging and changes in cerebral energy metabolism. *Trends in Neuroscience*, *7*, 203–208.
Snyder, E. M., et al. (2005). Regulation of NMDA receptor trafficking by amyloid-β. *Nature Neuroscience*, *8*, 1051–1058.
Strittmatter, W. J., et al. (1993). Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*, *90*, 1977–1981.
Suberbielle, E., et al. (2013). Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-β. *Nature Neuroscience*, *16*, 613–621.
Suzuki, A., et al. (2011). Astrocyte-neuron lactate transport is required for long-term memory formation. *Cell*, *144*, 810–823.
Thrane, A. S., Rangroo Thrane, V., & Nedergaard, M. (2014). Drowning stars: Reassessing the role of astrocytes in brain edema. *Trends in Neuroscience*, *37*, 620–628.
Vaishnavi, S. N., et al. (2010). Regional aerobic glycolysis in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 17757–17762.
Verghese, P. B., et al. (2013). ApoE influences amyloid-β (Aβ) clearance despite minimal apoE/Aβ association in physiological conditions. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, E1807–E1816.
von Bartheld, C. S., Bahney, J., & Herculano-Houzel, S. (2016). The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. *The Journal of Comparative Neurology*, *524*, 3865–3895.
Wang, G., Grone, B., Colas, D., Appelbaum, L., & Mourrain, P. (2011). Synaptic plasticity in sleep: Learning, homeostasis and disease. *Trends in Neuroscience*, *34*, 452–463.
Wang, G. X., Smith, S. J., & Mourrain, P. (2014). Fmr1 KO and fenobam treatment differentially impact distinct synapse populations of mouse neocortex. *Neuron*, *84*.
Wang, G. X., Smith, S. J., & Mourrain, P. (2016). Sub-synaptic, multiplexed analysis of proteins reveals fragile X related protein 2 is mislocalized in Fmr1 KO synapses. *eLife*, *5*.

Westmark, C. J., & Malter, J. S. (2007). FMRP mediates mGluR5-dependent translation of amyloid precursor protein. *PLoS Biology*, *5*, e52.

Won, J., et al. (2017). Melatonin as a novel interventional candidate for fragile X syndrome with autism spectrum disorder in humans. *International Journal of Molecular Science*, *18*, 1314.

Xie, L., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science*, *342*, 373−377.

Xu, Q., et al. (2006). Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. *The Journal of Neuroscience*, *26*, 4985−4994.

Young, M. E., Ohm, D. T., Dumitriu, D., Rapp, P. R., & Morrison, J. H. (2014). Differential effects of aging on dendritic spines in visual cortex and prefrontal cortex of the rhesus monkey. *Neuroscience*, *274*, 33−43.

Zada, D., Bronshtein, I., Lerer-Goldshtein, T., Garini, Y., & Appelbaum, L. (2019). Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. *Nature Communications*, *10*, 895.

Zhang, J., et al. (2008). Fragile X-related proteins regulate mammalian circadian behavioral rhythms. *American Journal of Human Genetics*, *83*, 43−52.

Chapter 7

Biomarkers of cognitive impairment in late-life depression

Breno S. Diniz[1] **and Meryl A. Butters**[2]

[1]*Department of Psychiatry, University of Toronto, Toronto, ON, Canada,* [2]*Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States*

Introduction

Late-life depression (LLD) is one of the most common neuropsychiatric disorders in older adults. In community-dwelling older adults, the prevalence of major depression ranges from 4% to 22% (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010) and the prevalence of clinically significant depressive symptoms (i.e., the presence of depressive symptoms that do not fulfill diagnostic criteria for a major depressive episode [MDE]) is even higher, ranging from 20% to 40% (Barcelos-Ferreira, Izbicki, Steffens, & Bottino, 2010; Thielke, Diehr, & Unutzer, 2010).

Cognitive impairment is very common among patients with LLD and the presence of cognitive impairment during an MDE has many important clinical implications. Cognitive impairment is a strong moderator of treatment response and is associated with refractoriness to antidepressant treatment (Kaneriya et al., 2016; Lenze et al., 2015). It is also associated with greater risk of dementia, specially Alzheimer's disease and vascular dementia (Diniz et al., 2014; Mourao, Mansur, Malloy-Diniz, Castro Costa, & Diniz, 2016). This chapter aims to review the biological mechanisms underlying cognitive impairment in LLD (Table 7.1).

Cognitive impairment in late-life depression

The presentation of cognitive impairment in LLD is very common and heterogeneous. About 50% of individuals with LLD present with objective cognitive impairment measured by neuropsychological evaluation (Nebes et al., 2003). In general, the most commonly affected cognitive domains in LLD are information processing speed, executive function, and episodic memory (Butters et al., 2004). Lifetime age of onset of major depression is an important feature of LLD and has a significant impact on the pattern of cognitive impairment. The published literature generally classifies patients as early-onset LLD (EOD) if their first episode of major depression occurred at younger age or as late-onset LLD (LOD) if the first MDE occurred after 60 or 65 years of age. Patients with LOD are generally characterized by more severe and generalized cognitive deficits compromising most cognitive domains (Herrmann, Goodwin, & Ebmeier, 2007). Executive functioning is particularly affected in LOD and may mediate the significant disability and functional impairment observed in these individuals (Alexopoulos et al., 2005; Pereira, Yassuda, Oliveira, & Forlenza, 2008; Yen, Rebok, Gallo, Jones, & Tennstedt, 2011). Patients with EOD may also present with significant cognitive impairment, notably of short-term episodic memory and information processing speed (Herrmann et al., 2007).

Neuroimaging findings

Structural and functional neuroimaging studies have been shedding light on cerebral changes related to cognitive impairment in LLD. A large body of evidence suggests that patients with LLD have a significantly higher frequency of cerebrovascular lesions (mainly periventricular and deep white matter hyperintensities and lacunar infarcts) and cerebral atrophy noted on MRI as compared to older adults without a history of depression (Greenwald et al., 1998; Lee, Payne, & Steffens, 2003; O'Brien, Firbank, & Krishnan, 2006; Taylor, Steffens, & MacFall, 2003). However, the pattern of

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00007-7

TABLE 7.1 Profile of peripheral biomarkers of cognitive impairment in late-life depression.

Biomarkers	Pattern of change
IL-1β	↑
IL-6	↑
TNF-α	–
sTNFr1	–
sTNFr2	↑
BDNF	↓
GSK-3β activity	↑
Proteostasis regulation	↓
Apoptosis markers	↑
Stem cell markers	↓

cerebral structural changes may be dependent on the age of onset LLD. LOD patients usually show more significant cerebrovascular lesions as compared to EOD patients (Baldwin & O'Brien, 2002; Hickie, Scott, & Naismith, 2001; Nebes, Reynolds, & Boada, 2002). These changes are most commonly located in the basal ganglia and in the fronto-subcortical circuitry and are associated with cognitive impairment, in particular, executive dysfunction (Herrmann, Le Masurier, & Ebmeier, 2008).

Conversely, patients with EOD frequently show significant regional cerebral atrophy, mostly in the hippocampal formation (Bell-McGinty et al., 2002; Janssen, Hulshoff Pol, & de Leeuw, 2007). Hippocampal atrophy correlates with the duration of the index depressive episode and the number of recurrent episodes (Sheline, Gado, & Kraemer, 2003; Sheline, Wang, Gado, Csernansky, & Vannier, 1996), and might be a harbinger of future dementia in some patients (Steffens, Payne, & Greenberg, 2002). Such structural changes are in parallel with progressive short-term episodic memory decline in EOD patients.

Inflammatory changes in late-life depression

Cytokines and acute phase proteins are important mediators of the inflammatory response. These proteins can be readily assessed in different biological matrices and, thus, can be reliable biomarkers of inflammatory activity in an individual patient. Inflammatory cytokines can be produced by central nervous system cells, such as activated microglia, exerting active biological effects in glial and neuronal functions. (Lee, Nagai, & Kim, 2002). Some of these effects are directly related to the pathophysiology of depression, also presenting long-term consequences, such as the emergence of neurodegenerative changes in the brain (Loftis, Huckans, & Morasco, 2010).

Several studies have examined peripheral levels of cytokines and acute phase proteins in patients with LLD. Interleukin-1β (IL-1β), a potent pro-inflammatory cytokine, was found to be significantly elevated in patients with LLD, in particular in patients with EOD (Diniz et al., 2010a, 2010b; Diniz, Teixeira, Talib, Gattaz, & Forlenza, 2010; Thomas et al., 2005). It is noteworthy that recurrent depressive episodes in adults were also associated with increased circulating levels of inflammatory markers like C-reactive protein (CRP) (Copeland, Shanahan, Worthman, Angold, & Costello, 2012), suggesting that recurrent depression is associated with cumulative pro-inflammatory burden.

TNF-α is the prototype pro-inflammatory cytokine and has been involved in the pathophysiology of several chronic inflammatory disorders (Chadwick et al., 2008). Although patients with LLD did not show changes in the levels of TNF-α, they presented with significantly higher levels of soluble TNF-α receptor 2 (sTNF-R2 or p75), with no significant change in the levels of soluble TNF-α receptor 1 (sTNF-R1 or p55). These findings suggest that, although patients with LLD do not have significant changes in TNF-α levels, they present with abnormal regulation of the TNF-α signaling system during a depressive episode (Diniz et al., 2010a, 2010b; Diniz, Teixeira, Talib, Gattaz, et al., 2010). In line with this, a recent study found that elevated serum levels of sTNF-R1 were associated to higher depressive symptoms, as measured by the Geriatric Depression Scale, in older adults 1 year after hip fracture (Matheny, Miller, & Shardell, 2011). Changes in pro-inflammatory cytokines have also been shown to be more pronounced in patients with LLD and

comorbid cognitive impairment (Diniz et al., 2015). Other pro-inflammatory cytokines and acute phase proteins, such as IL-6, CRP, and α1-antichymotrypsin, are also increased in patients with LLD (Dentino, Pieper, & Rao, 1999; Dimopoulos, Piperi, Psarra, Lea, & Kalofoutis, 2008; Matheny et al., 2011).

In sum, research findings suggest that LLD is characterized by a dysregulation of inflammatory control based on increased pro-inflammatory status. Such changes tend to correlate with the severity of depressive symptoms and cognitive impairment. Recurrent depressive episodes may have a cumulative pro-inflammatory effect. These pro-inflammatory changes are in excess of those expected during the aging or senescence process, suggesting that abnormalities in inflammatory control may play a significant role in the pathophysiology of LLD.

Neurotrophic factors in late-life depression

Neurotrophic factors are a broad family of proteins that play several roles in the central nervous system, mainly maintenance of neuronal homeostasis, neuroprotection against insults, neuronal repair and regeneration, and synaptic formation and strengthening (Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008).

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophic factor in the brain. Several studies found significantly lower circulating levels of BDNF in patients with LLD as compared to non-depressed individuals (Shi et al., 2010). When studies stratified LLD according to age of onset, patients with LOD had lower BDNF levels than those with EOD (Diniz et al., 2010a, 2010b; Diniz, Teixeira, Talib, Gattaz, et al., 2010). In addition, older individuals with sub-syndromal depression showed levels of BDNF that were intermediate between patients with major depression and non-depressed individuals, suggesting a gradient or depression dose effect (Shi et al., 2010).

Changes in BDNF levels have been associated with cognitive decline in LLD. A longitudinal study, including LLD patients with and without cognitive impairment, showed that despite non-significant differences in the baseline BDNF levels between LLD with or without cognitive impairment, the latter group showed a steeper decline in BDNF levels over 2 years of follow-up (Diniz et al., 2014). In another study that evaluated BDNF levels in the cerebrospinal fluid (CSF), LLD patients with comorbid mild cognitive impairment had the lowest BDNF values (Diniz et al., 2015). It is worth noting that there was no significant difference in CSF levels of biomarkers related to Alzheimer's disease (i.e., amyloid-β_{42}, total Tau and phosphorylated Tau protein). Such findings suggest that cognitive impairment may be independent of the emergence of neurodegenerative changes in LLD.

The insulin signaling cascade/glycogen synthase kinase 3β in late-life depression

Glycogen synthase kinase-3β (GSK-3β) is an intracellular enzyme that is involved in many cellular functions such as energy metabolism, structural plasticity, neurogenesis, and resilience to cellular injury (Peineau, Bradley, & Taghibiglou, 2008). Its activity is regulated by the phosphorylation of serine 9 epitope, rendering the enzyme inactive. A small study showed that patients with LLD had lower levels of phosphorylated GSK-3β with no changes in total GSK-3β in platelets, suggesting that GSK-3β is possibly overactive in patients with LLD (Diniz et al., 2011). Moreover, these changes were markedly pronounced in patients with more severe cognitive impairment and depressive symptoms, indicating that GSK-3β over-activation is a state marker of more severe depressive episodes and cognitive impairment in older individuals.

Multiplex biomarker changes related to cognitive impairment in late-life depression

Recent studies using proteomic methods and bioinformatic analysis shed light on the complex interplay between different biological pathways in the emergence of cognitive impairment in LLD. Such analysis revealed that a distinct set of circulating biomarkers were significantly associated with cognitive impairment in LLD. As expected, many of these biomarkers were involved in the regulation of inflammatory control (e.g., IL-12, sTNFr1, and sTNFr2), neurotrophic support (e.g., NGF), and insulin cascade control (e.g., IGFBP-3 and IGFBP-5) (Diniz et al., 2015; Diniz et al., 2016). Nonetheless, these studies uncovered the role of novel biomarkers and biological pathways implicated in cognitive impairment in LLD, especially proteostasis control (e.g., APOA-I and APOA-IV), control of cell cycle and apoptotic processes (e.g., GRO-α and hEGF), and stem cell exhaustion (e.g., stem cell factor and angiogenin). These results suggest that cognitive impairment in LLD is complex phenomenon and involves the interaction of multiple biomarkers and biological pathways.

Conclusion

Cognitive impairment is common among older adults with LLD. It is a multifaceted problem that leads to worse treatment response, relapse, worse quality of life, decreased functioning, and increased risk of dementia. Cognitive impairment in LLD probably arises as a consequence of multiple abnormalities, including structural brain changes (i.e., cerebrovascular vascular changes, gray matter atrophy) and molecular abnormalities, in particular in inflammatory and neurotrophic cascades.

References

Alexopoulos, G. S., Kiosses, D. N., Heo, M., Murphy, C. F., Shanmugham, B., & Gunning-Dixon, F. (2005). Executive dysfunction and the course of geriatric depression. *Biological Psychiatry.*, *58*(3), 204–210.

Baldwin, R. C., & O'Brien, J. (2002). Vascular basis of late-onset depressive disorder. *British Journal of Psychiatry.*, *180*, 157–160.

Barcelos-Ferreira, R., Izbicki, R., Steffens, D. C., & Bottino, C. M. (2010). Depressive morbidity and gender in community-dwelling Brazilian elderly: Systematic review and meta-analysis. *International Psychogeriatrics.*, *22*(5), 712–726.

Bell-McGinty, S., Butters, M. A., Meltzer, C. C., Greer, P. J., Reynolds, C. F., & Becker, J. T. (2002). Brain morphometric abnormalities in geriatric depression: Long-term neurobiological effects of illness duration. *The American Journal of Psychiatry.*, *159*, 1424–1427.

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H., … Becker, J. T. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry.*, *61*(6), 587–595.

Byers, A. L., Yaffe, K., Covinsky, K. E., Friedman, M. B., & Bruce, M. L. (2010). High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Archives of General Psychiatry.*, *67*(5), 489–496.

Chadwick, W., Magnus, T., Martin, B., Keselman, A., Mattson, M. P., & Maudsley, S. (2008). Targeting TNF-alpha receptors for neurotherapeutics. *Trends in Neurosciences.*, *31*, 504–511.

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2012). Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. *Biological Psychiatry.*, *71*(1), 15–21.

Dentino, A. N., Pieper, C. F., Rao, M. K., et al. (1999). Association of interleukin-6 and other biologic variables with depression in older people living in the community. *Journal of the American Geriatrics Society.*, *47*(1), 6–11.

Dimopoulos, N., Piperi, C., Psarra, V., Lea, R. W., & Kalofoutis, A. (2008). Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. *Psychiatry Research.*, *161*(1), 59–66.

Diniz, B. S., Lin, C. W., Sibille, E., Tseng, G., Lotrich, F., Aizenstein, H. J., … Butters, M. A. (2016). Circulating biosignatures of late-life depression (LLD): Towards a comprehensive, data-driven approach to understanding LLD pathophysiology. *Journal of Psychiatric Research.*, *82*, 1–7.

Diniz, B. S., Reynolds, C. F., 3rd, Begley, A., Dew, M. A., Anderson, S. J., Lotrich, F., … Butters, M. A. (2014). Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: A longitudinal study. *Journal of Psychiatric Research.*, *49*, 96–101.

Diniz, B. S., Sibille, E., Ding, Y., Tseng, G., Aizenstein, H. J., Lotrich, F., … Butters, M. A. (2015). Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. *Molecular Psychiatry.*, *20*(5), 594–601.

Diniz, B. S., Talib, L. L., Joaquim, H. P., de Paula, V. R., Gattaz, W. F., & Forlenza, O. V. (2011). Platelet GSK3B activity in patients with late-life depression: Marker of depressive episode severity and cognitive impairment? *The World Journal of Biological Psychiatry.*, *12*(3), 216–222.

Diniz, B. S., Teixeira, A. L., Machado-Vieira, R., Talib, L. L., Radanovic, M., Gattaz, W. F., & Forlenza, O. V. (2014). Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences.*, *69*(6), 845–851.

Diniz, B. S., Teixeira, A. L., Talib, L., Gattaz, W. F., & Forlenza, O. (2010). Interleukin-1beta serum level is increased in antidepressant-free elderly depressed patients. *The American Journal of Geriatric Psychiatry.*, *18*, 172–176.

Diniz, B. S., Teixeira, A. L., Talib, L. L., Mendonca, V. A., Gattaz, W. F., & Forlenza, O. V. (2010a). Increased soluble TNF receptor 2 in antidepressant-free patients with late-life depression. *Journal of Psychiatric Research.*, *44*(14), 917–920.

Diniz, B. S., Teixeira, A. L., Talib, L. L., Mendonça, V. A., Gattaz, W. F., & Forlenza, O. V. (2010b). Serum brain-derived neurotrophic factor level is reduced in antidepressant-free patients with late-life depression. *The World Journal of Biological Psychiatry.*, *11*(3), 550–555.

Greenwald, B. S., Kramer-Ginsberg, E., Krishnan, K. R., Ashtari, M., Auerbach, C., & Patel, M. (1998). Neuroanatomic localization of magnetic resonance imaging signal hyperintensities in geriatric depression. *Stroke.*, *29*(3), 613–617.

Herrmann, L. L., Goodwin, G. M., & Ebmeier, K. P. (2007). The cognitive neuropsychology of depression in the elderly. *Psychological Medicine.*, *37*, 1693–1702.

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery, and Psychiatry.*, *79*(6), 619–624.

Hickie, I., Scott, E., Naismith, S., et al. (2001). Late-onset depression: Genetic, vascular and clinical contributions. *Psychological Medicine.*, *31*(8), 1403–1412.

Janssen, J., Hulshoff Pol, H. E., de Leeuw, F. E., et al. (2007). Hippocampal volume and subcortical white matter lesions in late life depression: Comparison of early and late onset depression. *Journal of Neurology, Neurosurgery, and Psychiatry.*, *78*, 638–640.

Kaneriya, S. H., Robbins-Welty, G. A., Smagula, S. F., Karp, J. F., Butters, M. A., Lenze, E. J., ... Reynolds, C. F., 3rd (2016). Predictors and moderators of remission with aripiprazole augmentation in treatment-resistant late-life depression: An analysis of the IRL-GRey randomized clinical trial. *JAMA Psychiatry.*, *73*(4), 329–336.

Lee, Y. B., Nagai, A., & Kim, S. U. (2002). Cytokines, chemokines, and cytokine receptors in human microglia. *Journal of Neuroscience Research.*, *69*(1), 94–103.

Lee, S. H., Payne, M. E., Steffens, D. C., et al. (2003). Subcortical lesion severity and orbitofrontal cortex volume in geriatric depression. *Biological Psychiatry.*, *54*(5), 529–533.

Lenze, E. J., Mulsant, B. H., Blumberger, D. M., Karp, J. F., Newcomer, J. W., Anderson, S. J., ... Reynolds, C. F., 3rd (2015). Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: A randomised, double-blind, placebo-controlled trial. *Lancet.*, *386*(10011), 2404–2412.

Loftis, J. M., Huckans, M., & Morasco, B. J. (2010). Neuroimmune mechanisms of cytokine-induced depression: Current theories and novel treatment strategies. *Neurobiology of Disease.*, *37*(3), 519–533.

Matheny, M. E., Miller, R. R., Shardell, M. D., et al. (2011). Inflammatory cytokine levels and depressive symptoms in older women in the year after hip fracture: Findings from the Baltimore Hip Studies. *Journal of the American Geriatrics Society.*, *59*(12), 2249–2255.

Mourao, R. J., Mansur, G., Malloy-Diniz, L. F., Castro Costa, E., & Diniz, B. S. (2016). Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, *31*(8), 905–911.

Nebes, R. D., Pollock, B. G., Houck, P. R., Butters, M. A., Mulsant, B. H., Zmuda, M. D., & Reynolds, C. F., 3rd (2003). Persistence of cognitive impairment in geriatric patients following antidepressant treatment: A randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of Psychiatric Research.*, *37*(2), 99–108.

Nebes, R. D., Reynolds, C. F., Boada, F., et al. (2002). Longitudinal increase in the volume of white matter hyperintensities in late-onset depression. *International Journal of Geriatric Psychiatry.*, *17*(6), 526–530.

O'Brien, J. T., Firbank, M. J., Krishnan, M. S., et al. (2006). White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS study. *The American Journal of Geriatric Psychiatry.*, *14*(10), 834–841.

Peineau, S., Bradley, C., Taghibiglou, C., et al. (2008). The role of GSK-3 in synaptic plasticity. *British Journal of Pharmacology.*, *153*(Suppl 1), S428–S437.

Pereira, F. S., Yassuda, M. S., Oliveira, A. M., & Forlenza, O. V. (2008). Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment. *International Psychogeriatrics.*, *20*, 1104–1115.

Sheline, Y. I., Gado, M. H., & Kraemer, H. C. (2003). Untreated depression and hippocampal volume loss. *The American Journal of Psychiatry.*, *160*, 1516–1518.

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America.*, *93*, 3908–3913.

Shi, Y., You, J., Yuan, Y., Zhang, X., Li, H., & Hou, G. (2010). Plasma BDNF and tPA are associated with late-onset geriatric depression. *Psychiatry and Clinical Neurosciences.*, *64*, 249–254.

Steffens, D. C., Payne, M. E., Greenberg, D. L., et al. (2002). Hippocampal volume and incident dementia in geriatric depression. *The American Journal of Geriatric Psychiatry.*, *10*(1), 62–71.

Tapia-Arancibia, L., Aliaga, E., Silhol, M., & Arancibia, S. (2008). New insights into brain BDNF function in normal aging and Alzheimer disease. *Brain Research Reviews.*, *59*(1), 201–220.

Taylor, W. D., Steffens, D. C., MacFall, J. R., et al. (2003). White matter hyperintensity progression and late-life depression outcomes. *Archives of General Psychiatry.*, *60*(11), 1090–1096.

Thielke, S. M., Diehr, P., & Unutzer, J. (2010). Prevalence, incidence, and persistence of major depressive symptoms in the Cardiovascular Health Study. *Aging and Mental Health.*, *14*, 168–176.

Thomas, A. J., Davis, S., Morris, C., Jackson, E., Harrison, R., & O'Brien, J. T. (2005). Increase in interleukin-1beta in late-life depression. *The American Journal of Psychiatry.*, *162*(1), 175–177.

Yen, Y. C., Rebok, G. W., Gallo, J. J., Jones, R. N., & Tennstedt, S. L. (2011). Depressive symptoms impair everyday problem-solving ability through cognitive abilities in late life. *The American Journal of Geriatric Psychiatry.*, *19*(2), 142–150.

This page intentionally left blank

Chapter 8

Accelerated brain molecular aging in depression

Rammohan Shukla[1] **and Etienne Sibille**[1,2]

[1]Department of Neuroscience, University of Toledo, Toledo, OH, United States, [2]Departments of Psychiatry and of Pharmacology and Toxicology, Campbell Family Mental Health Research Institute of Centre for Addiction and Mental Health (CAMH), University of Toronto, Toronto, ON, Canada

Introduction

Aging, which is broadly defined as time-dependent functional changes, has gained attention for scientific study based on the knowledge we have gained on molecular and cellular basis of life and diseases (López-Otín et al., 2013). Alongside the growth of knowledge on aging, the parallel successes in modern medicine have resulted in unprecedented extension of human life span. The advances in both fields, however, have outpaced our ability to maintain optimal brain function and cognition (McQuail et al., 2015), which has led to an increased risk in the development of neurodegenerative and neuropsychiatric disorders in late life, including significant increases in symptoms related to depression (Fiske, Wetherell, & Gatz, 2009). Late-life depression (LLD) is a common neuropsychiatric disorder in older adults, with its occurrence mostly associated with cardiovascular, cerebrovascular, and neurodegenerative disorders (Diniz et al., 2016). To understand the neurobiology of LLD, it is important to identify its interactions with aging-associated disorders (Diniz et al., 2016). Several lines of evidence, including large-scale gene expression data, demonstrate positive correlations between most major depressive disorder (MDD)−related genes and age-dependent changes observed in control participants (Douillard-Guilloux, Guilloux, Lewis, & Sibille, 2013). This observation prompted us to hypothesize that MDD may engage age-related biological pathways, which we previously discussed in the context of an age-by-disease integration model (McKinney & Sibille, 2013; Sibille, 2013). Simultaneously, it also suggested that investigating the reciprocal links between aging and MDD may provide novel perspectives on disease mechanisms.

In this chapter, we will provide observations in support of an age-by-disease biological interaction hypothesis. First, we will briefly discuss the key factors addressing the effect of aging and depression on individual cognitive abilities. Here the similarities in the cognitive decline in the two states (aging and depression: unless required, will be referred as states hereafter) will be addressed in light of network models (Northoff & Sibille, 2014; Wang, Tegnér, Constantinidis, & Goldman-Rakic, 2004). Then, various pursuits to distinguish these states using molecular markers will be discussed. Our investigations of the molecular bases of depression in the human postmortem brain, which has uncovered a large and robust effect of age on multiple genes and biological pathways (Erraji-Benchekroun et al., 2005; Glorioso & Sibille, 2011), will also be summarized. Finally, with the support of all these observations as well as recent findings, an updated model of age-by-disease interaction and strategies to study it will be discussed. This model brings together basic research on normal aging with the investigation of neuropsychiatric and neurodegenerative diseases, and suggests that environment and genetic variability are contributing factors in defining risk and/or resiliency trajectories.

Neuronal correlates of cognitive changes in depression and aging

Information-processing speed is slowed down in both normal aging and depression with implications over range of cognitive functions which depend on time for attending and encoding of rapidly occurring information (Harada, Natelson Love, & Triebel, 2013; Korsnes & Ulstein, 2014; McClintock, Husain, Greer, & Cullum, 2010). Although it is difficult to pinpoint which cognitive sub-function is affected by aging, MDD and LLD, owing to the slow information-processing speed, a variety of cognitive phenomena, including but not limited to attention control, poorer encoding,

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00008-9

set-shifting, inhibition control, error monitoring, and cognitive planning, are impaired (Korsnes & Ulstein, 2014). These impairments are more severe in LLD than normal aging or depression in young persons (Drakeford et al., 2010). The convergent outcomes of aging, MDD, and LLD point to a unified neuronal network model, which can explain on the one hand, the similar outcome of aging and depression, and, on the other hand, the amplified outcomes observed in LLD where both aging and depression occur simultaneously.

For instance, based on the findings of selective loss of GABAergic markers in depression and in aging observed in many studies, including ours (Glorioso, Oh, Douillard, & Sibille, 2011; Sibille, Morris, Kota, & Lewis, 2011), we have proposed a pathophysiological working model of altered cognition and mood, linking genes with symptom dimension. This model is based on the knowledge of cortical micro circuitry as the basic functional unit of information processing in cortical structures (Northoff & Sibille, 2014). Briefly, in the frontal cortex, a region found to be important in cognitive control, the different information inputs to the dendrites of pyramidal cells are compartmentalized. Based on priority, certain inputs are inhibited by dendritic-targeting interneurons (inhibition control) that aid in focusing attention toward particular information. Based on our reported reduced expression of somatostatin (SST), cortistatin (CORT), and neuropeptide Y (NPY) in depression (discussed further, later), which are specifically expressed in dendritic-targeting interneurons, it can be proposed that deficits in these inhibitory markers alter the input/output of pyramidal neurons and therefore alter cortical microcircuit processing within key brain regions. In depression, this imbalance may translate in altered neural network level activity and surfaces as attention control, poorer encoding, set-shifting, inhibition control, and other associated symptoms (Northoff & Sibille, 2014).

Although the neural circuitry model explains most of the cognitive effects, symptoms of aging, depression, and LLD are currently indistinguishable at this level (Korsnes & Ulstein, 2014). Precisely, differentiating depression from aging calls for finding biomarkers specific for the different states. Next, we describe the molecular findings to differentiate these different states.

Peripheral and central biomarkers of "molecular aging" of the human brain

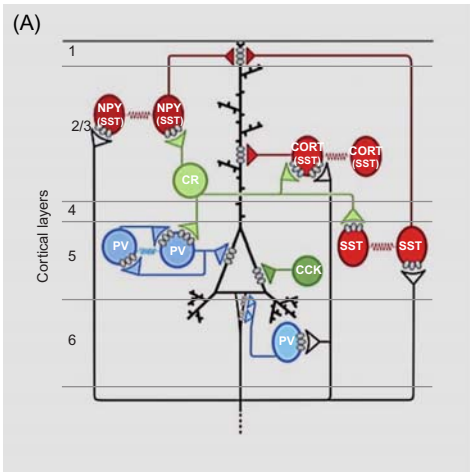
With high throughput multiplexing technologies, a comprehensive analysis of genes, transcripts, and proteins of the different states can be undertaken, which can aid in identifying molecular markers for appropriate diagnosis and therapeutic decisions. Studies using antibody arrays (Coppé et al., 2008) showed that senescent fibroblast cells secrete inflammatory, immune-modulatory cytokines, growth factors, and cell surface molecules also called as "Senescent-associated secretory phenotype" (SASP) proteins. Recently, Diniz et al. (2016) investigated the molecular pattern associated with SASP, referred as SASP index, in adults with LLD compared to never-depressed elderly individuals, and found that SASP is abnormally regulated and elevated in LLD. Although the SASP markers are peripheral, observations have indicated that astrocytes, which display typical characteristics of cellular senescence, are capable of triggering the SASP (Salminen et al., 2011).

Centrally, in a study from our group, the age-related changes of a large number of genes were investigated, using gene microarray technology, in prefrontal cortex samples from human subjects aged 13−79 years (Erraji-Benchekroun et al., 2005). With aging, approximately 7.5% of the genes changed significantly and consistently across the two prefrontal cortical areas investigated, and with similar changes observed in other studies (Blalock et al., 2003, 2004; Erraji-Benchekroun et al., 2005; Glorioso et al., 2011; Lee, Klopp, Weindruch, & Prolla, 1999; Lee, Weindruch, & Prolla, 2000; Lu et al., 2004; Miller, Horvath, & Geschwind, 2010). Overall, age-upregulated genes are mostly of glial origin and related to inflammation and cellular defenses, while downregulated genes display mostly neuron-enriched transcripts relating to cellular communication and signaling (Erraji-Benchekroun et al., 2005). Together, the consistency and specificity of age-related changes fulfill criteria for aging biomarkers. Using age-related trajectory regression analyses on these genes, we have shown that the predicted age for a particular individual is highly correlated with his/her chronological age (Erraji-Benchekroun et al., 2005; Glorioso et al., 2011). The predicted age, based on these markers, has been termed as "molecular age." Next, we review the overlap between age-dependent genes included in the molecular aging profile with those found in the context of disease pathways.

Deviation of molecular age from chronological age in disease states

The molecular age provides a functional assay to measure biological aging of the brain and to assess individual deviation from chronological age (Erraji-Benchekroun et al., 2005; Glorioso et al., 2011). Investigation of individual genes responsible for molecular aging in individuals with neurodegenerative and neuropsychiatric disorder suggests that molecular age can deviate from their expected trajectory in some affected individuals. To illustrate this, an example of a putative interaction between age and disease is provided by the investigation of BDNF and BDNF-dependent genes.

BDNF is a signaling neuropeptide that is critical during development and maintains plasticity and proper functioning of many targeted neuronal cells. BDNF is downregulated with increasing age, whereas expression may decrease by as much as 60% between the ages of 20 and 60 years (Erraji-Benchekroun et al., 2005; Webster, Herman, Kleinman, & Shannon Weickert, 2006). Interestingly, we have also reported evidence of decreased BDNF levels in the amygdala and anterior cingulate cortex of subjects affected with depression compared to controls (Guilloux et al., 2012; Sibille et al., 2011; Tripp et al., 2012). Moreover, the slope of decrease in BDNF expression in subjects with depression appears to parallel that of control subject, but at lower level, demonstrating reduced expression at most age. The fact that low expression in young depressed subjects' overlaps with levels that are reached at older ages in control subjects who have not developed depression suggests that although reduction in BDNF may be a critical contributing factor to developing pathophysiology, additional factors must be at play. To investigate those factors, we studied the trajectory of BDNF and multiple genes whose expressions are known to depend on BDNF signaling, including SST and NPY during normal aging and in the context of major depression (Guilloux et al., 2012; Rakofsky, Ressler, & Dunlop, 2012). The expressions of these genes, as for BDNF, were downregulated with increasing age. Interestingly, the expression profiles of these BDNF-dependent genes displayed increasing rates of change with age compared to BDNF (i.e., steeper slopes) and greater overall effect sizes in the context of depression (Fig. 8.1D) (Douillard-Guilloux et al., 2013). Together, this suggests an age-by-disease interaction that, in addition of changes in BDNF



(B)

Markers	Age	MDD
NPY	–1.27	–1.29
P–value	*.003*	*.0097*
CORT	–1.13	–1.72
P–value	*.004*	*.003*
SST	–1.48	–1.63
P-value	*.00005*	*.012*

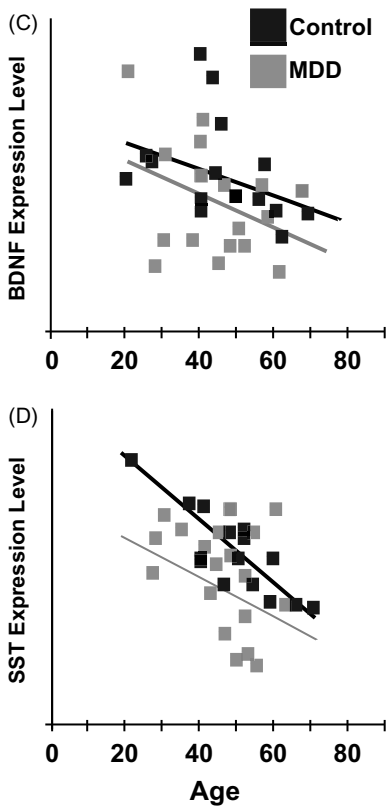


FIGURE 8.1 Dendritic inhibition, a biological module at the intersection of age and psychiatric disorders. (A) Excitatory pyramidal neurons (PYR) are regulated by different types of inhibitory GABA neurons. SST-, NPY-, and CORT-positive GABA neurons target PYR distal dendrites. Parvalbumin- (PV) and cholecystokinin (CCK)-positive GABA neurons target PYR cell body and axon initial segment calretinin (CR)-positive GABA neurons regulate other GABA neurons. (B) Markers of interneurons that target PYR dendrites show decreased expression with age, and great effect or statistical significance of changes in subjects with major depression. (C) Age regulation of BDNF. BDNF expression is significantly and inversely correlated with chronological age in control and depressed subjects and respective to age-matched control subjects, subjects with major depression display greater BDNF downregulation (D) Age regulation of SST. SST expression decreases with age in control subject at most ages. *(A and B) Sibille E. Molecular ageing of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues Clin Neurosci. 2013;15 (1):53–65. Copyright © Les Laboratoires Servier 2013. (C and D) Adapted from Douillard-Guilloux, G., Guilloux, J. P., Lewis, D. A., & Sibille, E. (2013). Anticipated brain molecular aging in major depression. American Journal of Geriatric Psychiatry, 21(5), 450–460. https://doi.org/10.1016/j.jagp.2013.01.040.*

function, further pushes the gene function in disease-promoting diseases. In light of these findings, the following aspects of age-by-disease interaction can be derived:

1. The difference in magnitude of expression level changes in individuals with brain disease and those without during aging is attributable to the disease (Fig. 8.1C and D).
2. Age-dependent changes in expression of disease-related genes are a risk factor for disease and associated symptoms.
3. BDNF and its associated age-dependent changes may represent an upstream mediator for age-dependent changes of disease-related genes.
4. Additional factors must be at play in establishing initial changes in upstream disease-related gene changes (i.e., low BDNF) and in moderating the apparent "acceleration" of age-dependent trajectories in disease-promoting directions.
5. Age-related changes occurring earlier than their expected trajectory (i.e., in adult subjects) may represent pathogenic features.

Next, based on these observations we have proposed, and now update an "age-by-disease" interaction model as well as strategies to study and test this model.

Proposed model of age-by-disease interaction

The considerable overlap between the cognitive and molecular correlates of brain aging and biological pathways implicated in MDD and LLD suggests a model for age-by-disease molecular interactions in which brain aging promotes biological changes associated with diseases. Based on the markers of aging and their expression changes with age, we propose that the human brain, with advancing age, moves toward a state that is consistent with those observed in MDD, LLD, or other neurological disorders (McKinney & Sibille, 2013). However, it is clear that not all elderly subjects develop neuropsychiatric and/or neurodegenerative disorders. This suggests that the age-dependent changes are not sufficient to induce overt pathophysiology and associated disease symptoms but are appropriate for the biological landscape of an elderly subject.

However, similar changes in a younger biological context may induce depression in midlife subjects. Hence the deviation of molecular age (the predicted age) from chronological age observed in our data might be more critical than expression changes and can be attributable to the diseased state. Based on these observations, supported by the fact that gene expression changes during advancing age occur in disease-promoting directions, our proposed model is that aging represents an intrinsic vulnerability to pathophysiological changes leading to symptom dimensions (e.g., cognitive decline, low mood) and brain disorders. More specifically, the deviation of disease-related gene expression outside the expected trajectories, which can be seen as homeostatic range, might mark the "at-risk" or "protected" trajectories depending upon the modulators (Fig. 8.2). Further investigations on the modulators that affect these deviations may

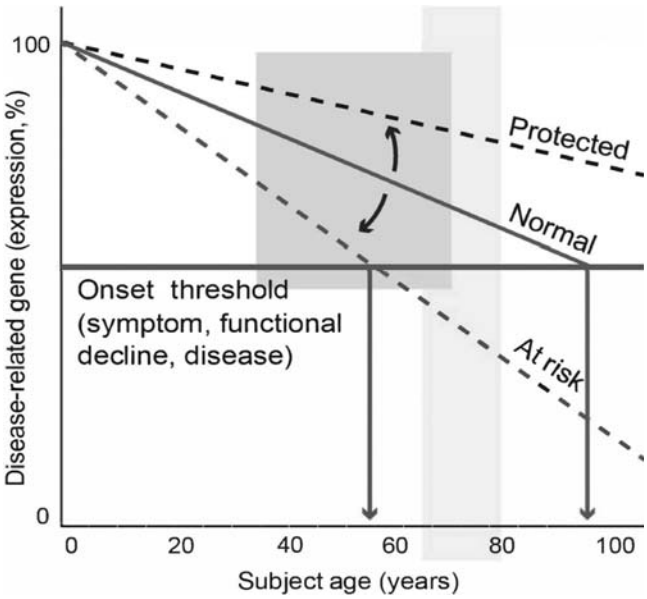


FIGURE 8.2 A proposed age-by-disease molecular interaction model. The graph depicts the age-dependent change in expression that is frequently observed for genes that are otherwise implicated in brain-related disorders (a decrease is shown here). Progression below a threshold (horizontal line) marks the onset of disease symptoms. Changes in the trajectory of age-related changes in expression of disease-related genes (Y-axis) determine the age (X-axis), or even if, an individual develops disease symptoms (left vertical arrows). According to this model, modulators (curved arrows above and below the normal line), genetic or environmental, place subjects on an "at risk" or protected trajectory for developing symptoms of brain-related disorders, LLD. *Adapted from Glorioso, C., & Sibille, E. (2011). Between destiny and disease: Genetics and molecular pathways of human central nervous system aging. Progress in Neurobiology, 93(2), 165–181. https://doi.org/10.1016/j.pneurobio.2010.11.006 and Glorioso, C., Oh, S., Douillard, G. G., & Sibille, E. (2011). Brain molecular aging, promotion of neurological disease and modulation by Sirtuin5 longevity gene polymorphism. Neurobiology of Disease, 41(2), 279–290. https://doi.org/10.1016/j.nbd.2010.09.016.*

provide insight to the disorders, their intrinsic variability, and critical information on mechanisms of disease onset or resilience. Environmental and genetic factors are obvious candidates for such investigations, and identifying their impact on the two modes (at-risk or protected) may require new experimental strategies. While working with live subjects, owing to the brain's capacity to buffer functional changes up until later years, the functional decline cannot be assessed till 60–65 years of age (Fig. 8.2, light gray shading). Molecular aging which displays continuous, lifelong, and mostly linear trajectory in adult subjects can let us assess the differences in molecular ages in midlife range using postmortem brain samples (Fig. 8.2, gray shading). As a proof of concept study to understand the genetic modulation of the deviation, we used the "molecular age" assay to characterize brain tissue of individual carrying a specific DNA variant located upstream from a candidate gene from the Sirtuin family of longevity-related genes (*SIRT5*) (Glorioso et al., 2011). We found that subjects carrying a low-expressing polymorphism of SIRT5 displayed increased molecular ages compared with carriers of the "protective" DNA variant, as measured in anterior cingulate cortex postmortem brain samples. These postmortem studies can be followed by studies demonstrating its association with putative changes in functional trajectories or with altered disease risk ratios in live subjects.

Genetic associations with functional outcomes can be performed using resources from large-scale epidemiological studies, such as the health and body composition, cardiovascular health study, or Framingham heart studies, which were specifically designed to investigate critical factors at the vigor-to-frailty age period. These studies may also facilitate the investigation of the moderating effects of the environment (i.e., exercise, caloric restriction, nutritional factors such as antioxidants and omega-3 fatty acids, medication, etc.), which are more difficult to assess in postmortem conditions due to smaller cohort sizes and limited antemortem information.

Conclusion

Here, we propose a framework to investigate the development of MDD and LLD, which we termed as age-by-disease interaction hypothesis. The hypothesis positions age-related changes in gene expression as the mechanism driving dysfunctions in cognitive and biological process leading to MDD and LLD. The implications of a proposed age-by-disease biological interaction model are profound, as it provides an investigational framework for identifying critical moderating factors, outlines opportunities for early interventions or preventions, and finally may form the basis for a dimensional definition of diseases that goes beyond the current categorical system. Earlier versions of this hypothesis were previously described (McKinney & Sibille, 2013; Sibille, 2013).

References

Blalock, E. M., Chen, K.-C., Sharrow, K., Herman, J. P., Porter, N. M., Foster, T. C., & Landfield, P. W. (2003). Gene microarrays in hippocampal aging: Statistical profiling identifies novel processes correlated with cognitive impairment. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(9), 3807–3819. Available from https://doi.org/23/9/3807, [pii].

Blalock, E. M., Geddes, J. W., Chen, K. C., Porter, N. M., Markesbery, W. R., & Landfield, P. W. (2004). Incipient Alzheimer's disease: Microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(7), 2173–2178. Available from https://doi.org/10.1073/pnas.0308512100.

Coppé, J.-P., Patil, C. K., Rodier, F., Sun, Y., Muñoz, D. P., Goldstein, J., … Campisi, J. (2008). Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biology*, *6*(12), e301. Available from https://doi.org/10.1371/journal.pbio.0060301.

Diniz, B. S., Reynolds, C. F., Sibille, E., Lin, C.-W., Tseng, G., Lotrich, F., … Butters, M. A. (2016). Enhanced molecular aging in late-life depression: The senescent-associated secretory phenotype. *The American Journal of Geriatric Psychiatry*, *25*, 64–72. Available from https://doi.org/10.1016/j.jagp.2016.08.018.

Douillard-Guilloux, G., Guilloux, J. P., Lewis, D. A., & Sibille, E. (2013). Anticipated brain molecular aging in major depression. *American Journal of Geriatric Psychiatry*, *21*(5), 450–460. Available from https://doi.org/10.1016/j.jagp.2013.01.040.

Drakeford, J. L., Edelstyn, N. M. J., Oyebode, F., Srivastava, S., Calthorpe, W. R., & Mukherjee, T. (2010). Recollection deficiencies in patients with major depressive disorder. *Psychiatry Research*, *175*(3), 205–210. Available from https://doi.org/10.1016/j.psychres.2008.08.010.

Erraji-Benchekroun, L., Underwood, M. D., Arango, V., Galfalvy, H., Pavlidis, P., Smyrniotopoulos, P., … Sibille, E. (2005). Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. *Biological Psychiatry*, *57*(5), 549–558. Available from https://doi.org/10.1016/j.biopsych.2004.10.034.

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in older adults. *Annual Review of Clinical Psychology*, *5*, 363–389. Available from https://doi.org/10.1146/annurev.clinpsy.032408.153621.

Glorioso, C., Oh, S., Douillard, G. G., & Sibille, E. (2011). Brain molecular aging, promotion of neurological disease and modulation by Sirtuin5 longevity gene polymorphism. *Neurobiology of Disease*, *41*(2), 279–290. Available from https://doi.org/10.1016/j.nbd.2010.09.016.

Glorioso, C., & Sibille, E. (2011). Between destiny and disease: Genetics and molecular pathways of human central nervous system aging. *Progress in Neurobiology*, *93*(2), 165−181. Available from https://doi.org/10.1016/j.pneurobio.2010.11.006.

Guilloux, J.-P., Douillard-Guilloux, G., Kota, R., Wang, X., Gardier, A. M., Martinowich, K., ... Sibille, E. (2012). Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression. *Molecular Psychiatry*, *17*(11), 1130−1142. Available from https://doi.org/10.1038/mp.2011.113.

Harada, C. N., Natelson Love, M. C., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine*, *29*(4), 737−752. Available from https://doi.org/10.1016/j.cger.2013.07.002.

Korsnes, M. S., & Ulstein, I. D. (2014). Cognitive effects of late life depression: Review of neuropsychological findings. *Journal of Behavioral and Brain Science*, *4*(3), 141−157. Available from https://doi.org/10.4236/jbbs.2014.43018.

Lee, C. K., Klopp, R. G., Weindruch, R., & Prolla, T. A. (1999). Gene expression profile of aging and its retardation by caloric restriction. *Science (New York, N.Y.)*, *285*(5432), 1390−1393. Available from https://doi.org/10.1126/science.285.5432.1390.

Lee, C. K., Weindruch, R., & Prolla, T. A. (2000). Gene-expression profile of the ageing brain in mice. *Nature Genetics*, *25*(3), 294−297. Available from https://doi.org/10.1038/77046.

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., Kroemer, G., Adler, A. S., ... Artandi, S. E. (2013). The hallmarks of aging. *Cell*, *153*(6), 1194−1217. Available from https://doi.org/10.1016/j.cell.2013.05.039.

Lu, T., Pan, Y., Kao, S.-Y., Li, C., Kohane, I., Chan, J., & Yankner, B. A. (2004). Gene regulation and DNA damage in the ageing human brain. *Nature*, *429*(6994), 883−891. Available from https://doi.org/10.1038/nature02661.

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology*, *24*(1), 9−34. Available from https://doi.org/10.1037/a0017336.

McKinney, B. C., & Sibille, E. (2013). The age-by-disease interaction hypothesis of late-life depression. *American Journal of Geriatric Psychiatry*, *93*, 165−181. Available from https://doi.org/10.1016/j.jagp.2013.01.053.

McQuail, J. A., Frazier, C. J., & Bizon, J. L. (2015). Molecular aspects of age-related cognitive decline: The role of GABA signaling. *Trends in Molecular Medicine*, *21*(7), 450−460. Available from https://doi.org/10.1016/j.molmed.2015.05.002.

Miller, J. A., Horvath, S., & Geschwind, D. H. (2010). Divergence of human and mouse brain transcriptome highlights Alzheimer disease pathways. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(28), 12698−12703. Available from https://doi.org/10.1073/pnas.0914257107.

Northoff, G., & Sibille, E. (2014). Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings. *Molecular Psychiatry*, *19*(9), 966−977. Available from https://doi.org/10.1038/mp.2014.68.

Rakofsky, J. J., Ressler, K. J., & Dunlop, B. W. (2012). BDNF function as a potential mediator of bipolar disorder and post-traumatic stress disorder comorbidity. *Molecular Psychiatry*, *17*, 22−35. Available from https://doi.org/10.1038/mp.2011.121.

Salminen, A., Ojala, J., Kaarniranta, K., Haapasalo, A., Hiltunen, M., & Soininen, H. (2011). Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. *European Journal of Neuroscience*, *34*(1), 3−11. Available from https://doi.org/10.1111/j.1460-9568.2011.07738.x.

Sibille, E. (2013). Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. *Dialogues in Clinical Neuroscience*, *15*(1), 53−65. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 3622469&tool = pmcentrez&rendertype = abstract>.

Sibille, E., Morris, H. M., Kota, R. S., & Lewis, D. A. (2011). GABA-related transcripts in the dorsolateral prefrontal cortex in mood disorders. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *14*(6), 721−734. Available from https://doi.org/10.1017/S1461145710001616.

Tripp, A., Oh, H., Guilloux, J.-P., Martinowich, K., Lewis, D. A., & Sibille, E. (2012). Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *The American Journal of Psychiatry*, *169*(11), 1194−1202. Available from https://doi.org/10.1176/appi.ajp.2012.12020248.

Wang, X.-J., Tegnér, J., Constantinidis, C., & Goldman-Rakic, P. S. (2004). Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(5), 1368−1373. Available from https://doi.org/10.1073/pnas.0305337101.

Webster, M. J., Herman, M. M., Kleinman, J. E., & Shannon Weickert, C. (2006). BDNF and trkB mRNA expression in the hippocampus and temporal cortex during the human lifespan. *Gene Expression Patterns*, *6*(8), 941−951. Available from https://doi.org/10.1016/j.modgep.2006.03.009.

Chapter 9

Cognitive dysfunction in late-life psychiatric disorders: phenotypes, risk factors, and treatment targets

Christina F. Chick[1,2], **Casey Buck**[1] and **Ruth O'Hara**[1,2,3]

[1]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States,* [2]*Sierra Pacific Mental Illness Research Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States,* [3]*Stanford/VA Alzheimer's Center, Palo Alto, CA, United States*

Individuals with late-life psychiatric disorders exhibit distinctive cognitive profiles, which differ from normal aging in both the nature and severity of cognitive impairment (O'Hara, 2012). The field of Geriatric Psychiatry has advanced to the stage that it is increasingly recognized that distinct profiles of cognitive dysfunction and associated neurophysiological impairments play a significant role in the etiological bases, diagnosis, prognosis, and treatment of a broad range of disorders in late life, including late-life depression, anxiety, bipolar disorder, schizophrenia, and posttraumatic stress disorder (PTSD). We review the evidence in support of (1) the shared etiology of cognitive dysfunction and psychiatric disorders in late life, including neurodegenerative models of vascular function, white matter integrity, cortical thickness, and genetic risk factors; (2) the utility of cognitive dysfunction in distinguishing phenotypes of late-life psychiatric disorders; (3) the potential for late-life psychiatric symptoms to predict subsequent cognitive decline; (4) the potential for cognitive decline to predict emotional dysregulation and subsequent cognitive impairment and decline; (5) the severity of cognitive dysfunction as a predictor of pharmacologic and psychotherapeutic treatment response; and (6) the role of cognitive dysfunction in contributing to the negative association of medical disorders and mental health with age. We end by briefly discussing potential treatment targets, such as cognitive training and neuromodulatory interventions, and suggesting directions for future research.

Using cognitive profiles to refine late-life psychiatric phenotypes

Cognitive dysfunction is a primary feature of late-life psychiatric disorders. Although healthy aging is associated with a decline in performance across various domains of cognitive function, including psychomotor speed, attention and inhibition, working memory, explicit verbal memory, visual memory, and visuospatial ability, these performance declines are more severe in older adults with psychiatric disorders (Andreescu & Varon, 2015; Hogan, 2003; Meesters et al., 2013; Wei et al., 2019). Before discussing the domains of cognitive impairment associated with specific psychiatric diagnoses, we briefly introduce definitions of cognitive impairment and associated diagnoses. Dementia refers to a broad loss of cognitive functions, which often include language, memory, and decision-making, and associated decline in ability to perform daily tasks. It can have multiple etiologies, including vascular, frontotemporal, Lewy-body, Alzheimer's disease (AD), and other neurodegenerative disorders. Mild cognitive impairment (MCI), cognitive problems without disruption of the ability to perform daily tasks, often precedes dementia. Individuals with severe memory impairments are categorized as having amnestic mild cognitive impairment (aMCI), and those with intact function in other cognitive domains are characterized as having single-domain aMCI. However, individuals with memory impairments may also have compounded impairments in other domains of cognitive function, including executive function, language, processing speed, and visuospatial skills. Those with impairments in memory as well as one or more other cognitive domains are characterized as having multidomain aMCI. Both forms of aMCI are risk factors for the

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00009-0

development of AD (Gorelick et al., 2011). Individuals with cognitive impairment in any domain other than memory are characterized as having nonamnestic MCI. As with aMCI, those with nonamnestic MCI are further classified into single-domain nonamnestic MCI or multidomain nonamnestic MCI. Profiles of cognitive dysfunction or impairment can be useful in refining phenotypes of late-life psychiatric disorders. We describe what is known about these cognitive phenotypes below.

Depression

A recent longitudinal study of 273 community-dwelling older adults found that, compared to nondepressed controls, those with depression had higher rates of dysfunction and decline in all cognitive domains tested (Riddle et al., 2017). This is consistent with a previous study, which showed that of 1265 nondemented older adults, those with depression had greater impairments in overall cognition as compared to controls, as measured by the Mini-Mental State Examination (MMSE; Ganguli, Du, Dodge, Ratcliffe, & Chang, 2006). Specific domains of cognitive functioning that are frequently impaired in late-life depression include psychomotor speed, information processing speed, attention, inhibition, working memory, verbal fluency, verbal memory, and visuospatial memory (Almeida, Hankey, Yeap, Golledge, & Flicker, 2016; Olaya, Montena, Ayuso-Mateos, & Haro, 2019; Wei et al., 2019). Older adults with more severe depressive symptoms have been found to have slower processing speed and lower set-shifting abilities, as reflected by poorer scores on both Trails A and B tests (Ganguli et al., 2006). Older individuals with depression have also been found to have impaired language abilities, as evidenced by lower scores on neuropsychological assessment measures such as Boston Naming Test, Letter Fluency, and Category Fluency (Ganguli et al., 2006). Late-life depressive symptoms are also associated with lower scores on memory tests, including the California Verbal Leaning Test-2 and both immediate and delayed story recall (Ganguli et al., 2006; Shimada et al., 2014). A meta-analysis of 23 prospective studies found that late-life depression is also associated with increased risk for developing dementia and cognitive decline (Diniz, Butters, Albert, Dew, & Reynolds, 2013).

Anxiety

Geriatric anxiety is linked to impairments in working memory, attention, and problem solving (Andreescu & Varon, 2015; Hogan, 2003). A study by our group found that, of 102 community-dwelling older adults, those with anxiety showed deficits in inhibition, processing speed, and attention shifting, but not in word fluency (Beaudreau & O'Hara, 2009). In geriatric generalized anxiety disorder (GAD), more severe symptoms are associated with greater impairments in short-term memory and working memory (Andreescu & Varon, 2015). Anxiety in older adults is also associated with an increased risk for developing dementia (Becker et al., 2018; Gulpers et al., 2016).

Schizophrenia and bipolar disorder

Both late-life schizophrenia and bipolar disorder are associated with deficits in verbal memory, verbal fluency, and executive function (Meesters et al., 2013). Additionally, both disorders are associated with an increased risk for developing dementia (Aprahamian, Nunes, & Forlenza, 2013). While most research on cognitive functioning in bipolar disorder has been conducted on younger populations, cognitive deficits in verbal memory, executive function, attention, visual memory, and mental speed have been observed in older adults with bipolar disorder (Aprahamian et al., 2013). Individuals with late-life bipolar disorder often have cognitive deficits that vary in intensity, based on mood level (i.e., cognitive dysfunction increases during depressive and manic episodes). However, even during euthymic states, cognitive impairment is still present (Palmer, Loughran, & Meeks, 2010).

Posttraumatic stress disorder

PTSD is associated with learning and memory deficits in older adults. In one study, 19 older adult veterans with PTSD showed impairments in both short-term and delayed memory for lists of information, with a lesser degree of impairment in memory for structured information (e.g., stories; Mackin, Lesselyong, & Yaffe, 2012). Older veterans with PTSD also perform more poorly than veteran controls on learning tests (Schuitvoerder et al., 2013). Another study of older adults found that those with the most severe PTSD symptoms also performed more poorly on tests of executive function and concentration (Mota et al., 2016). Interestingly, one of the studies referenced above (Mackin et al., 2012) found that comorbid depression did not affect cognitive performance.

Differentiating anxiety from depression in late life

Late-life anxiety and depression are associated with partially overlapping domains of cognitive impairment. Both disorders have been linked to executive dysfunction and higher rates of memory decline (DeLuca et al., 2005; O'Hara, 2012; Sapolsky, 2000), and these symptoms are exacerbated when anxiety and depression are comorbid (Basso et al., 2007; O'Hara, 2012). Indeed, more severe anxiety symptoms in concurrent late-life depression are associated with poorer cognitive control, higher emotion dysregulation, and more worry (Spinhoven, van der Veen, Voshaar, & Comijs, 2017). Nonetheless, late-life anxiety and depression are associated with distinctive cognitive phenotypes. In comparing GAD with major depressive disorder (MDD) in older adults, a study of 127 found that those with GAD were impaired in tests of memory and set-shifting, and but only those with geriatric MDD displayed impairments in tests of memory, processing speed, as well as global cognitive functioning, compared to those with no psychiatric illness (Mantella et al., 2007). However, there were no significant differences in impairment on any specific cognitive domain as tested by the neuropsychological assessments between anxious and depressed subjects (Mantella et al., 2007). The two disorders also have partially overlapping risk factors. One study based on 3056 community-dwelling older adults in the Netherlands found that external locus of control was predictive of both GAD and MDD (Beekman et al., 2000). The same study found that a broad variety of risk factors predicted specific risk for GAD, including chronic illness, low level of education, low level of emotional support, and exposure to significant negative life events such as war (Beekman et al., 2000). In contrast, younger age was the only risk factor specific to MDD (Beekman et al., 2000). External locus of control was the only common variable found between the two late-life disorders (Beekman et al., 2000).

Differentiating schizophrenia from bipolar disorder in late life

Both individuals with late-life bipolar disorder and those with schizophrenia perform more poorly on measures of overall cognitive function than healthy controls (Meesters et al., 2013; Palmer et al., 2010). Both disorders are also linked with impairments in visual memory and problem solving (Palmer et al., 2010). However, those with bipolar disorder have similar or even superior performance compared to healthy controls in multiple cognitive domains (Meesters et al., 2013; Palmer et al., 2010). The degree to which these late-life disorders impact cognitive function differs, as patients with late-life schizophrenia are typically more cognitively impaired than those with late-life bipolar disorder. Individuals with late-life bipolar disorder perform better on tasks of verbal skills and crystallized knowledge, processing speed, and verbal memory compared to those with schizophrenia (Depp et al., 2007). This discrepancy in severity of cognitive dysfunction between schizophrenia and bipolar disorder is less apparent in late life than in younger populations (Depp et al., 2007). This may be due to the trajectory of the disorders: Individuals with schizophrenia show deficits in cognitive function that remain stable with age, whereas those with late-life bipolar disorder exhibit progressive cognitive dysfunction over time (Aprahamian et al., 2013; Lewandowski, Cohen, & Ongur, 2011; Meesters et al., 2013). Indeed, cognitive dysfunction typically does not continue to progress in late-life schizophrenia, and individuals with late-onset schizophrenia (over age of 40 years) often exhibit lesser impairment in multiple domains of cognitive function than those with early onset (Maglione, Thomas, & Jeste, 2014; Palmer et al., 2010). Whereas cognitive dysfunction sometimes precedes the onset of bipolar disorder, this effect has not been documented in schizophrenia (though more research is needed prior to drawing conclusions; Rajji & Mulsant, 2008).

Worry

There is also emerging evidence that, in defining late-life psychiatric disorders, other functional systems beyond neurocognitive dysfunction and negative valence must be considered. One example is the perseverative thought process of worry, as a critical domain impacting late-life anxiety and depressive disorders. Counterintuitively, higher levels of worry have been associated with attenuated associations between (1) late-life anxiety and depressive symptoms and (2) inhibitory and delayed verbal memory processes (Beaudreau et al., 2017). One study found that, of 42 community-dwelling older adults with anxiety and/or depressive symptoms, higher levels of worry were associated with fewer errors on the Stroop task (Beaudreau et al., 2017). The same study found that individuals with severe late-life depression and cooccurring high worry exhibited superior delayed verbal memory processes, as compared with those with severe late-life depression and low worry (Beaudreau et al., 2017). High worry, however, did not have the same protective factors for cognitive functioning in individuals with low depression. Subsequent work has identified a polymorphism (Val158Met) in the catechol-O-methyltransferase (COMT) genotype as a potential explanation for these paradoxical results (Beaudreau et al., 2017). This intriguing line of work shows that worry may attenuate the effects of depression and anxiety on cognitive processes under specific conditions. Nonetheless, perseverative thought has

generally been implicated as a mechanism for anxiety and depression across adulthood (Ruscio, Seitchik, Gentes, Jones, & Hallon, 2011). One study reported that individuals who reported higher rates of perseverative thought exhibited a more negative response to subsequent stressors. The same study found that intrusions of negative thoughts were associated with higher prevalence and severity of anxiety and depressive symptoms (Ruscio et al., 2011).

Neurophysiology associated with cognitive impairment in late-life psychiatric disorders

Overlapping neurophysiological processes have been proposed to contribute to both cognitive impairment and late-life psychiatric disorders. These processes include vascular disease, white matter integrity, gray matter volume (i.e., cortical thickness), and genetic polymorphisms. The specific cognitive domains that are impaired can sometimes inform whether cognitive impairments are attributed to vascular or other neurophysiological causes.

Depression

Late-life depression has been linked to increased risk for all-cause dementia, vascular dementia, and AD, though vascular dementia is more common than AD in patients with geriatric depression (Diniz et al., 2013). A leading theory linking late-life depression to vascular dementia is the *vascular-depression−dementia hypothesis*, which proposes that cerebrovascular disease perpetuates late-life depressive symptoms and increases the risk for development of vascular dementia. This hypothesis is supported by increased rates of white matter hyperintensities (WMHs) found in individuals with late-life depression. Although development of WMH is part of the natural aging process, it is more prominent in geriatric depression. A systematic review study found that older adults with depression had periventricular hyperintensity rates 2.57 times higher (based on five studies) and deep WMH rates 2.64 times higher (based on seven studies), than age-matched healthy controls (Barnes et al., 2012; Herrmann, Le Masurier, & Ebmeier, 2008). This has been attributed to underlying cerebrovascular conditions, which manifest as WMH and are thought to increase susceptibility to depression by disrupting frontostriatal circuits. Consistent with this theoretical perspective, deficits in processing speed and executive functions—two cognitive domains associated with frontostriatal activation—are frequently impaired in late-life depression (Herrmann et al., 2008).

Another neurophysiological change frequently associated with late-life depression is decreased hippocampal volume. The hippocampus facilitates a variety of learning and memory functions and is especially important in consolidating short-term memory into long-term memory (Sapolsky, 2000). Hippocampal atrophy is associated with cognitive deficits involving explicit memory (i.e., intentional recall of facts or experiences), and the severity of hippocampal atrophy may be related to age of depression onset. Atrophy or damage to the hippocampus has also been associated with a higher risk for dementia and to poorer treatment response (Barnes et al., 2012; Mah, Binns, & Steffens, 2015).

A link has also been established between the apolipoprotein E (APOE) ε4 allele (APOE* ε4) and late-life depression. APOE is a plasma protein involved in the transport of cholesterol and other lipids. A genetic polymorphism codes for variants of this protein, and the ε4 allele is a well-established risk factor for the development of AD (Bekris, Yu, Bird, & Tsuang, 2010). In older adults, the APOE* ε4 allele has been associated with higher rates of depressive symptoms and steeper decline in verbal memory (Lavretsky et al., 2003; Skoog et al., 2015). The APOE* ε4 allele is also known to affect brain structures involved in other memory functions, including hippocampal volume. Moreover, the onset of depression increases the risk for developing MCI and dementia via interaction with the ε4 allele. One study found that, of 56 older adults with both depression and MCI, those who had the ε4 allele, compared to those without the ε4 allele, had higher rates of cognitive decline during a 1-year follow-up period (Sakurai & Montero-Odasso, 2017).

Anxiety

Evidence suggests that late-life anxiety and dementia may share neurophysiological pathways and that anxiety may even contribute to the onset of dementia. This evidence is summarized in hypotheses about the role of anxiety in (1) cardiovascular disease and (2) cumulative stress (Gulpers et al., 2016). Regarding the first hypothesis, late-life anxiety may contribute to the development of dementia via effects on the cardiovascular system. Anxiety is linked to hypertension, hypercoagulability, and atherosclerosis, which facilitate vascular damage. In turn, vascular damage may contribute to vascular neurodegenerative diseases such as vascular dementia (Becker et al., 2018). Thus, by exacerbating symptoms of cardiovascular disease, anxiety may contribute to the development of dementia.

Regarding the second hypothesis, anxiety may also contribute to the development of dementia through interactions with stress physiology and subsequent consequences for brain structure and function. According to the cumulative stress hypothesis, repeated exposure to stress has long-term consequences for brain structure and function. One brain structure

harmed by repeated stress is the hippocampus, which, in addition to memory functions, is also involved in the regulation and inhibition of stress responses (McEwen, 1998). The hippocampus facilitates stress responses by aiding in the release of various neuromodulators (e.g., excitatory amino acids, serotonin, and glucocorticoids). While these neuromodulators facilitate adaptive responses to stress in the short term, they also have long-term consequences for cognitive function (McEwen, 1998). It should be noted that associations between rates of anxiety and dementia increase with age, suggesting that anxiety is a prodromal expression of dementia, rather than a causal factor (Gulpers et al., 2016). Nonetheless, there is also longitudinal evidence that late-life anxiety may contribute to the development of dementia via interactions with vascular disease and stress response (Gulpers et al., 2016).

Schizophrenia

Individuals with schizophrenia are more predisposed to the development of various chronic conditions, including atrial fibrillation, peripheral vascular disease, cerebrovascular disease, diabetes, and substance abuse (Ribe et al., 2015). Potential consequences of these conditions include white matter atrophy and small deep infarcts, both of which have been associated with cognitive decline and higher rates of dementia (Gorelick et al., 2011; Reitz, Luchsinger, & Mayeux, 2008; Ribe et al., 2015). As with late-life anxiety and depression, individuals with schizophrenia are also more likely to develop various vascular conditions, which may explain the increased risk for MCI and dementia (Barnes et al., 2012; Becker et al., 2018; Diniz et al., 2013; Gulpers et al., 2016; Ribe et al., 2015).

Schizophrenia and accelerated aging

A leading theory attributes symptoms of schizophrenia to rapid neurodegeneration, consistent with accelerated aging (Fischer & Agüera-Ortiz, 2018; Ribe et al., 2015; Shahab et al., 2019). One neurophysiological process that has been interpreted as consistent with this process is decreased cortical thickness (Shahab et al., 2019). In schizophrenia, age-related decreases in cortical thickness, particularly of the frontal and temporal cortices, occur more rapidly than in natural aging. This is supported by greater cognitive dysfunction in individuals with schizophrenia, although the course and specific domains of these deficits (including visuospatial memory, language, short-term memory, and executive functioning) are heterogeneous, and no clear trajectory is typically observed (Rajji et al., 2013).

In addition to rapid loss of cortical thickness, individuals with schizophrenia experience accelerated loss of white matter integrity (Shahab et al., 2019). Cognitive impairments in young- and middle-aged adults with schizophrenia are similar to those observed in otherwise healthy older adults, and it has been proposed that this is caused by the loss of white matter integrity in both populations. That is, the neurobiological process of white matter loss in schizophrenia may result in a decline in cognitive function that is functionally similar to that of accelerated aging (Jeste, Wolkowitz, & Palmer, 2011). Moreover, compared to other psychiatric disorders, such as major depressive disorder and borderline personality disorder, schizophrenia is associated with the most accelerated brain aging; individuals with schizophrenia have lifespans shortened by up to 20 years (Shahab et al., 2019). It is possible that, for this reason, schizophrenia is underrepresented and understudied in older patient populations (Meesters et al., 2013).

Disentangling late-life psychiatric symptoms from prodromes of other neurodegenerative disorders

It can be difficult to distinguish cognitive impairments caused by underlying vascular conditions from those symptomatic of a psychiatric disorder or prodromal to an underlying neurodegenerative disease, such as AD. However, the cognitive phenotypes associated with certain psychiatric disorders can be useful in distinguishing late-life psychiatric disorders from prodromes of neurodegenerative disorders. For example, the profile of cognitive impairments associated with schizophrenia has been useful in determining whether cognitive dysfunction should be classified as a symptom of schizophrenia or as prodromal to AD. Unlike individuals with AD, who tend to experience rapid memory impairment, individuals with schizophrenia typically maintain learned information (Palmer et al., 2010). The Montreal Cognitive Assessment is useful in differentiating these disorders, because it provides a more sensitive measure of MCI compared to the MMSE (Palmer et al., 2010).

Another factor informing the pathology of cognitive dysfunction in relation to psychiatric symptoms is the age of onset. As onset of schizophrenia and bipolar disorder typically occurs prior to 40 years of age, those with onset after this period should be assessed for other neurodegenerative causes. Late-onset schizophrenia, though possible, is rare; a review of 41 studies estimates that the incidence rate of schizophrenia over age 65 is only 7.5%, and is predominantly

female (Stafford, Howard, & Krikbridge, 2018). Individuals with late-onset schizophrenia do not exhibit a markedly different profile of cognitive deficits as compared to those with early-onset schizophrenia (Palmer et al., 2010).

Psychiatric disorders as a risk factor for subsequent cognitive decline

Late-life depressive symptoms are associated with increased risk for cognitive impairment and AD (Almeida et al., 2016). Specifically, more severe progression of depressive symptoms over time has been associated with accelerated progression to AD (Barca et al., 2017). Onset of depression may also increase risk for subsequent MCI and dementia in interaction with the ε4 allele of the APOE polymorphism. One study of 56 older adults with MCI found that the APOE*ε4 polymorphism was associated with the development of cognitive decline during 1 year of follow-up (Sakurai & Montero-Odasso, 2017).

There is also evidence that age of depression onset influences progression of cognitive dysfunction in late life, though this evidence is mixed. A longitudinal study of 437 community-dwelling older adults found that those with early-onset depression experienced more rapid decrease in cognitive functioning across multiple cognitive domains (e.g., episodic memory, executive function, verbal fluency, and attention/working memory) as compared to both older adults with late-onset depression and controls (Riddle et al., 2017). However, in the same study, older adults with both early- and late-onset depression had higher rates of cognitive dysfunction and cognitive decline in all domains tested, compared to controls (Riddle et al., 2017). In contrast, another study found that history of depression during young or middle adulthood might be unrelated to risk for developing cognitive deficits in late life. Of 1,027 community-dwelling older adults in Spain, individuals who reported having experienced depression at some point during their lifetime performed similarly to nondepressed individuals on memory and verbal fluency tasks (Olaya et al., 2019). If this retrospective self-report of depressive symptoms is to be relied upon, it suggests that the presence of depressive symptoms during middle adulthood may not be a risk factor for cognitive dysfunction in late life.

In patients with schizophrenia, age of onset does influence severity of cognitive symptoms in late life. Although cognitive dysfunction in schizophrenia typically does not increase over time, individuals with late-onset schizophrenia (over age of 40 years old) typically exhibit lesser impairment in various domains of cognitive function than do those with early onset (Maglione et al., 2014; Palmer et al., 2010). Cognitive domains in which reduced dysfunction is associated with later age of onset include processing speed, verbal memory, and some aspects of executive function (Palmer et al., 2010). Additionally, individuals with late-life schizophrenia may exhibit cognitive dysfunction prior to the onset of the disorder (Rajji & Mulsant, 2008). Unlike those with schizophrenia, individuals with late-life bipolar disorder typically do not exhibit cognitive dysfunction prior to the onset of the disorder (though insufficient research exists to draw conclusions; Rajji & Mulsant, 2008). In late-life bipolar disorder, cognitive dysfunction increases over time and with subsequent bipolar episodes (Lewandowski et al., 2011).

Cognitive function as a predictor of pharmacologic and psychotherapeutic treatment response

Cognitive impairment has been implicated not only in exacerbation of psychiatric symptoms but also in poorer response to pharmacologic treatment in late-life psychiatric disorders (Mohlman & Gorman, 2005; Sneed et al., 2007; Sneed et al., 2010). For example, executive dysfunction has been associated with poorer pharmacologic treatment response in those with late-life disorders, though this may be due in part to poorer treatment compliance (Cristancho et al., 2018; Manning et al., 2015). However, individuals with poorer executive function might also benefit more than those with higher executive functioning from cognitive interventions such as cognitive-behavioral therapy.

Given the potential bidirectional relationship between cognitive dysfunction and psychiatric symptoms, treatment of one has been thought to influence the other. There is some evidence that pharmacological treatments targeting cognitive function have reduced psychiatric distress, and vice-versa, in those with late-life disorders. Augmenting dopaminergic activity in late-life bipolar disorder has resulted in modest improvements in cognition, particularly in processing speed and working memory (Aprahamian et al., 2013). Additionally, aripiprazole prescribed for treatment-resistant late-life depression has been associated with improved set-shifting performance as well as greater rates of remission as compared to a placebo (Kaneriya et al., 2016; Lenze et al., 2015). Selective serotonin reuptake inhibitors (SSRIs), combined with cognitive-behavioral therapy, were found to reduce peak cortisol levels in patients with late-life GAD (Rosnick et al., 2016). In light of the cumulative stress hypothesis described above, these results might have implications for reducing stress and improving cognition in these individuals.

However, other pharmacological treatments for late-life disorders have generally shown either modest or nonsignificant effects in improving or delaying deterioration of cognitive function. Tricyclic antidepressants have not been associated with cognitive improvements among patients with late-life depression (Alexopoulos, Katz, Reynolds, Carpenter, & Docherty, 2001; Nebes et al., 2003). Results have been mixed regarding the efficacy of SSRIs in improving cognitive function in late-life depression. Paroxetine was not found to improve cognitive dysfunction in depressed older adults (Nebes et al., 2003), while sertraline was found to moderately improve one measure of attention and executive function, but only in treatment responders (Devanand et al., 2003). Antidepressant treatments donepezil and sertraline have been found ineffective in preventing cognitive impairment in healthy older adults (Munro et al., 2012) and in improving cognition in depressed patients with AD (Reynolds et al., 2011). In older adults with both AD and depression, sertraline did not improve psychiatric symptoms (Rosenberg et al., 2010). Similarly, some studies have found that cognitive remediation therapy has produced limited improvements for older patients with schizophrenia (Golas et al., 2015; Kontis, Huddy, Reeder, Landau, & Wykes, 2013). However, other studies have found beneficial effects of cognitive remediation therapy in older adults with psychiatric disorders; for example, one study found a reduction in positive symptoms and less steep decline in daily functioning in geriatric schizophrenia patients who received cognitive remediation therapy (Thomas, Puig, & Twamley, 2017).

As pharmacologic treatments are less effective in patients with higher levels of cognitive dysfunction, a treatment approach focusing on improving cognitive deficits may prove beneficial in reducing symptoms of late-life psychiatric disorders. Poor cognitive control has been implicated in diminished executive function and emotion regulation, as well as exacerbation of psychiatric symptoms (Spinhoven et al., 2017). A common reason for antidepressant nonresponse in late-life disorders is more severe cognitive impairment. Older adults who are not responsive to pharmacologic treatments have been found to be impaired in the executive functions of planning and organizing (Pimontel et al., 2015). Thus, treatment augmentation focusing on these domains may be a more effective approach for treatment response in those with late-life depression.

Developing and identifying treatment targets such as cognitive training and augmentation

Brain training is an emerging approach to treatment of psychiatric disorders and cognitive impairment. The goal of brain training is to improve cognitive functioning by strengthening relevant underlying neural circuits. It is thought that this can be accomplished by performing repetitive and adaptive behavioral tasks that engage these circuits. Evidence suggests that brain training, modified to target different psychiatric disorder-related neural circuits, can be effective in treating schizophrenia and depression in young and middle-aged adults (Etkin, Gyurak, & O'Hara, 2013). A popular method of brain training is computerized skill training, which can target cognitive domains including processing speed, attention, memory, and other executive functions. Computer-based cognitive training has been associated with significant memory improvements in those with late-life depression (Naismith et al., 2011). Such training has also been linked to improvements in learning, memory, executive functioning, global cognition, and depressive symptoms in patients with AD (Sitzer, Twamley, & Jeste, 2006). While research is still limited, findings suggest that certain types of cognitive training can improve cognitive functioning in late-life disorders, possibly by promoting neuroplasticity (Brinke, Davis, Bahra, & Liu-Ambrose, 2017; Naismith et al., 2011).

Brain stimulation is an increasingly common approach to the treatment of late-life disorders, particularly those that are nonresponsive to medications. Repetitive transcranial magnetic stimulation (rTMS) has been effective in treating depression in younger adults (Slotema, Blom, Hoek, & Sommer, 2010); however, results are mixed regarding its efficacy in late life. The limited research in older adults is promising, as rTMS has resulted in greater rates of remission as well as improved language functioning and episodic memory in older adults with depression (Kaster et al., 2018). Similarly, rTMS has resulted in improvements in action naming and auditory sentence comprehension in patients with AD (Liu, Rajji, Blumberger, Daskalakis, & Mulsant, 2014). However, rTMS has produced limited improvements in executive functioning, a domain largely impaired in late-life depression (Illieva et al., 2018). The mixed results regarding efficacy of rTMS in augmenting cognitive function in late-life disorders might be due to the brain atrophy associated with aging; in particular, late-life depression is associated with atrophy of the prefrontal cortex (Illieva et al., 2018). As a result, relative to protocols that have been effective in treating younger adults, increased intensity and frequency of treatments might be necessary to produce results in depressed older adults.

Noninvasive neuromodulatory treatments have also been effective in treating dementia, late-life schizophrenia and late-life depression (Liu et al., 2014). Electroconvulsive therapy (ECT) has been used to treat various mood disorders

by increasing neuroplasticity. ECT has been linked with reduced symptoms of depression in older adults with depression with dementia, and bilateral ECT has been found effective in treatment of older patients with early-onset schizophrenia (Liu et al., 2014). Unilateral ECT has been associated with greater improvements in cognition in patients with late-life depression as compared to bilateral ECT (Kumar et al., 2016). Additionally, ECT has been found effective in treating treatment-resistant geriatric depression as well as in preventing relapse (Geduldig & Kellner, 2016). Whereas both ECT and pharmacological treatments often produce side effects, including disturbances to cognitive functioning, no such side effects have been documented for rTMS. This motivates increased focus on rTMS as a favorable treatment strategy, particularly in populations with existing cognitive dysfunction (Kaster et al., 2018; Liu et al., 2014). Ultimately, research is still limited regarding the duration of rTMS effects, and the degree to which they produce cognitive improvements that generalize to settings encountered in real life (Kaster et al., 2018; Liu et al., 2014). However, extant research has identified the potential for noninvasive brain stimulation techniques, such as rTMS, to improve cognitive [and emotional] functioning in late-life psychiatric disorders.

Potential future directions for neuromodulatory research include neuroendocrine function and sleep. One study found that a glucocorticoid antagonist receptor improved memory, executive function, and worry severity for patients with higher baseline cortisol levels (Lenze et al., 2014). These improvements remained after discontinuation of the glucocorticoid antagonist receptor medication (mifepristone). However, low to no improvements were found for patients who did not have higher baseline cortisol levels (Lenze et al., 2014). This finding is especially relevant for late-life anxiety and schizophrenia, as higher cortisol levels have been implicated in late-life GAD diagnoses as well as found as a risk factor for schizophrenia (Rosnick et al., 2016). Cognitive Behavioral Therapy (CBT), a form of psychotherapy focusing on challenging negative thoughts and behaviors, has been linked with reducing peak cortisol levels in older adults with GAD (Rosnick et al., 2016). CBT augmentation of SSRI escitalopram has been associated with a significant reduction of peak cortisol levels in older adults with GAD compared to escitalopram alone (Rosnick et al., 2016).

Another underlying mechanism potentially affecting late-life disorders is sleep. Sleep alterations have been observed in affective, anxiety, personality, and schizophrenic disorders (Baglioni et al., 2016). Cognitive-behavioral therapy delivered by telephone (CBT-T) has been effective in reducing insomnia and improving health-related quality of life in older adults with GAD, even after a one-year follow-up (Brenes, Danhauer, Lyles, Anderson, & Miller, 2016). Disturbed sleep is linked to both late-life anxiety and depression, as both disorders share a U-shaped association with sleep (Van den Berg et al., 2009). That is, individuals who have total sleep time longer or shorter than average are more likely to have a depressive or anxiety disorder (Van den Berg et al., 2009). A brief CBT for insomnia (CBT-I) intervention was effective in decreasing depressive symptoms among community-dwelling older adults (Van den Berg et al., 2009).

Offering a window to neurocircuitry and the development of transdiagnostic measures for geriatric psychiatry

The connection between cognitive dysfunction and psychiatric distress, both cross-sectionally and in bidirectional longitudinal models, may be related to common neurocircuitry underlying both cognitive deficits and psychiatric disorders (Etkin et al., 2013; Sapolsky, 2000). For example, there is overlap in the lateral prefrontal neuronal substrates underlying (a) cognitive control in emotional contexts and (b) processing of stimuli that are motivationally salient and influence behavior, but are not emotional per se (Mather, 2012; O'Hara, 2012). These areas of overlap for cognitive control have also been implicated in executive functioning, supporting the theorized bidirectional relationship between cognitive dysregulation and the exacerbation of psychiatric symptoms in late-life disorders (Etkin et al., 2013; Hantke, Gyurak, Van Moorleghem, et al., 2017; Katz et al., 2010; O'Hara, 2012).

Activation in, and anatomy of, key brain regions has been associated with both cognitive dysfunction and psychiatric symptoms in late-life disorders. Aberrant activation in the anterior cingulate cortex is frequently associated with geriatric depression (Katz et al., 2010; O'Hara, 2012). Activation in this region, as measured through positron emission tomography, has also predicted treatment response among those with late-life affective disorders (De Crescenzo et al., 2017). Hippocampal atrophy, and associated memory problems, are frequently observed in both late-life depressive and anxiety disorders (O'Hara, 2012; Sapolsky, 2000).

Additionally, white matter loss and hyperintensities have been associated with cognitive decline and with increased rates of dementia, late-life depression, anxiety, and schizophrenia (Barnes et al., 2012; Herrmann et al., 2008; Jeste et al., 2011; Shahab et al., 2019). As we have discussed, WMHs are commonly attributed to underlying vascular causes, which is consistent with findings that these late-life disorders often cooccur with vascular conditions (Barnes et al., 2012; Becker et al., 2018; Herrmann et al., 2008; Ribe et al., 2015). Given the significant overlap in neuronal measures of cognitive function and late-life psychiatric disorders, additional research into this shared neurocircuitry is warranted.

Conclusion

Cognitive deficits are core symptoms of late-life psychiatric disorders. Profiles of cognitive dysfunction can be useful in defining disorder-specific phenotypes, and in distinguishing early symptoms of psychiatric disorders from prodromes of underlying neurodegenerative disorders. Additionally, pathophysiological processes that exacerbate cognitive dysfunction and psychiatric symptoms may also influence response to various interventions. The partial overlap in brain structures supporting cognitive function and emotion regulation, particularly in the lateral prefrontal cortex, supports the interpretation that these processes reflect underlying common processes. While it has been established that cognitive dysfunction is a core symptom of late-life psychiatric disorders, less emphasis has been placed on investigating cognitive function as a risk factor for the development of these psychiatric disorders. Additional longitudinal studies are needed for further elucidation of the relationship between cognitive function and neuropsychiatric symptoms. Methods such as accelerated longitudinal modeling (Thompson, Hallmayer, & O'Hara, 2011) will be useful in identifying heterogeneous trajectories of cognitive and psychiatric dysfunction across individuals, as these trajectories may be associated with different optimal treatment strategies. There is cause for cautious optimism that treatments targeting cognitive dysfunction may be effective in reducing psychiatric symptoms, and vice-versa, although many studies on this topic have found null or modest effects. Also promising (but early stages of development) are noninvasive treatments such as cognitive "brain" training, which have been demonstrated as effective in improving limited domains of cognitive functioning in older adults.

References

Alexopoulos, G. S., Katz, I. R., Reynolds, C. F., Carpenter, D., & Docherty, J. P. (2001). The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. *Postgrad Medicine*, 1–86.

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2016). Depression as a risk factor for cognitive impairment in later life: The Health in Men cohort study. *International Journal of Geriatric Psychiatry*, *31*(4), 412–420. Available from https://doi.org/10.1002/gps.4347.

Andreescu, C., & Varon, D. (2015). New research on anxiety disorders in the elderly and an update on evidence-based treatments. *Current Psychiatry Reports*, *17*(7), 53. Available from https://doi.org/10.1007/s11920-015-0595-8.

Aprahamian, I., Nunes, P. V., & Forlenza, O. V. (2013). Cognitive impairment and dementia in late-life bipolar disorder. *Current Opinion in Psychiatry*, *26*(1), 120–123. Available from https://doi.org/10.1097/YCO.0b013e32835ac5f6.

Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., ... Riemann, D. (2016). Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychological Bulletin*, *142*(9), 969–990.

Barca, M. L., Persson, K., Eldholm, R., Benth, J. S., Kersten, H., Knapskog, A. B., ... Engedal, K. (2017). Trajectories of depressive symptoms and their relationship to the progression of dementia. *Journal of Affective Disorders*, *222*, 146–152. Available from https://doi.org/10.1016/j.jad.2017.07.008.

Barnes, D. E., Yaffe, K., Byers, A. L., McCormick, M., Scahefer, C., & Whitmer, R. A. (2012). Midlife vs late-life depressive symptoms and risk of dementia: Differential effects for Alzheimer disease and vascular dementia. *Archives of General Psychiatry*, *69*(5), 493–498. Available from https://doi.org/10.1001/archgenpsychiatry.2011.1481.

Basso, M. R., Lowery, N., Ghormley, C., Combs, D., Purdie, R., Neel, J., ... Bornstein, R. (2007). Comorbid anxiety corresponds with neuropsychological dysfunction in unipolar depression. *Cognitive Neuropsychiatry*, *12*(5), 437–456.

Beaudreau, S. A., & O'Hara, R. (2009). The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging*, *24*(2), 507–512. Available from https://doi.org/10.1037/a0016035.

Beaudreau, S. A., Hantke, N. C., Mashal, N., Gould, C. E., Henderson, V. W., & O'Hara, R. (2017). Unlocking neurocognitive substrates of late-life affective symptoms using the research domain criteria: Worry is an essential dimension. *Frontiers in Aging Neuroscience*, *9*, 380. Available from https://doi.org/10.3389/fnagi.2017.00380, eCollection 2017.

Becker, E., Orellana Rios, C. L., Lahmann, C., Rücker, G., Bauer, J., & Boeker, M. (2018). Anxiety as a risk factor of Alzheimer's disease and vascular dementia. *British Journal of Psychiatry*, *213*(5), 654–660. Available from https://doi.org/10.1192/bjp.2018.173.

Beekman, A. T., de Beurs, E., van Balkom, A. J., Deeg, D. J., van Dyck, R., & van Tilburg, W. (2000). Anxiety and depression in later life: Co-occurrence and communality of risk factors. *The American Journal of Psychiatry*, *157*, 89–95.

Bekris, L. M., Yu, C. E., Bird, T. D., & Tsuang, D. W. (2010). Genetics of Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, *23*(4), 213–227. Available from https://doi.org/10.1177/0891988710383571.

Brenes, G. A., Danhauer, S. C., Lyles, M. F., Anderson, A., & Miller, M. E. (2016). Effects of telephone-delivered cognitive-behavioral therapy and nondirective supportive therapy on sleep, health-related quality of life, and disability. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *24*(10), 846–854.

Brinke, L. F., Davis, J. C., Bahra, C. K., & Liu-Ambrose, T. (2017). Effects of computerized cognitive training on neuroimaging outcomes in older adults: A systematic review. *BMC Geriatrics*, *17*(1), 139.

Cristancho, P., Lenze, E. J., Dixon, D., Miller, J. P., Mulsant, B. H., Reynolds, C. F., & Butters, M. A. (2018). Executive function predicts antidepressant treatment noncompletion in late-life depression. *The Journal of Clinical Psychiatry*, *79*(3). Available from https://doi.org/10.4088/JCP.16m11371.

De Crescenzo, F., Ciliberto, M., Menghini, D., Treglia, G., Ebmeier, K. P., & Janiri, L. (2017). Is ^{18}F-FDG-PET suitable to predict clinical response to the treatment of geriatric depression? A systematic review of PET studies. *Aging & Mental Health*, *21*(9), 889−894. Available from https://doi.org/10.1080/13607863.2016.1247413.

DeLuca, A. K., Lenze, E. J., Mulsant, B. H., Butters, M. A., Karp, J. F., Dew, M. A., … Reynolds, C. F. (2005). Comorbid anxiety disorder in late life depression: Association with memory decline over four years. *International Journal of Geriatric Psychiatry*, *20*(9), 848−854.

Depp, C. A., Moore, D. J., Sitzer, D., Palmer, B. W., Eyler, L. T., Roesch, S., … Jeste, D. V. (2007). Neurocognitive impairment in middle-aged and older adults with bipolar disorder: Comparison to schizophrenia and normal comparison subjects. *Journal of Affective Disorders*, *101*(1−3), 201−209.

Devanand, D. P., Pelton, G. H., Marston, K., Camacho, Y., Roose, S. P., Stern, Y., & Sackheim, H. A. (2003). Sertraline treatment of elderly patients with depression and cognitive impairment. *International Journal of Geriatric Psychiatry*, *18*(2), 123−130.

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *British Journal of Psychiatry*, *202*(5), 329−335. Available from https://doi.org/10.1192/bjp.bp.112.118307.

Etkin, A., Gyurak, A., & O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in Clinical Neuroscience*, *15*(4), 419−429.

Fischer, C. E., & Agüera-Ortiz, L. (2018). Psychosis and dementia: Risk factor, prodrome, or cause? *International Psychogeriatrics*, *30*(2), 209−219. Available from https://doi.org/10.1017/S1041610217000874.

Ganguli, M., Du, Y., Dodge, H. H., Ratcliffe, G. G., & Chang, C. C. (2006). Depressive symptoms and cognitive decline in late life: A prospective epidemiological study. *Archives of General Psychiatry*, *63*(2), 153−160.

Geduldig, E. T., & Kellner, C. H. (2016). Electroconvulsive therapy in the elderly: New findings in geriatric depression, *Curr Psychiatry Rep*, *18*(4), 40. Available from https://doi.org/10.1007/s11920-016-0674-5.

Golas, A. C., Kalache, S. M., Tsoutsoulas, C., Mulsant, B. H., Bowie, C. R., & Rajji, T. K. (2015). Cognitive remediation for older community-dwelling individuals with schizophrenia: A pilot and feasibility study. *International Journal of Geriatric Psychiatry*, *30*(11), 1129−1134. Available from https://doi.org/10.1002/gps.4329.

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., … Seshadri, S. (2011). Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals and from the American heart association/American stroke association. *Stroke*, *42*(9), 2672−2713.

Gulpers, B., Ramakers, I., Hamel, R., Köhler, S., Oude Voshaar, R., & Verhey, F. (2016). Anxiety as a predictor for cognitive decline and dementia: A systematic review and meta-analysis. *American Journal of Geriatric Psychiatry* (10), 823−842. Available from https://doi.org/10.1016/j.jagp.2016.05.015.

Hantke, N. C., Gyurak, A., Van Moorleghem, K., Waring, J. D., Adamson, M. M., O'Hara, R., & Beaudreau, S. A. (2017). Disentangling cognition and emotion in older adults: The role of cognitive control and mental health in emotional conflict adaptation. *International Journal of Geriatric Psychiatry*, *32*, 840−848.

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: A systematic review. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(6), 619−624.

Hogan, M. J. (2003). Divided attention in older but not younger adults is impaired by anxiety. *Experimental Aging Research*, *29*(2), 111−136.

Illieva, I. P., Alexopoulos, G. S., Dubin, M. J., Morimoto, S. S., Victoria, L. W., & Gunning, F. M. (2018). Age-related repetitive transcranial magnetic stimulation effects on executive function in depression: A systematic review. *American Journal of Geriatric Psychiatry*, *26*(3), 334−346. Available from https://doi.org/10.1016/j.jagp.2017.09.002.

Jeste, D. V., Wolkowitz, O. M., & Palmer, B. W. (2011). Divergent trajectories of physical, cognitive, and psychological aging in schizophrenia. *Schizophrenia Bulletin*, *37*(3), 451−455. Available from https://doi.org/10.1093/schbul/sbr026.

Kaneriya, S. H., Robbins-Welty, G. A., Smagula, S. F., Karp, J. F., Butters, M. A., Lenze, E. J., … Reynolds, C. F., 3rd (2016). Predictors and moderators of remission with aripiprazole augmentation in treatment-resistant late-life depression: An analysis of the IRL-Grey randomized clinical trial. *JAMA Psychiatry*, *73*(4), 329−336. Available from https://doi.org/10.1001/jamapsychiatry.2015.3447.

Kaster, T. S., Daskalakis, Z. J., Noda, Y., Knyahnytska, Y., Downar, J., Rajji, T. K., … Blumberger, D. M. (2018). Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: A prospective randomized controlled trial. *Neuropsychopharmacology*, *43*(11), 2231−2238. Available from https://doi.org/10.1038/s41386-018-0121-x.

Katz, R., De Sanctis, P., Mahoney, J. R., Sehatpour, P., Murphy, C. F., Gomez-Ramirez, M., … Foxe, J. J. (2010). Cognitive control in late-life depression: Response inhibition deficits and dysfunction of the anterior cingulate cortex. *American Journal of Geriatric Psychiatry*, *18*(11), 1017−1025. Available from https://doi.org/10.1097/JGP.0b013e3181d695f2.

Kontis, D., Huddy, V., Reeder, C., Landau, S., & Wykes, T. (2013). Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with schizophrenia. *American Journal of Geriatric Psychiatry*, *21*(3), 218−230. Available from https://doi.org/10.1016/j.jagp.2012.12.013.

Kumar, S., Mulsant, B. H., Liu, A. Y., Blumberger, D. M., Daskalakis Z. J. & Rajji, T. K. (2016). Systematic review of cognitive effects of Electroconvulsive Therapy in late-life depression, *Am J Geriatr Psychiatry* 24(7), 547−65. Available from 10.1016/j.jagp.2016.02.053.

Lavretsky, H., Ercoli, L., Siddarth, P., Bookheimer, S., Miller, K., & Small, G. (2003). Apolipoprotein epsilon4 allele status, depressive symptoms, and cognitive decline in middle-aged and elderly persons without dementia. *American Journal of Geriatric Psychiatry*, *11*(6), 667−673.

Lenze, E. J., Hershey, T., Newcomer, J. W., Karp, J. F., Blumberger, D., Anger, J., … Dixon, D. (2014). Antiglucocorticoid therapy for older adults with anxiety and co-occurring cognitive dysfunction: Results from a pilot study with mifepristone. *International Journal of Geriatric Psychiatry*, *29*(9), 962−969. Available from https://doi.org/10.1002/gps.4085.

Lenze, E. J., Mulsant, B. H., Blumberger, D. M., Karp, J. F., Newcomer, J. W., Anderson, S. J., ... Reynolds, C. F., 3rd (2015). Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: A randomised, double-blind, placebo-controlled trial. *Lancet*, *386*(10011), 2404–2412. Available from https://doi.org/10.1016/S0140-6736(15)00308-6.

Lewandowski, K. E., Cohen, B. M., & Ongur, D. (2011). Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychological Medicine*, *41*(2), 225–241. Available from https://doi.org/10.1017/S0033291710001042.

Liu, A. Y., Rajji, T. K., Blumberger, D. M., Daskalakis, Z. J., & Mulsant, B. H. (2014). Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *American Journal of Geriatric Psychiatry*, *22*(3), 216–240. Available from https://doi.org/10.1016/j.jagp.2013.02.017.

Mackin, R. S., Lesselyong, J. A., & Yaffe, K. (2012). Pattern of cognitive impairment in older veterans with posttraumatic stress disorder evaluated at a memory disorders clinic. *International Journal of Geriatric Psychiatry*, *27*(6), 637–642. Available from https://doi.org/10.1002/gps.2763.

Maglione, J. E., Thomas, S. E., & Jeste, D. V. (2014). Late-onset schizophrenia: Do recent studies support categorizing LOS as a subtype of schizophrenia? *Current Opinion in Psychiatry*, *27*(3), 173–178. Available from https://doi.org/10.1097/YCO.0000000000000049.

Mah, L., Binns, M. A., & Steffens, D. C. (2015). Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer's disease. *The American Journal of Psychiatry*, *23*(5), 466–476. Available from https://doi.org/10.1016/j.jagp.2014.10.005.

Manning, K. J., Alexopolous, G. S., Banerjee, S., Morimoto, S. S., Seirup, J. K., Kimstra, S. A., ... Gunning-Dixon, F. (2015). Executive functioning complaints and escitalopram treatment response in late-life depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *23*(5), 440–445. Available from https://doi.org/10.1016/j.jagp.2013.11.005.

Mantella, R. C., Butters, M. A., Dew, M. A., Mulsant, B. H., Begley, A. E., Tracey, B., ... Lenze, E. J. (2007). Cognitive impairment in late-life generalized anxiety disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *15*(8), 673–679.

Mather, M. (2012). The emotion paradox in the aging brain. *Annals of the New York Academy of Sciences*, *1251*, 33–49. Available from https://doi.org/10.1111/j.1749-6632.2012.06471.x.

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44.

Meesters, P. D., Schouws, S., Stek, M., de Haan, L., Smit, J., Smit, J., ... Comijs, H. (2013). Cognitive impairment in late life schizophrenia and bipolar I disorder. *International Journal of Geriatric Psychiatry*, *28*(1), 82–90. Available from https://doi.org/10.1002/gps.3793.

Mohlman, J., & Gorman, J. M. (2005). The role of executive functioning in CBT: A pilot study with anxious older adults. *Behaviour Research and Therapy*, *43*(4), 447–465.

Mota, N., Tsai, J., Kirwin, P. D., Harpaz-Rotem, I., Krystal, J. H., Southwick, S. M., & Pietrzak, R. H. (2016). Late-life exacerbation of PTSD symptoms in US veterans: Results from the National Health and Resilience in Veterans Study. *The Journal of Clinical Psychiatry*, *77*(3), 348–354. Available from https://doi.org/10.4088/JCP.15m10101.

Munro, C., Longmire, C. F., Drye, L. T., Martin, B. K., Frangakis, C. E., Meinert, C. L., ... Lyketsos, C. G. (2012). Cognitive outcomes after sertraline treatment in patients with depression of Alzheimer disease. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *20*(12), 1036–1044. Available from https://doi.org/10.1097/JGP.0b013e31826ce4c5.

Naismith, S. L., Diamond, K., Carter, P. E., Norrie, L. M., Redoblado-Hodge, M. A., Lewis, S. J., & Hickie, I. B. (2011). Enhancing memory in late-life depression: The effects of a combined psychoeducation and cognitive training program. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *19*(3), 240–248. Available from https://doi.org/10.1097/JGP.0b013e3181dba587.

Nebes, R. D., Pollock, B. G., Houck, P. R., Butters, M. A., Mulsant, B. H., Zmuda, M. D., & Reynolds, C. F., 3rd (2003). Persistence of cognitive impairment in geriatric patients following antidepressant treatment: A randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of Psychiatric Research*, *37*(2), 99–108.

O'Hara, R. (2012). The reciprocal relationship of neurocognitive and neuropsychiatric function in late life. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *20*(12), 1001–1005.

Olaya, B., Montena, M. V., Ayuso-Mateos, J. L., & Haro, J. M. (2019). Course of depression and cognitive decline at 3-year follow-up: The role of age of onset. *Psychology and Aging*, *34*(4), 475–485. Available from https://doi.org/10.1037/pag0000354.

Palmer, B. W., Loughran, C. I., & Meeks, T. W. (2010). Cognitive impairment among older adults with late-life schizophrenia or bipolar disorder. *Continuum (Minneapolis, Minn.)*, *16*, 135–152. Available from https://doi.org/10.1212/01.CON.0000368216.09706.6b.

Pimontel, M. A., Rindskopf, D., Rutherford, B. R., Brown, P. J., Roose, S. P., & Sneed, J. R. (2015). A meta-analysis of executive dysfunction and antidepressant treatment response in late-life depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *24*(1), 31–41. Available from https://doi.org/10.1016/j.jagp.2015.05.010.

Rajji, T. K., & Mulsant, B. H. (2008). Nature and course of cognitive function in late-life schizophrenia: A systematic review. *Schizophrenia Research*, *102*(1-3), 122–140. Available from https://doi.org/10.1016/j.schres.2008.03.015.

Rajji, T. K., Voineskos, A. N., Butters, M. A., Miranda, D., Arenovich, T., Menon, M., ... Mulsant, B. H. (2013). Cognitive performance of individuals with schizophrenia across several decades: A study using the MATRICS consensus cognitive battery. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *21*(2), 108–118. Available from https://doi.org/10.1016/j.jagp.2012.10.011.

Reitz, C., Luchsinger, J. A., & Mayeux, R. (2008). Vascular disease and cognitive impairment. *Expert Review of Neurotherapeutics*, *8*(8), 1171–1174. Available from https://doi.org/10.1586/14737175.8.8.1171.

Reynolds, C. F., Butters, M. A., Lopez, O., Pollock, B. G., Dew, M. A., Mulsant, B. H., … DeKosky, S. T. (2011). Maintenance treatment of depression in old age: A randomized, double-blind, placebo controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Archives of General Psychiatry*, *68*(1), 51–60. Available from https://doi.org/10.1001/archgenpsychiatry.2010.184.

Ribe, A. R., Laursen, T. M., Charles, M., Katon, W., Fenger-Grøn, M., Davydow, D., … Vestergaard, M. (2015). Long-term risk of dementia in persons with schizophrenia: A Danish population-based cohort study. *JAMA Psychiatry*, *72*(11), 1095–1101. Available from https://doi.org/10.1001/jamapsychiatry.2015.1546.

Riddle, M., Potter, G. G., McQuoid, D. R., Steffens, D. C., Beyer, J. L., & Taylor, W. D. (2017). Longitudinal cognitive outcomes of clinical phenotypes of late-life depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *25*(10), 1123–1134. Available from https://doi.org/10.1016/j.jagp.2017.03.016.

Rosenberg, P. B., Drye, L. T., Martin, B. K., Frangakis, C., Mintzer, J. E., Weintraub, D., … Lyketsos, C. G. (2010). Sertraline for the treatment of depression in Alzheimer disease. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *18*(2), 136–145. Available from https://doi.org/10.1097/JGP.0b013e3181c796eb.

Rosnick, C. B., Wetherell, J. L., White, K. S., Andreescu, C., Dixon, D., & Lenze, E. J. (2016). Cognitive-behavioral therapy augmentation of SSRI reduces cortisol levels in older adults with generalized anxiety disorder: A randomized clinical trial. *Journal of Consulting and Clinical Psychology*, *84*(4), 345–352. Available from https://doi.org/10.1037/a0040113.

Ruscio, A. M., Seitchik, A. E., Gentes, E. L., Jones, J. D., & Hallon, L. S. (2011). Perseverative thought: A robust predictor of response to emotional challenge in generalized anxiety disorder and major depressive disorder. *Behaviour Research and Therapy*, *49*(12), 867–874. Available from https://doi.org/10.1016/j.brat.2011.10.001.

Sakurai, R., & Montero-Odasso, M. (2017). Apolipoprotein E4 allele and gait performance in mild cognitive impairment: Results from the gait and brain study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *72*(12), 1676–1682. Available from https://doi.org/10.1093/gerona/glx075.

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*(10), 925–935.

Schuitvoerder, S., Rosen, J. W., Twamley, E. W., Ayers, C. R., Sones, H., Lohr, J. B., … Thorp, S. R. (2013). A meta-analysis of cognitive functioning in older adults with PTSD. *Journal of Anxiety Disorders*, *27*(6), 550–558. Available from https://doi.org/10.1016/j.janxdis.2013.01.001.

Shahab, S., Mulsant, B. H., Levesque, M. L., Calarco, N., Nazeri, A., Wheeler, A. L., … Voineskos, A. N. (2019). Brain structure, cognition, and brain age in schizophrenia, bipolar disorder, and healthy controls. *Neuropsychopharmacology*, *44*(5), 898–906. Available from https://doi.org/10.1038/s41386-018-0298-z.

Shimada, H., Park, H., Makizako, H., Doi, T., Lee, S., & Suzuki, T. (2014). Depressive symptoms and cognitive performance in older adults. *Journal of Psychiatric Research*, *57*, 149–156.

Sitzer, D. I., Twamley, E. W., & Jeste, D. V. (2006). Cognitive training in Alzheimer's disease: A meta-analysis of the literature. *Acta Psychiatrica Scandinavica*, *114*(2), 75–90.

Skoog, I., Waern, M., Duberstein, P., Blennow, K., Zetterberg, H., Börjesson-Hanson, A., … Kern, S. (2015). A 9-year prospective population-based study on the association between the APOE*E4allele and late-life depression in Sweden. *Biological Psychiatry*, *78*(10), 730–736. Available from https://doi.org/10.1016/j.biopsych.2015.01.006.

Slotema, C. W., Blom, J. D., Hoek, H. W., & Sommer, I. E. C. (2010). Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *The Journal of Clinical Psychiatry*, *71*(7), 873–884. Available from https://doi.org/10.4088/JCP.08m04872gre.

Sneed, J. R., Culang, M. E., Keilp, J. G., Rutherford, B. R., Devanand, D. P., & Roose, S. P. (2010). Antidepressant medication and executive dysfunction: A deleterious interaction in late-life depression. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *18*(2), 128–135. Available from https://doi.org/10.1097/JGP.0b013e3181c796d2.

Sneed, J. R., Roose, S. P., Keilp, J. G., Krishnan, K. R., Alexopoulos, G. S., & Sackeim, H. A. (2007). Response inhibition predicts poor antidepressant treatment response in very old depressed Patients. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *15*(7), 553–563.

Spinhoven, P., van der Veen, D. C., Voshaar, R. C. O., & Comijs, H. C. (2017). Worry and cognitive control predict course trajectories of anxiety in older adults with late-life depression. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *44*, 134–140. Available from https://doi.org/10.1016/j.eurpsy.2017.05.002.

Stafford, J., Howard, R., & Krikbridge, J. B. (2018). The incidence of very late-onset psychotic disorders: A systematic review and meta-analysis, 1960–2016. *Psychological Medicine*, *48*, 1775–1786. Available from https://doi.org/10.1017/S0033291717003452.

Thomas, K. R., Puig, O., & Twamley, E. W. (2017). Age as a moderator of change following compensatory cognitive training in individuals with severe mental illnesses. *Psychiatric Rehabilitation Journal*, *40*(1), 70–78. Available from https://doi.org/10.1037/prj0000206.

Thompson, W. K., Hallmayer, J., & O'Hara, R. (2011). Design considerations for characterizing psychiatric trajectories across the life span: Application to effects of APOE-Ë on cerebral cortical thickness in Alzheimer's disease. *The American Journal of Psychiatry*, *168*(9), 894–903. Available from https://doi.org/10.1176/appi.ajp.2011.10111690.

Van den Berg, J. F., Luijendijk, H. J., Tulen, J. H. M., Hofman, A., Neven, A. K., & Tiemeier, H. (2009). Sleep in depression and anxiety disorders. *The Journal of Clinical Psychiatry*, *70*(8), 1105–1113.

Wei, J., Ying, M., Xie, L., Chandrasekar, E. K., Lu, H., Wang, T., & Li, C. (2019). Late-life depression and cognitive function among older adults in the U.S.: The National Health and Nutrition Examination Survey, 2011-2014. *Journal of Psychiatric Research*, *111*, 30–35. Available from https://doi.org/10.1016/j.jpsychires.2019.01.012.

Further reading

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F., 3rd (2014). Adding psychotherapy to antidepressant medication in depression and anxiety disorders: A meta-analysis. *World Psychiatry*, *13*(1), 56−67. Available from https://doi.org/10.1002/wps.20089.

Guest, P. C., Chan, M. K., Gottschalk, M. G., & Bahn, S. (2014). The use of proteomic biomarkers for improved diagnosis and stratification of schizophrenia patients. *Biomarkers in Medicine*, *8*(1), 15−27. Available from https://doi.org/10.2217/bmm.13.83.

Holvast, F., Massoudi, B., Oude Voshaar, R. C., & Verhaak, P. F. M. (2017). Non-pharmacological treatment for depressed older patients in primary care: A systematic review and meta-analysis. *PLoS One*, *12*(9). Available from https://doi.org/10.1371/journal.pone.0184666.

Kaup, A. R., Byers, A. L., Falvey, C., Simonseck, E. M., Satterfield, S., Ayonayon, H. N., ... Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, *73*(5), 525−531. Available from https://doi.org/10.1001/jamapsychiatry.2016.0004.

Morimoto, S. S., Kanellopoulos, D., Manning, K. J., & Alexopoulos, G. S. (2015). Diagnosis and treatment of depression and cognitive impairment in late-life. *Annals of the New York Academy of Sciences*, *1345*(1), 36−46. Available from https://doi.org/10.1111/nyas.12669.

O'Hara, R., Miller, E., Liao, C. P., Way, N., Lin, X., & Hallmayer J. (2006). COMT genotype, gender and cognition in community-dwelling, older adults, Neurosci Lett. 409(3), 205−209.

Teng, E., Tassniyom, K., & Lu, P. H. (2012). Reduced quality-of-life ratings in mild cognitive impairment: Analyses of subject and informant responses. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *20*(12), 1016−1025. Available from https://doi.org/10.1097/JGP.0b013e31826ce640.

Tomasik, J., Lago, S. G., Vázquez-Bourgon, J., Papiol, S., Suárez-Pinilla, P., Crespo-Facorro, B., & Bahn, S. (2019). Association of insulin resistance with schizophrenia polygenic risk score and response to antipsychotic treatment. *JAMA Psychiatry*. Available from https://doi.org/10.1001/jamapsychiatry.2019.0304.

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K., Neylan, T., ... Marmar, C. (2010). Post-traumatic stress disorder and risk of dementia among U.S. veterans. *Archives of General Psychiatry*, *67*(6), 608−613. Available from https://doi.org/10.1001/archgenpsychiatry.2010.61.

This page intentionally left blank

Chapter 10

Suicide in late life

Joshua T. Jordan[1,2] **and Lauren A. Anker**[2,3]

[1]Department of Psychiatry, University of California San Francisco, San Francisco, CA, United States, [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [3]Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Healthcare System, Palo Alto, CA, United States

Prevalence

Suicide has received increased recognition as a major public health concern in the United States, as rates of death by suicide have increased by 30% over the past 20 years (Centers for Disease Control and Prevention, 2018). From 2006 to 2016, the average rate of death by suicide in the United States was approximately 12.6 per 100,000 (Drapeau & McIntosh, 2017). These rates are highest among middle-aged adults (45−64), at 18.3 per 100,000; however, adults over 65 have high rates of death by suicide relative to the general population (15.4 per 100,000), and adults aged 85 and older have one of the highest rates of suicide (17.4 per 100,000; Drapeau & McIntosh, 2017).

Suicidal ideation

The prevalence of suicidal ideation in late life has not been well established in the literature. Some estimates of suicidal ideation in older adults suggest that 9%−12% of community-dwelling older adults have had some thoughts of death or suicide within the past year, that approximately 1% of primary care patients have suicidal ideation, and that 42% of late-life patients with major depression have suicidal ideation (Dombrovski, Szanto, & Reynolds, 2005). According to data from the Collaborative Psychiatric Epidemiological Studies, which consists of three epidemiological studies conducted in the United States (Heeringa, Wagner, Torres, Duan, & Adams, 2004), approximately 6.5% of adults over the age of 65 report suicidal ideation at some point in the past 12 months, and 3.0% go so far as to make a suicide plan. Approximately 1.9% of adults experience their first suicidal thoughts after the age of 55, and the odds of having suicidal ideation increases approximately threefold when the older adult has recently been exposed to a serious accident or illness (Beristianos, Maguen, Neylan, & Byers, 2017).

Suicide attempts and death by suicide

The rate with which older adults attempt suicide is lower than that in younger populations. Approximately 6%−7% of all suicide attempts in the United States are made by adults over 65, meaning that they account for fewer suicide attempts than middle-aged and younger adults (Miller, Azrael, & Hemenway, 2004; Spicer & Miller, 2000). While older adults may account for a small proportion of all suicide attempts in the United States, they account for 18%−20% of all suicides, meaning that the likelihood of death from a suicide attempt is higher in this population. Indeed, estimates from multiple studies have shown that the case fatality rate among adults over 65 that attempt suicide ranges from 30% to 40%, while middle-aged adults have a fatality rate of 14%−20%, and younger adults have a fatality rate of approximately 7%−11% (Elnour & Harrison, 2008; Miller et al., 2004; Spicer & Miller, 2000). This is likely due to several reasons: older adults tend to be more physically frail than younger populations, they are more likely to live alone (thus reducing the likelihood that they will be rescued after their attempt), they make more determined/planned suicide attempts (Conwell et al., 1998), and they are more likely to use lethal methods than younger populations (Conwell & Thompson, 2008).

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00010-7

Suicide method

As individuals age, the more likely they are to use a lethal method in their suicide attempt. For instance, approximately 60% of male suicide decedents between 50 and 64 use firearms, as opposed to 80% of male suicide decedents over 65, whereas 20% of males between 50 and 64 use hanging/suffocation as opposed to 9% over 65 (Choi, DiNitto, Marti, Kaplan, & Conwell, 2017). Furthermore, these same estimates suggest that approximately 11% of male suicide decedents die by overdose between 50 and 64, compared to 4% of those 65 and above. For women decedents between 50 and 64, overdose is the most common method (41%), followed by firearms (33%) and hanging/suffocation (15%). For women 65 and older, firearms (39%) are the most common, followed by overdose (33%) and hanging/suffocation (14%) (Choi, DiNitto, Marti, Kaplan, & Conwell, 2017). Given that overdoses have the lowest case fatality rate of all methods for suicide, it is interesting to see that older adults are less likely to use this approach when they attempt suicide. This does not entirely account for the elevated fatality rate among older adults, however. For example, if one were to apply the method-specific distribution of older adults to younger adults, this would increase the fatality rate from 7% to 14%, which would still not come close to the fatality rate for older adults (Miller et al., 2004).

Risk factors

Risk factors for suicide are plentiful, but their ability to predict suicidal behaviors is particularly poor (Franklin et al., 2017). Although there are established correlates of suicidal behaviors, the presence of risk factors does not necessarily mean that an individual will have suicidal thoughts or will attempt suicide. Some known general risk factors for suicide include a current suicide plan or aborted attempt, previous history of suicide, psychiatric disorders or physical illness, psychosocial stressors, family history of suicide, psychological features (e.g., impulsivity, hopelessness, psychological pain, agitation, aggression), cognitive features, certain demographic characteristics (e.g., being male, widowed, Caucasian), and other features such as access to lethal means (American Psychiatric Association, 2010). Here, we discuss correlates of suicidality that are more specific to older adults.

Gender

There is a paradoxical effect of gender on suicide. Historically, women are more likely to make suicide attempts than men, but men are significantly more likely than women to die by suicide. Surprisingly, the rate with which men and women attempt suicide appears to be similar at 65 and older, as 43 per 100,000 women attempt suicide, and 45 per 100,000 men attempt suicide. The fatality rate is different, however, as men over the age of 65 have a fatality rate of 45%, and women at 14% (Spicer & Miller, 2000). Thus, about half of men that attempt suicide over the age of 65 die from their attempt, and one of seven women 65 and older who attempt suicide die from their attempt. This is largely due to the fact that men are more likely to use methods that have higher fatality rates, as evidenced by the fact that they are twice as likely to use firearms than women (Choi, DiNitto, Marti, Kaplan, & Conwell, 2017).

Race and ethnicity

Variability in suicide rates exists in different cultures and ethnicities. Caucasian males over the age of 45 have the highest rates of suicide in the United States (Heron et al., 2009). According to the World Health Organization, the rate of suicide by older Caucasian males is over four times the national rate (World Health Organization, 2018). While suicide in Caucasian males peaks in later life, African-American males experience two peaks in their suicide rates, one in early adulthood and then again in later life (Van Orden & Conwell, 2011). African-American and Caucasian women have similar patterns of suicide rates, such that both groups' suicide rates peak in middle age and then decline in later life (Van Orden & Conwell, 2011). Older Hispanic and African-American individuals are not only less likely to attempt suicide than Caucasians, but they have a lower fatality rate as well (Spicer & Miller, 2000).

Socioeconomic status

Socioeconomic status has been implicated as a risk factor for suicide in older adults as well. Older adults with depression who reside in low-income census tracts have higher rates of suicidal ideation than depressed older adults in middle- to high-income census areas (Cohen et al., 2006). A large study of 515 older adults attending primary care settings observed that participants who had median household incomes less than $30,000 per year were more likely to experience suicidal ideation than older adults that lived in higher-income census tracts, even when covarying for

demographic, clinical, medical, functional, and psychosocial variables (Cohen et al., 2010), and another study observed that having financial strain increased the odds of suicidal ideation more than twofold among 1226 depressed older primary care patients. Older adults in the middle to high socioeconomic range may also be susceptible to suicide in some circumstances—for example, loss of socioeconomic status may increase risk for suicide, as it could theoretically create significant psychological distress. A recent study by Dombrovski and colleagues observed that older adults with suicidal ideation or suicide attempt were more likely to have experienced a loss in status, even when controlling for objective markers of social status as well as psychopathology (Dombrovski, Aslinger, Weight, & Szanto, 2018). Thus objective socioeconomic status may be less important than a perceived drop in socioeconomic status in predicting suicidal ideation.

Social factors

Social factors have been heavily implicated in late-life suicide. It is well known that divorced or widowed individuals are more susceptible to suicide and that the death of a spouse increases the risk for suicide as well, particularly among men (Dombrovski et al., 2005). The literature supports the notion that living alone, feeling lonely, having interpersonal problems, and low social support contributes to suicidality in later life (Van Orden & Conwell, 2011). Indeed, a recent meta-analysis by Chang and colleagues across 31 studies with 203,152 participants found that older adults with discordant social relationships were 57% more likely to have suicidal ideation (Chang, Chan, & Yip, 2017). Risk for suicidal ideation was higher if the discordant social relationship reported was mistreatment or perceived loneliness, both of which increased the odds for suicidal ideation more than twofold. While social problems can increase the likelihood that an individual will develop suicidal ideation, this also suggests that older adults with strong social support and greater connectedness to others may be protected from suicidal ideation (Turvey et al., 2002).

Mental illness

Virtually all suicides occur in individuals who have a psychiatric disorder, as 90% of suicides occur in individuals who have a clear psychiatric disorder such as depression, while the remaining 10% have some symptoms of psychopathology or have a history of personality disorder (Cavanagh, Carson, Sharpe, & Lawrie, 2003; Ernst et al., 2004). Suicide in later life is no exception. Conwell and colleagues observed that approximately 71%−97% of suicides among older adults occur in the context of an Axis I disorder, based on several psychological autopsy studies (Conwell, Van Orden, & Caine, 2011). Affective disorders (primarily major depression) are the most prominent among older suicide decedents, while anxiety and psychotic disorders are less common. Older adults with an affective disorder are 44−113 times more likely to die by suicide than older adults without an affective disorder (Conwell et al., 2011).

The role that personality disorders play in late-life suicide is less well defined. A recent review reported prevalence estimates among suicide decedents that ranged from 1.5% to 16% depending on the sample studied; however, studies examining personality disorders in late-life suicide are scarce, and thus far suggest a stronger relationship with ideation rather than death (Szücs, Szanto, Aubry, & Dombrovski, 2018). To date, obsessive−compulsive personality disorder and avoidant personality disorder are the only personality disorders that have been associated with death by suicide, while all others (with the exception of histrionic personality disorder) are associated with suicidal ideation (Szücs et al., 2018).

Alcohol use disorder also increases risk for suicide in older adults. Psychological autopsy studies suggest that it is present in approximately 3%−43% of elderly suicide decedents (Conwell et al., 2011). It is the second most common psychiatric disorder in late-life suicide, second only to depression (Blow, Brockmann, & Barry, 2004), and may be an understated risk factor for late-life suicide, as most research focuses on whether or not the older adult met criteria for an alcohol abuse or dependence diagnosis per DSM-IV-TR criteria. As pointed out by Blow et al. (2004), many older adults do not experience the legal/social/psychological consequences to meet criteria for the disorder, due to fewer obligations (e.g., work). Moreover, older adults are more sensitive to alcohol than younger and middle-aged adults, and results in higher and longer-lasting blood alcohol levels. Thus, smaller amounts of alcohol may have a larger impact and may not be as apparent as it is in younger and middle-aged adults, highlighting the need for research to better understand the role of alcohol in late-life suicide beyond diagnostic status.

Physical illness and functional impairment

Physical health problems are present in approximately half of late-life suicide decedents (Choi, DiNitto, Marti, & Conwell, 2017). The rate of older adults in the general population with physical illness and disability is too high for it

to be considered a specific risk factor for suicidality, however (Conwell et al., 2011). A variety of physical illnesses in later life have been associated with an increased risk for suicide, and studies show that malignant diseases, male genital disorders, arthritis/arthrosis, chronic obstructive pulmonary disease, and liver disease appear to be the most consistent correlates of suicidal behavior, with less evidence for diabetes and renal disease (Fässberg et al., 2016). There is also less evidence for cardiovascular diseases as well. Although approximately 30%–40% of patients that undergo coronary artery bypass grafts (CABG) have depression (Tully & Baker, 2012), we are not aware of any literature examining the association between CABG and subsequent suicidality. More importantly, presence or absence of a physical illness may not be the driver behind suicidality, however, as it may be the burden of physical illness as well as functional disabilities resulting from the physical illness that increases risk for suicide.

Suicide risk, for example, appears to increase with the number of medical illnesses. An investigation by Juurlink and colleagues in Ontario examined physical illness in 1354 older adult suicide decedents and compared them to 5416 controls matched by age, gender, and residential income. They found that a number of individual physical illnesses were associated with suicide—but that individuals with three illnesses were 3.5 times more likely to die by suicide, and individuals with five illnesses were 5.7 times more likely to die by suicide (Juurlink, Herrmann, Szalai, Kopp, & Redelmeier, 2004). Another study found that the burden of physical illness was higher among older psychiatric inpatients who attempted suicide than older psychiatric inpatients who did not attempt suicide (Bergman, Barak, Sigler, & Aizenberg, 2011).

Functional disability—which are limitations in activities of daily living—has also been implicated in suicide risk for older adults. The majority of studies examined in a systematic review by Lutz and Fiske observed an association between functional disability and suicidal ideation in adults over the age of 50 (Lutz & Fiske, 2018). This may be due to a loss of autonomy and fear of losing control (Van Orden & Conwell, 2011).

Neurodegeneration, cognition, and suicide

Another medical illness that may increase risk for suicide in later life is dementia. Given that diagnosis of dementia represents a major loss of independence and marked progressive decline in functioning, news of this irreversible diagnosis could potentially bring about thoughts of suicide. Interestingly, there are conflicting reports in the literature regarding suicide and dementia (Conejero et al., 2018). The risk of death by suicide is highest in the earliest stages of Alzheimer's type dementia, particularly in the first 3 months following diagnosis, and then declines (Cipriani, Vedovello, Lucetti, Di Fiorino, & Nuti, 2013; Draper, Peisah, Snowdon, & Brodaty, 2010). One recent estimate suggests that the rate of death by suicide within the year following a dementia diagnosis is 424 per 100,000, which is approximately 30 times higher than the national suicide rate (Annor et al., 2019). This drops to 66 per 100,000 in the 12–24 months after diagnosis, and five per 100,000 after 2 years of diagnosis. This is proposed to be largely due to disease progression, as an individual will be unable to develop and carry through a suicide plan in the latter stages of the disease (Conejero et al., 2018). Thus, in a sense, advanced stages of neurodegenerative diseases may be a protective factor against suicide. The risk for suicidal thoughts and acts varies by dementia subtype, however. A recent study of 56,000 primary care patients in the Veterans Health Administration by Lai and colleagues found differing rates of suicidal ideation and plans or attempts among patients with dementia (Lai, Kaup, Yaffe, & Byers, 2018). Specifically, patients with Alzheimer's disease had the lowest 2-year prevalence of suicidal ideation (0.77%) and plans/attempts (0.06%), followed by Lewy body dementia (1.66% ideation, 0.03% attempt), mixed dementia (2.31% ideation, 0.26% attempt), and vascular dementia (2.59% ideation, 0.20% attempt). Patients with frontotemporal dementia (FTD) had the highest rate of suicide ideation (3.56%) and suicide attempt (0.42%) among all dementia subtypes (Lai et al., 2018). Although the sample was primarily male (98%), the fact that FTD—which is often associated with impairments with inhibition, planning, and compulsive behaviors—suggests that frontal lobe dysfunction may confer an increased risk for both suicidal ideation and attempts.

Prior literature examining structural and functional neuroimaging studies among young- and middle-aged adults suicide attempters or ideators have found differences in the prefrontal cortex (PFC), particularly in the dorsolateral, dorsomedial, ventromedial, and ventrolateral PFC, which are all part of the frontal lobes; differences in the cingulate gyrus have been found as well (Jollant, Lawrence, Olié, Guillaume, & Courtet, 2011; Myung et al., 2016; Pu et al., 2015; van Heeringen, Bijttebier, Desmyter, Vervaet, & Baeken, 2014; van Heeringen, Wu, Vervaet, Vanderhasselt, & Baeken, 2017). This would suggest that executive functioning as a whole is implicated in suicidality. Older adults are particularly susceptible to executive dysfunction in late-life depression (Lockwood, Alexopoulos, & van Gorp, 2002), which would suggest that older adults with executive dysfunction may be at elevated risk for suicidal ideation and attempts, and may not be restricted solely to individuals with FTD.

Imaging studies of older adults have found that those with a history of suicide attempts have observed a noticeable reduction of volume in the dorsomedial PFC relative to controls, as well as decreased gray and white matter in the frontal, parietal, and temporal regions, in addition to the insula, lentiform nucleus, midbrain, and cerebellum (Hwang et al., 2010). Other studies have observed reduced response to rewards in the ventromedial PFC (Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013), as well as reduced volume in the corpus callosum and putamen (Cyprien et al., 2011; Dombrovski et al., 2013). Neurocognitive studies have observed worse performance on tests of executive functioning (specifically in set-shifting and inhibition), as well as global executive functioning among depressed older adults that attempted suicide (Clark et al., 2011; Dombrovski et al., 2008; King et al., 2000; McGirr, Dombrovski, Butters, Clark, & Szanto, 2012; Richard-Devantoy, Szanto, Butters, Kalkus, & Dombrovski, 2015; Wyart et al., 2016). These deficits seem to be present among older adults with ideation that have not made an attempt as well (Gujral et al., 2013; Kasckow et al., 2016), suggesting that executive dysfunction increases the overall likelihood that an older adult will be at risk for suicide, not just among those with suicidal ideation.

Contemporary psychological theories of suicide

A multitude of theories of suicide have been proposed over the years, starting with Émile Durkheim's Sociological Theory in 1897. Theories of suicidal behavior have largely focused on understanding the mechanisms through which an individual develops the desire to die and have only recently begun to focus on the mechanisms that subserve the transition from suicidal ideation to suicide attempt. As we note early on in this chapter, older adults are less likely to make a suicide attempt than younger adults; however, when they do, there is a much greater probability that the attempt will be lethal. Thus, the focus here will be on contemporary theories of suicide, as these focus more on the transition from ideation to action. An excellent review written by Stanley and colleagues provides an overview of the majority of psychological and sociological theories of suicide as it pertains to older adults, which not only covers the material presented in this chapter, but discusses other theories not touched upon here (Stanley, Hom, Rogers, Hagan, & Joiner, 2016).

The interpersonal theory of suicide (IPTS) is perhaps the most well-known contemporary theory of suicide and was developed by Thomas Joiner (Joiner, 2005). It was the first of the "ideation-to-action" theories of suicide. Joiner's theory essentially proposes that suicide occurs when the desire for death interacts with a capability for suicide (Van Orden et al., 2010). In the IPTS, the perception that one is a burden on others and that one does not belong (referred to as perceived burdensomeness and thwarted belongingness, respectively) are proximal causes of suicidal desire. The acquired capability for suicide is a novel contribution to theories of suicide and proposes that individuals develop a capability to enact lethal self-harm through an increased pain tolerance as well as a reduced fear of death (Joiner, 2005). Individuals acquire this capability for suicide through repeated exposure to painful and provocative life events, thereby desensitizing them to the fear of death and the pain associated with it. In the framework of the IPTS, older adults may be susceptible to suicidal ideation particularly in the context of physical and/or cognitive decline, as they may have concerns that they are becoming a burden on their loved ones. Moreover, older adults may have experienced more adverse and painful life events over time than younger generations, particularly with medical conditions, thereby desensitizing them to the fear of death. There is some evidence that perceived burdensomeness is associated with late-life suicidal ideation (Cukrowicz, Cheavens, Van Orden, Ragain, & Cook, 2011; Cukrowicz, Jahn, Graham, Poindexter, & Williams, 2013), particularly as it pertains to their perception of being a burden on younger generations (Jahn & Cukrowicz, 2011). Furthermore, there is some evidence that older adults are less afraid of death than younger adults (Cicirelli, 2001). The IPTS has yet to be extensively studied in older adults—however, it has considerable promise in understanding both why and how older adults die by suicide.

The integrated motivational—volitional (IMV) model of suicide (O'Connor, 2011) was the second ideation-to-action model of suicidal behavior and proposes that suicide is the result of essentially three different stages: (1) there is a premotivational phase; (2) there is a motivational phase in which the individual develops suicidal ideation and intent; (3) the volitional phase is when the individual acts on their suicidal thoughts. The premotivational phase is rooted within the diathesis-stress model: individuals have biological, genetic, or cognitive vulnerability factors combined with stressful life events that increase their risk for suicide by making them more sensitive to defeat. The motivation for suicide develops when defeat or humiliation (which can be characterized by social rejection or loss) turns into entrapment. Finally, the transition from motivation to volition occurs when the individual has the acquired capability for suicide. This is rooted in the IPTS but expands on other ways in which an individual can develop capability (e.g., access to means, exposure to suicide, glamorization of suicide by media, cognitive rehearsal of suicide). There are moderators at each of the transitional stages (e.g., reasons for living, connectedness to others) that can buffer or amplify one's transition to the next stage in the IMV (see O'Connor, 2011, for more details). The IMV has yet to be tested in older adults; however, its

emphasis on moderators is helpful in conceptualizing risk for suicide, and where potential interventions may be particularly helpful (Stanley et al., 2016).

The most recent of the ideation-to-action theories of suicide is referred to as the Three-Step Theory ("3ST"; Klonsky & May, 2015), which states that suicide attempts occur based on a series of contingent relationships. First, suicidal ideation occurs when an individual experiences pain *and* hopelessness. "Pain" does not have to necessarily be psychological or emotional in the 3ST—pain can be due to a variety of factors, including physical suffering, perceived burdensomeness/thwarted belongingness per the IPTS, defeat/humiliation and entrapment per the IMV, and so on (Klonsky & May, 2015). Suicidal ideation only occurs in the context of pain with hopelessness. Second, among those with suicidal ideation, connectedness differentiates between those with moderate to strong suicidal ideation. Connectedness per the 3ST is defined broadly to include anything that keeps an individual interested in continuing to live or attached to life (e.g., family, employment, religion). If an individual's connection to life is less than their pain, their suicidal ideation will strengthen. Finally, among those whose connection to life is less than their pain, the transition from ideation to attempt occurs when an individual has the acquired capability for suicide. In the 3ST, this consists of three separate categories: dispositional (genetics; e.g., lower pain sensitivity), acquired (as originally defined in the IPTS), and practical (access to lethal means, knowledge of how to end one's life). Similar to the IMV, the 3ST has yet to be studied in older adults.

Each of these theories can contribute to how we understand suicide in later life. The motivation for suicide in later life, based on these theories, occurs in the context of psychological pain that can arise from several different pathways that may co-occur: (1) the older adult may perceive themselves as being a burden on others and/or that they do not belong; (2) they may suffer from a medical illness (which can increase the likelihood that they perceive themselves to be a burden to others); (3) there is loss (for older adults, this can mean interpersonal loss, functional impairment, perceived or objective loss of socioeconomic status). The desire for death becomes amplified when there is a sense of entrapment and/or hopelessness (i.e., that things will not or cannot change). And finally, the transition from ideation to attempt occurs through several pathways as well: older adults may develop a capability for suicide due to a reduced fear of death (through an accumulation of stressful life experiences), increased pain tolerance to use more lethal means (perhaps due to physical pain from a medical illness), desensitization to the method used through practice (e.g., an older adult with diabetes that is used to injecting insulin), and access to lethal means (all methods become more lethal with age).

Although the ideation-to-action theories have gained traction over the past decade, research has focused primarily on younger populations, and the IPTS is the only theory thus far to have been tested in older adult samples. All three theories have received empirical support across a variety of populations; however, research is sorely needed to test these theories in older adults, as they have potentially important clinical implications.

Suicide risk assessment

Assessing risk for suicide is particularly difficult to determine, given the low prevalence of suicide attempts in the population. Given that older adults are less likely to make a suicide attempt than younger age groups, this makes it even more difficult to predict who will make a suicide attempt. A meta-analysis of 3428 risk factor effect sizes over the last 50 years found that the prediction of suicide or suicidal behaviors was only slightly better than chance (Franklin et al., 2017), which has raised concerns about clinicians' ability to assess which individuals are at elevated risk for suicide. Even among patient populations who are particularly susceptible to suicide—psychiatric inpatients—a recent meta-analysis showed that clinician judgment of suicide risk has low sensitivity (proportion of positive cases identified as positive) at approximately 31%, and the positive predictive value (PPV; proportion of true positive cases) of clinician-rated suicide risk is similarly poor at approximately 22% (Woodford et al., 2017). This means that even among a group that is well known to have elevated risk for suicide (Chung et al., 2017), 69% of high-risk patients are misclassified as low risk, and 78% of those classified as high-risk are in fact at low risk. This is largely impacted by the prevalence of suicide attempts, as prevalence imposes a ceiling on the PPV (Carter et al., 2017). Because of this, it has been proposed that after an initial assessment and management plan is developed, a needs assessment, followed by the identification of modifiable risk factors for suicide and then implementing treatments that are effective in reducing suicidal behaviors, is preferable to risk stratification (Carter & Spittal, 2018). This method has been implemented in the United Kingdom, Australia, and New Zealand (Carter & Spittal, 2018), and is a practical patient-centered approach to mitigate risk for suicide. In the context of late-life suicide, some of the risk factors outlined in the previous section are modifiable and can serve as the basis for empirically guided risk assessment and management of older adults at risk for suicide. This is predicated upon the notion that suicidal ideation is identified in the first place, as suicidal ideation is a necessary precursor to suicide.

This is not easy to accomplish. Older adults are more reluctant than younger and middle-aged adults to disclose suicidal ideation (Duberstein et al., 1999). An estimate from the National Violent Death Reporting System suggests that approximately one quarter of suicide decedents over the age of 50 disclosed their suicidal thoughts or plans within a month (or less) before their suicide, which means that disclosure of any sort—to anybody—is relatively uncommon (Choi, DiNitto, Marti, & Kaplan, 2017). Older adults are more likely to disclose their intent if they have a recent depressed mood, a health problem, alcohol or other substance abuse issues, or if there are major life stressors (e.g., relationship problems or job and financial problems). They are also more likely to disclose their intent if they are receiving mental health or substance abuse treatment. Furthermore, individuals ≥ 70 years old are more likely to disclose their intent, particularly if they have health problems (Choi, DiNitto, Marti, & Kaplan, 2017). Because older adults may be more reluctant to disclose suicidal thoughts, it is of the utmost importance that the clinician is mindful of subtle indicators of suicidal ideation: for example, the idea that life is not worth living is uncommon in later life, and may be indicative of actual suicidal thoughts (Van Orden et al., 2015). Other indicators—such as the acknowledgment that the patient feels as though they are a burden on others—may indicate that they are having some thoughts of suicide. It is important that a collaborative therapeutic relationship is developed to allow the patient to feel comfortable to disclose their thoughts about death and suicide (Bhar & Brown, 2012). Furthermore, sequencing the manner in which the patient is asked about suicidal thoughts may be helpful in obtaining more accurate responses. For example, asking less direct questions at first (e.g., "have you thought that life is no longer worth living?"), followed by direct questions (e.g., "have you thought about doing something to end your life?"), may assist the clinician in obtaining a more accurate disclosure of suicidal thoughts (Bhar & Brown, 2012).

One method for assessing suicide risk in older adults is through the use of self-report measures. For instance, the Beck Scale for Suicide Ideation (Beck, Kovacs, & Weissman, 1979) is a 21-item self-report questionnaire that assesses various aspects of suicidal ideation (e.g., duration of suicidal thoughts, preparatory behaviors). A Geriatric Scale for Suicidal Ideation (GSIS; Heisel & Flett, 2006) has been developed. The GSIS is a 31-item multidimensional self-report measure that consists of four factors: suicide ideation, death ideation, loss of personal and social worth, and perceived meaning in life. The scale has strong psychometric properties, and construct and criterion validity for the subscales have been established (Alphs et al., 2016). The GSIS suicide ideation subscale has been shown to differentiate between psychiatric patients and nonpatients (Heisel & Flett, 2006) and has good test-retest reliability (Heisel & Flett, 2016).

While self-report measures directly assessing suicidality can help identify individuals at risk for suicide, they are face-valid instruments and therefore easier to deliberately avoid positive answers on questions of suicidal ideation. Thus indirect instruments can be effective in identifying suicidal individuals that may be unwilling to disclose these thoughts. The Reasons for Living Inventory (RFL; Linehan, Goodstein, Nielsen, & Chiles, 1983) and Beck Hopelessness Scale (Beck, Weissman, Lester, & Trexler, 1974) are two popular measures that do not directly assess suicidal ideation, but assess risk factors for suicide (reduced reasons for living and hopelessness). The RFL has been adapted for older adults (RFL-OA; Edelstein et al., 2009), and a Geriatric Hopelessness Scale has been developed as well (Fry, 1984), although a revision of the original scale may be needed to improve its use as a measure of suicide risk (Heisel & Flett, 2005). And, considering that perceived burdensomeness is one risk factor that may be particularly sensitive for older adults, the Interpersonal Needs Questionnaire (Van Orden, Cukrowicz, Witte, & Joiner, 2011) may be a sensitive measure to detect latent suicidal ideation.

One of the most commonly used measures of late-life depression, the Geriatric Depression Scale (GDS; Yesavage et al., 1983), also has some utility in detecting suicidal ideation among older adults (Heisel, Flett, Duberstein, & Luness, 2005). Although the scale does not explicitly address suicidal ideation or other suicide-related behaviors, a five-item subscale addressing whether (1) the individual feels their life is empty, (2) if they feel happy most of the time, (3) whether they think it is wonderful to be alive, (4) if they feel worthless, and (5) if they feel hopeless, has been shown to discriminate between older adults with and without suicidal ideation (Heisel, Duberstein, Lyness, & Feldman, 2010). A cutoff score of 5 for men and 3 for women on the total GDS has been shown to optimize sensitivity and specificity in detecting suicidal ideation, whereas a cutoff score of 1 on the suicide ideation subscale is optimal for sensitivity and specificity (Alphs et al., 2016).

Other factors must also be taken into consideration when assessing risk for suicide beyond presence or absence of suicidal ideation, of course. The risk factors outlined in the previous section are important to consider in late-life suicide assessment, and the ideation-to-action theories provide potential frameworks to conceptualize suicide risk. However, as noted previously, the stratification of risk into "low" or "high" may not be clinically useful for older adults.

Management and treatment

Although a number of treatments have been designed to focus on common psychiatric illnesses such as depression and anxiety-related disorders, there has historically been little effort to develop suicide-specific interventions. An excellent

overview of primary care interventions, community-based outreach programs, and telephone counseling programs for suicide prevention in late life can be found in Lapierre et al. (2011). Given that older adults are at heightened risk for lethal suicide attempts, one intervention that we recommend for all older adults at risk for suicide is means restriction. For a comprehensive guide to means restriction, we encourage the reader to follow the framework outlined by Bryan, Stone, and Rudd (2011). Here, we review individual interventions for suicidal behaviors, some of which have been adapted for older adults.

The most well-known treatment to prevent suicide is dialectical behavior therapy (DBT), which was initially designed for individuals with borderline personality disorder (Linehan, 1993). DBT focuses on providing skills to help individuals regulate their emotions, tolerate distress, improve their effectiveness in interpersonal relationships, and increase mindfulness (Linehan, 1993). DBT has been adapted for older adults, and this modified approach emphasizes behaviors functionally related to depression as well as an emphasis on reducing rigid maladaptive coping styles (Lynch, 2000). One pilot study of 34 older adults with depression compared 17 older adults receiving medication and clinical management with 17 older adults receiving this modified DBT as well as medication management and found that the DBT condition observed a greater reduction in depressive symptoms (Lynch, Morse, Mendelson, & Robins, 2003). There was no difference in suicidal ideation at posttreatment, however, and no subsequent studies have examined the utility of DBT in reducing suicidality among older adults. Given that individuals with borderline personality disorder have difficulties with executive functioning (Ruocco, 2005), which is often impaired in late-life suicide, it stands to reason that this treatment could be beneficial in preventing late-life suicide.

In recent years, a separate approach has been developed to specifically target suicidality. The Collaborative Assessment and Management of Suicidality (CAMS) is an approach designed to help suicidal individuals (Jobes, 2016). CAMS is designed to develop a strong therapeutic relationship with the suicidal individual while simultaneously targeting suicidal "drivers," which are problems that lead the individual to feel suicidal. The first session with CAMS focuses on a thorough risk assessment in which the therapist and patient sit side-by-side and fill out an assessment form called the Suicide Status Form (SSF). The SSF includes patient-rated indices of suicide risk (e.g., hopelessness, agitation, reasons for living, and reasons for dying) to fully explore their reasons for feeling suicidal. Next, the therapist and patient walk through a standardized risk assessment protocol designed to explore risk factors (e.g., frequency/intensity of suicidal thoughts, suicide plan, suicide rehearsal, relationship problems, insomnia, legal/financial problems). This ultimately leads to an extensive safety plan and collaborative discussion of a treatment plan to resolve their suicidality. Subsequent sessions focus on mitigating suicidal drivers, and the CAMS protocol is discontinued after three consecutive sessions in which the patient rates a low likelihood of making a suicide attempt and effectively manages their suicidal thoughts/feelings. CAMS is nondenominational in that it does not ascribe to a specific therapeutic modality, which leaves the clinician to flexibly use interventions that he or she is comfortable with that will effectively reduce the patient's suicidal drivers. There is evidence that CAMS is more effective than treatment as usual (Jobes, Wong, Conrad, Drozd, & Neal-Walden, 2005) and there is some evidence that it may be as effective as DBT (Andreasson et al., 2016). CAMS may be particularly effective for older adults, given that it places a heavy emphasis on building a collaborative therapeutic relationship, is rooted in an evidence-based assessment of risk factors for suicide, and focuses on treating suicidal drivers. It has yet to be adapted for and studied in this population, however.

Popular treatments for depression have been adapted for older adults. Cognitive behavioral therapy (CBT), an evidence-based treatment for depression, has shown small-to-moderate effects in reducing suicidal ideation and behaviors (Leavey & Hawkins, 2017). CBT has been adapted for older adults, as has a CBT protocol for preventing suicide in late life (Bhar & Brown, 2012). The basic premise of the adapted CBT protocol for suicide prevention is to (1) develop an extensive safety plan (which identifies warning signs, a list of internal coping strategies the patient can use when feeling suicidal, telephone numbers of supportive contacts and places that can provide distraction, telephone numbers of mental health professionals, and ways to restrict access to lethal means); (2) increase hope and reasons for living (e.g., creation of a coping card that lists reasons for living; creation of a Hope Kit that contains mementos of meaningful items, such as pictures); (3) improve social resources (e.g., joining a senior citizen organization); (4) improve problem-solving by utilizing a systematic method to approach and solve problems (Areán, Perri, Nezu, Schein, & Joseph, 1993); (5) improve adherence to medical regimen; (6) cognitive restructuring (e.g., examine evidence for and against negative thoughts and identify an alternative, less negative thought); (7) develop an intensive activity schedule to restore routine/structure and increase pleasant activities (to increase mastery); (8) engage in homework assignments outside of session (e.g., constructing a Hope Kit); and (9) develop a relapse prevention plan (use imagery to imagine the thoughts and feelings that led to the suicidal crisis, then reimagine the thoughts and feelings by responding to them with the skills learned in treatment, and then imagine a scenario that may occur in the future in which the patient might experience suicidal thoughts, and how they might proceed with the situation) (Bhar & Brown, 2012).

Treatment typically lasts for 12 sessions: the first four sessions focus on risk assessment, developing a safety plan, and instilling hope and reasons for living; the following five sessions focus on cognitive restructuring and behavior change, and the final three sessions are used to determine whether the patient has learned and is capable of applying their new skills to manage a suicidal crisis (Bhar & Brown, 2012). We are not aware of any trials that have examined the efficacy of this protocol on late-life suicide, however.

Because executive dysfunction appears to be a risk factor for suicidal thoughts and behaviors, it has been proposed that psychotherapies geared toward mitigating executive function deficits in late-life depression may also mitigate risk for suicide (Gustavson et al., 2016). Older adults with depression and executive dysfunction tend to benefit the most from behavioral treatments (Beaudreau, Rideaux, O'Hara, & Arean, 2015; Goodkind et al., 2016), meaning that CBT for late-life suicide prevention may be an especially effective treatment. One other behavioral treatment particularly effective in treating late-life depression, problem-solving therapy (PST), has been shown to be effective among depressed older adults with executive dysfunction (Areán et al., 2010), and has been shown to improve cognition in late-life depression (Mackin et al., 2014), which makes it a logical intervention for late-life suicide prevention. Briefly, PST requires that the patient identifies specific goals, generate multiple possible solutions, weigh the costs and benefits to each of these possible solutions, and develop and implement a plan to carry out the optimal solution (Areán et al., 1993).

There is some evidence that PST could be effective in treating late-life suicidality. PST with antidepressant medication has reduced suicidal ideation more than treatment as usual among depressed older adults in primary care in the Improving Mood—Promoting Access to Collaborative Treatment (IMPACT) study (Unützer et al., 2006). Another study that tested a modified form of PST for executive dysfunction (PST-ED; Areán, 2014) was compared with supportive therapy (ST) among older adults with depression and executive dysfunction (Gustavson et al., 2016). Two hundred and twenty-one older adults were randomized to PST-ED or ST and underwent treatment for 12 weeks, with a follow-up assessment at 36 weeks. Participants assigned to the PST-ED group observed greater reduction in suicidal ideation relative to the ST group (60.4% in PST-ED observed a reduction in suicidal ideation, vs 44.6% in the ST group) at the end of treatment and at the 36-week follow-up (Gustavson et al., 2016). In a secondary analysis, a second study compared in-person or telehealth PST to support calls among 158 homebound older adults with depression and found that telehealth PST was superior to supportive phone calls in reducing suicidal ideation (Choi, Marti, & Conwell, 2016). Reduction in suicidal ideation was mediated by reductions in hopelessness. Interestingly, in-person PST did not reduce ideation more than supportive calls, but the authors suggested that this was due to the fact that the in-person PST group had lower baseline ratings of suicidal ideation. Nevertheless, their findings suggest that telehealth PST can be effective in reducing suicidal ideation for older adults who are unable to make it to the clinic.

Along a similar vein, a newer home-delivered psychotherapy designed to help older adults with depression and cognitive impairment (up to moderate dementia), called problem adaptation therapy (PATH), was proposed to potentially mitigate suicide risk in older adults with cognitive impairment (Kiosses et al., 2017). PATH focuses on improving emotion regulation, which is often impaired in executive dysfunction. It does this by first identifying situations/problems that prevent positive emotions (e.g., negative emotions or lack of pleasant activities), followed by a plan to regulate emotions through problem-solving (via PST), and integrating tools from PATH (e.g., compensatory strategies, finding ways to shift attention) to help the patient avoid negatively charged situations (Kiosses et al., 2016). PATH also allows a caregiver to participate in treatment to help the patient regulate their emotions. In a secondary analysis of 74 older adults with major depression and cognitive impairment, Kiosses and colleagues observed that although PATH did not reduce suicidal ideation more than ST, it reduced negative emotions more than ST—which was associated with reductions in suicidal ideation (Kiosses et al., 2017). In other words, an improvement in negative emotions mediates reductions in suicidal ideation. Thus, approaches such as PATH may have some utility in reducing suicidal ideation among older adults with cognitive impairment.

Another psychotherapy that has the potential to be effective for older adults is interpersonal psychotherapy (IPT), given that interpersonal factors play a large role in late-life suicide. IPT for older adults has been shown to decrease suicidal ideation (Szanto, Mulsant, Houck, Dew, & Reynolds, 2003), and IPT has been adapted specifically for older adults with suicidal ideation (Heisel, Duberstein, Talbot, King, & Tu, 2009). IPT functions off of the premise that there is a bidirectional relationship between depression and interpersonal functioning, such that an individual's difficulties in interpersonal functioning contribute to depression, which in turn interferes with interpersonal functioning (Stuart & Robertson, 2003). Suicidality is viewed as an expression of hopelessness that interpersonal needs cannot be satisfied (Heisel et al., 2009). At the beginning stages of the protocol, therapists assess suicide history and current suicidality (e.g., ideation, plans) and provide psychoeducation surrounding IPT's conceptualization of suicidality. Therapists listen for interpersonal stressors that increase the patient's risk for suicide and provide psychoeducation regarding the

association between their psychosocial stressors and suicidal ideation and that the patient needs to selectively remove themselves from problematic relationships and seek out supportive relationships. Thus, in the beginning stages of IPT, the patient and therapist develop a working hypothesis surrounding the factors that develop, maintain, and strengthen the patient's suicidal ideation. It is agreed upon by both therapist and patient to focus on reducing suicidality over the remaining treatment sessions. The therapist's personal cell phone number is given to the patient in the event of imminent suicide risk. For subsequent sessions, the therapist assesses suicide risk and links suicidal ideation to interpersonal difficulties. Treatment focuses on understanding and expressing their interpersonal needs, improving social support, increasing pleasant activities with others, and reducing exposure to painful interpersonal interactions. Toward the end of treatment, patients focus on developing relationships with others and reaching out for support from others or professionals should suicidal thoughts and feelings return (Heisel et al., 2009). The initial uncontrolled pilot study of this protocol among 12 older adults showed reduced suicidal ideation over the course of treatment, an improvement in depressive symptoms, and was deemed to be a satisfactory treatment by the patients (Heisel et al., 2009). A second uncontrolled pilot study of 17 older adults had similar findings (Heisel, Talbot, King, Tu, & Duberstein, 2016). There is a need for randomized controlled trials to examine the efficacy of IPT relative to treatment as usual.

Although several treatment modalities exist for late-life suicidality, there are few studies examining their efficacy. Both CBT and PST are promising behavioral treatments that leverage executive function deficits that may be present in the older adult with suicidal ideation to reduce suicide risk, and PATH may be one behaviorally oriented approach that can reduce suicide risk in more cognitively impaired older adults, whereas IPT leverages interpersonal connection to reduce the risk for suicide. The CBT and IPT frameworks have been adapted specifically for suicide prevention, while PST and PATH have not. Thus the mechanism of suicide risk reduction occurs through a separate mechanism (e.g., reduction of hopelessness and/or negative emotions), while the CBT and IPT adaptations directly target suicidality. Both DBT and CAMS are promising interventions that have been used for younger adults, but have yet to be rigorously tested—or, in the case of CAMS—adapted for older adults.

Summary and future directions

Older adults are at elevated risk for suicide compared to younger populations, as their attempts are more likely to be fatal. Although general risk factors for suicide apply to this age group, there are other factors that contribute to suicide that are more likely to occur in this population, such as burden from physical illness and functional impairment, as well as neurodegeneration. Despite the fact that suicide is a major problem in this population, there are no evidence-based treatments that have been rigorously tested to target suicidality in older adults. Several psychotherapies—such as IPT, CBT, and PST—have promise in reducing suicide risk, but have not been adequately tested in these populations. Other well-known approaches for suicide prevention in younger populations—DBT, and the CAMS—have also yet to be rigorously studied or tested in older adults.

Although considerable research has been conducted on late-life suicide, significant work still needs to be done in two key areas. There is growing evidence that executive dysfunction may play a role in late-life suicide, but neurobiological and neurobehavioral profiles have yet to be fully explored, as this may assist clinicians in identifying older adults who are more susceptible to suicidal thoughts and behaviors. However, the area that arguably needs the most emphasis in clinical research moving forward is in the adaptation and development of interventions that can be effectively applied to older adults who are experiencing suicidal thoughts. As noted, there are several promising interventions that have been shown to effectively reduce suicide risk in younger populations but have yet to be modified or robustly tested in older adults.

References

Alphs, L., Brashear, H. R., Chappell, P., Conwell, Y., Dubrava, S., Khin, N. A., … Yaffe, K. (2016). Considerations for the assessment of suicidal ideation and behavior in older adults with cognitive decline and dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *2*(1), 48–59.

American Psychiatric Association. (2010). *Practice guidelines for the assessment and treatment of patients with suicidal behaviors*. Arlington, VA.

Andreasson, K., Krogh, J., Wenneberg, C., Jessen, H. K. L., Krakauer, K., Gluud, C., … Nordentoft, M. (2016). Effectiveness of dialectical behavior therapy versus Collaborative Assessment and Management of Suicidality treatment for reduction of self-harm in adults with borderline personality traits and disorder—a randomized observer-blinded clinical trial. *Depression and Anxiety*, *33*(6), 520–530.

Annor, F. B., Bayakly, R. A., Morrison, R. A., Bryan, M. J., Gilbert, L. K., Ivey-Stephenson, A. Z., … Simon, T. R. (2019). Suicide among persons with dementia, Georgia, 2013 to 2016. *Journal of Geriatric Psychiatry and Neurology*, *32*(1), 31–39.

Areán, P.A. (2014). Problem solving therapy for executive dysfunction.

Areán, P. A., Perri, M. G., Nezu, A. M., Schein, R. L., & Joseph, C. F. (1993). Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. *Journal of Consulting and Clinical Psychology*, *61*(6), 1003−1010.

Areán, P. A., Raue, P., Mackin, R. S., Kanellopoulos, D., McCulloch, C., & Alexopoulos, G. S. (2010). Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. *The American Journal of Psychiatry*, *167*(11), 1391−1398.

Beaudreau, S. A., Rideaux, T., O'Hara, R., & Arean, P. (2015). Does cognition predict treatment response and remission in psychotherapy for late-life depression? *The American Journal of Geriatric Psychiatry*, *23*(2), 215−219. Available from https://doi.org/10.1016/j.jagp.2014.09.003.

Beck, A. T., Kovacs, M., & Weissman, A. (1979). Assessment of suicidal intention: The Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology*, *47*(2), 343−352. Available from https://doi.org/10.1037/0022-006X.47.2.343.

Beck, A. T., Weissman, A., Lester, D., & Trexler, L. (1974). The measurement of pessimism: The Hopelessness Scale. *Journal of Consulting and Clinical Psychology*, *42*(6), 861−865.

Bergman, L., Barak, Y., Sigler, M., & Aizenberg, D. (2011). Suicide attempts and burden of physical illness among depressed elderly inpatients. *Archives of Gerontology and Geriatrics*, *52*(1), 115−117.

Beristianos, M. H., Maguen, S., Neylan, T. C., & Byers, A. L. (2017). Trauma exposure and risk of suicidal ideation among older adults. *The American Journal of Geriatric Psychiatry*, *24*(8), 639−643.

Bhar, S. S., & Brown, G. K. (2012). Treatment of depression and suicide in older adults. *Cognitive and Behavioral Practice*, *19*, 116−125.

Blow, F., Brockmann, L., & Barry, K. (2004). Role of alcohol in late-life suicide. *Alcoholism: Clinical and Experimental Research*, *28*(5), 48S−56S.

Bryan, C., Stone, S., & Rudd, M. (2011). A practical, evidence-based approach for means-restriction counseling with suicidal patients. *Professional Psychology: Research and Practice*, *42*(5), 339−346.

Carter, G., Milner, A., McGill, K., Pirkis, J., Kapur, N., & Spittal, M. J. (2017). Predicting suicidal behaviours using clinical instruments: Systematic review and meta-analysis of positive predictive values for risk scales. *British Journal of Psychiatry*, *210*(6), 387−395.

Carter, G., & Spittal, M. J. (2018). Suicide risk assessment: Risk stratification is not accurate enough to be clinically useful and alternative approaches are needed. *Crisis: The Journal of Crisis Intervention and Suicide Prevention*, *39*, 229−234.

Cavanagh, J. T. O., Carson, A. J., Sharpe, M., & Lawrie, S. M. (2003). Psychological autopsy studies of suicide: A systematic review. *Psychological Medicine*, *33*(3), 395−405.

Centers for Disease Control and Prevention. (2018). *Suicide rising across the US*. Retrieved from <https://www.cdc.gov/vitalsigns/suicide/index.html>.

Chang, Q., Chan, C., & Yip, P. (2017). A meta-analytic review on social relationships and suicidal ideation among older adults. *Social Science & Medicine*, *191*, 65−76.

Choi, N., DiNitto, D., Marti, C., & Conwell, Y. (2017). Physical health problems as a late-life suicide precipitant: Examination of coroner/medical examiner and law enforcement reports. *The Gerontologist*, gnx143.

Choi, N. G., DiNitto, D. M., Marti, C. N., & Kaplan, M. S. (2017). Older suicide decedents: Intent disclosure, mental and physical health, and suicide means. *American Journal of Preventive Medicine*, *53*(6), 772−780.

Choi, N. G., DiNitto, D. M., Marti, C. N., Kaplan, M. S., & Conwell, Y. (2017). Suicide means among decedents aged 50 + years, 2005−2014: Trends and associations with sociodemographic and precipitating factors. *The American Journal of Geriatric Psychiatry*, *25*(12), 1404−1414.

Choi, N., Marti, C., & Conwell, Y. (2016). Effects of problem-solving therapy on depressed low-income homebound older adults' death/suicidal ideation and hopelessness. *Suicide & Life-Threatening Behavior*, *46*(3), 323−336.

Chung, D. T., Ryan, C. J., Hadzi-Pavlovic, D., Singh, S. P., Stanton, C., & Large, M. M. (2017). Suicide rates after discharge from psychiatric facilities: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*(7), 694−702.

Cicirelli, V. G. (2001). Personal meanings of death in older adults and young adults in relation to their fears of death. *Death Studies*, *25*(8), 663−683.

Cipriani, G., Vedovello, M., Lucetti, C., Di Fiorino, A., & Nuti, A. (2013). Dementia and suicidal behavior. *Aggression and Violent Behavior*, *18*(6), 656−659.

Clark, L., Dombrovski, A. Y., Siegle, G. J., Butters, M. A., Shollenberger, C. L., Sahakian, B. J., & Szanto, K. (2011). Impairment in risk-sensitive decision-making in older suicide attempters with depression. *Psychology and Aging*, *26*(2), 321−330. Available from https://doi.org/10.1037/a0021646.

Cohen, A., Chapman, B., Gilman, S., Delmerico, A., Wieczorek, W., Duberstein, P., & Lyness, J. (2010). Social inequalities in the occurrence of suicidal ideation among primary care patients. *The American Journal of Geriatric Psychiatry*, *18*(12), 1146−1154.

Cohen, A., Houck, P., Szanto, K., Dew, M., Gilman, S., & Reynolds, C., III (2006). Social inequalities in response to antidepressant treatment in older adults. *Archives of General Psychiatry*, *63*(1), 50−56.

Conejero, I., Navucet, S., Keller, J., Olié, E., Courtet, P., & Gabelle, A. (2018). A complex relationship between suicide, dementia, and amyloid: A narrative review. *Frontiers in Neuroscience*, *12*, 371.

Conwell, Y., Duberstein, P. R., Cox, C., Hermann, J., Forbes, N., & Caine, E. D. (1998). Age differences in behaviors leading to completed suicide. *The American Journal of Geriatric Psychiatry*, *6*(2), 122−126.

Conwell, Y., & Thompson, C. (2008). Suicidal behavior in elders. *The Psychiatric Clinics of North America*, *31*(2), 333−356.

Conwell, Y., Van Orden, K., & Caine, E. D. (2011). Suicide in older adults. *The Psychiatric Clinics of North America*, *34*(2), 451−468. Available from https://doi.org/10.1016/j.psc.2011.02.002, ix.

Cukrowicz, K. C., Cheavens, J. S., Van Orden, K. A., Ragain, R. M., & Cook, R. L. (2011). Perceived burdensomeness and suicide ideation in older adults. *Psychology and Aging*, *26*(2), 331−338. Available from https://doi.org/10.1037/a0021836.

Cukrowicz, K., Jahn, D., Graham, R., Poindexter, E., & Williams, R. (2013). Suicide risk in older adults: Evaluating models of risk and predicting excess zeros in a primary care sample. *Journal of Abnormal Psychology*, *122*(4), 1021−1030.

Cyprien, F., Courtet, P., Malafosse, A., Maller, J., Meslin, C., Bonafé, A.. . . . . (2011). Suicidal behavior is associated with reduced corpus callosum area. *Biological Psychiatry*, *70*(4), 320−326.

Dombrovski, A., Aslinger, E., Wright, A., & Szanto, K. (2018). Losing the battle: Perceived status loss and contemplated or attempted suicide in older adults. *International Journal of Geriatric Psychiatry*, *33*(7), 907−914.

Dombrovski, A. Y., Butters, M. A., Reynolds, C. F., Houck, P. R., Clark, L., Mazumdar, S., & Szanto, K. (2008). Cognitive performance in suicidal depressed elderly: Preliminary report. *The American Journal of Geriatric Psychiatry*, *16*(2), 109−115. Available from https://doi.org/10.1097/JGP.0b013e3180f6338d.

Dombrovski, A. Y., Siegle, G. J., Szanto, K., Clark, L., Reynolds, C. F., 3rd, & Aizenstein, H. (2013). The temptation of suicide: Striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression. *Psychological Medicine*, *42*(6), 1203−1215.

Dombrovski, A. Y., Szanto, K., Clark, L., Reynolds, C. F., & Siegle, G. J. (2013). Reward signals, attempted suicide, and impulsivity in late-life depression. *JAMA Psychiatry*, *70*(10), 1020−1030.

Dombrovski, A. Y., Szanto, K., & Reynolds, C. F., III (2005). Epidemiology and risk factors for suicide in the elderly: 10-Year update. *Aging Health*, *1*(1), 135−145. Available from https://doi.org/10.2217/1745509X.1.1.135.

Drapeau, C.W., & McIntosh, J.L. (2017). *U.S.A. suicide 2016: Official final data.*Washington, DC: American Association of Suicidology.

Draper, B., Peisah, C., Snowdon, J., & Brodaty, H. (2010). Early dementia diagnosis and the risk of suicide and euthanasia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *6*(1), 75−82.

Duberstein, P. R., Conwell, Y., Seidlitz, L., Lyness, J. M., Cox, C., & Caine, E. D. (1999). Age and suicidal ideation in older depressed inpatients. *The American Journal of Geriatric Psychiatry*, *7*(4), 289−296.

Edelstein, B. A., Heisel, M. J., McKee, D. R., Martin, R. R., Koven, L. P., Duberstein, P. R., & Britton, P. C. (2009). Development and psychometric evaluation of the reasons for living—Older Adults Scale: A suicide risk assessment inventory. *The Gerontologist*, *49*(6), 736−745.

Elnour, A. A., & Harrison, J. (2008). Lethality of suicide methods. *Injury Prevention*, *14*, 39−45.

Ernst, C., Lalovic, A., Lesage, A., Seguin, M., Tousignant, M., & Turecki, G. (2004). Suicide and no axis I psychopathology. *BMC Psychiatry*, *4*, 7. Available from https://doi.org/10.1186/1471-244X-4-7.

Fässberg, M., Cheung, G., Canetto, S., Erlangsen, A., Lapierre, S., Lindner, R., . . . Waern, M. (2016). A systematic review of physical illness, functional disability, and suicidal behaviour among older adults. *Aging & Mental Health*, *20*(2), 166−194.

Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., Huang, X., . . . Nock, M. K. (2017). Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological Bulletin*, *143*(2), 187−232. Available from https://doi.org/10.1037/bul0000084.

Fry, P. S. (1984). Development of a geriatric scale of hopelessness: Implications for counseling and intervention with the depressed elderly. *Journal of Counseling Psychology*, *31*(3), 322−331.

Goodkind, M. S., Gallagher-Thompson, D., Thompson, L. W., Kesler, S. R., Anker, L., Flournoy, J., . . . O'Hara, R. M. (2016). The impact of executive function on response to cognitive behavioral therapy in late-life depression. *International Journal of Geriatric Psychiatry*, *31*(4), 334−339. Available from https://doi.org/10.1002/gps.4325.

Gujral, S., Dombrovski, A. Y., Butters, M., Clark, L., Reynolds, C. F., & Szanto, K. (2013). Impaired executive function in contemplated and attempted suicide in late life. *The American Journal of Geriatric Psychiatry*, *22*(8), 811−819. Available from https://doi.org/10.1016/j.jagp.2013.01.025.

Gustavson, K. A., Alexopoulos, G. S., Niu, G. C., McCulloch, C., Meade, T., & Areán, P. A. (2016). Problem-solving therapy reduces suicidal ideation in depressed older adults with executive dysfunction. *The American Journal of Geriatric Psychiatry*, *24*(1), 11−17. Available from https://doi.org/10.1016/j.jagp.2015.07.010.

Heeringa, S. G., Wagner, J., Torres, M., Duan, N., & Adams, B. (2004). Sample designs and sampling methods for the Collaborative Psychiatric Epidemiology Studies (CPES). *International Journal of Methods in Psychiatric Research*, *13*(4), 221−240.

Heisel, M. J., Duberstein, P. R., Lyness, J. M., & Feldman, M. D. (2010). Screening for suicide ideation among older primary care patients. *Journal of the American Board of Family Medicine*, *23*(2), 260−269.

Heisel, M. J., Duberstein, P. R., Talbot, N. L., King, D. A., & Tu, X. M. (2009). Adapting interpersonal psychotherapy for older adults at risk for suicide: Preliminary findings. *Professional Psychology: Research and Practice*, *40*(2), 156−164. Available from https://doi.org/10.1037/a0014731.

Heisel, M. J., & Flett, G. L. (2005). A psychometric analysis of the Geriatric Hopelessness Scale (GHS): Towards improving assessment of the construct. *Journal of Affective Disorders*, *87*(2−3), 211−220.

Heisel, M. J., & Flett, G. L. (2006). The development and initial validation of the Geriatric Suicide Ideation Scale. *The American Journal of Geriatric Psychiatry*, *14*(9), 742−751.

Heisel, M. J., & Flett, G. L. (2016). Investigating the psychometric properties of the Geriatric Suicide Ideation Scale (GSIS) among community-dwelling older adults. *Aging & Mental Health*, *20*(2), 208−221.

Heisel, M. J., Flett, G. L., Duberstein, P. R., & Luness, J. M. (2005). Does the Geriatric Depression Scale (GDS) distinguish between older adults with high versus low levels of suicidal ideation? *The American Journal of Geriatric Psychiatry*, *13*(10), 876−883.

Heisel, M. J., Talbot, N. L., King, D. A., Tu, X. M., & Duberstein, P. R. (2016). Adapting interpersonal psychotherapy for older adults at risk for suicide. *The American Journal of Geriatric Psychiatry*, *23*(1), 87−98.

Heron, M., Hoyert, D., Murphy, S., Xu, J., Kochanek, K., & Tejada-Vera, B. (2009). Deaths: Final data for 2006. *National Vital Statistics Reports*, *57*(14), 1−134.

Hwang, J.-P., Lee, T.-W., Tsai, S.-J., Chen, T.-J., Yang, C.-H., Lirng, J.-F., & Tsai, C.-F. (2010). Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *Journal of Geriatric Psychiatry and Neurology*, *23*(3), 171−184.

Jahn, D. R., & Cukrowicz, K. C. (2011). The impact of the nature of relationships on perceived burdensomeness and suicide ideation in a community sample of older adults. *Suicide & Life-Threatening Behavior*, *41*(6), 635–649.

Jobes, D. (2016). *Managing suicidal risk: A collaborative approach* (2nd ed.). New York, NY: Guilford Press.

Jobes, D., Wong, S. A., Conrad, A. K., Drozd, J. F., & Neal-Walden, T. (2005). The Collaborative Assessment and Management of Suicidality versus treatment as usual: A retrospective study with suicidal outpatients. *Suicide & Life-Threatening Behavior*, *35*(5), 483–497.

Joiner, T. (2005). *Why people die by suicide*. Cambridge, MA: Harvard University Press.

Jollant, F., Lawrence, N. L., Olié, E., Guillaume, S., & Courtet, P. (2011). The suicidal mind and brain: A review of neuropsychological and neuroimaging studies. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *12* (5), 319–339. Available from https://doi.org/10.3109/15622975.2011.556200.

Juurlink, D., Herrmann, N., Szalai, J., Kopp, A., & Redelmeier, D. (2004). Medical illness and the risk of suicide in the elderly. *Archives of Internal Medicine*, *164*(11), 1179–1184.

Kasckow, J., Youk, A., Anderson, S., Dew, M., Butters, M., Marron, M., ... Reynolds, C., III (2016). Trajectories of suicidal ideation in depressed older adults undergoing antidepressant treatment. *Journal of Psychiatric Research*, *73*, 96–101.

King, D. A., Conwell, Y., Cox, C., Henderson, R. E., Denning, D. G., & Caine, E. D. (2000). A neuropsychological comparison of depressed suicide attempters and nonattempters. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(1), 64–70. Available from https://doi.org/10.1176/jnp.12.1.64.

Kiosses, D., Gross, J., Banerjee, S., Duberstein, P., Putrino, D., & Alexopoulos, G. (2017). Negative emotions and suicidal ideation during psychosocial treatments in older adults with major depression and cognitive impairment. *The American Journal of Geriatric Psychiatry*, *25*(6), 620–629.

Kiosses, D., Ravdin, L., Gross, J., Raue, P., Kotbi, N., & Alexopoulos, G. (2016). Problem adaptation therapy (PATH) for older adults with major depression and cognitive impairment: A randomized clinical trial. *JAMA Psychiatry*, *72*(1), 22–30.

Klonsky, E. D., & May, A. M. (2015). The Three-Step Theory (3ST): A new theory of suicide rooted in the "ideation-to-action" framework. *International Journal of Cognitive Therapy*, *8*(2), 114–129.

Lai, A. X., Kaup, A. R., Yaffe, K., & Byers, A. L. (2018). High occurrence of psychiatric disorders and suicidal behavior across dementia subtypes. *The American Journal of Geriatric Psychiatry*, *26*(12), 1191–1201.

Lapierre, S., Erlangsen, A., Waern, M., De Leo, D., Oyama, H., Scocco, P., ... International Research Group for Suicide among the Elderly. (2011). A systematic review of elderly suicide prevention programs. *Crisis: The Journal of Crisis Intervention and Suicide Prevention*, *32*(2), 88–98.

Leavey, K., & Hawkins, R. (2017). Is cognitive behavioural therapy effective in reducing suicidal ideation and behaviour when delivered face-to-face or via e-health? A systematic review and meta-analysis. *Cognitive Behaviour Therapy*, *46*(5), 353–374.

Linehan, M. (1993). *Cognitive-behavioral treatment of borderline personality disorder* (1st ed.). New York, NY: Guilford Press.

Linehan, M. M., Goodstein, J. L., Nielsen, S. L., & Chiles, J. A. (1983). Reasons for staying alive when you are thinking of killing yourself: The Reasons for Living Inventory. *Journal of Consulting and Clinical Psychology*, *51*(2), 276–286. Available from https://doi.org/10.1037/0022-006X.51.2.276.

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *The American Journal of Psychiatry*, *159*(7), 1119–1126. Available from https://doi.org/10.1176/appi.ajp.159.7.1119.

Lutz, J., & Fiske, A. (2018). Functional disability and suicidal behavior in middle-aged and older adults: A systematic critical review. *Journal of Affective Disorders*, *227*, 260–271.

Lynch, T. R. (2000). Treatment of elderly depression with personality disorder comorbidity using dialectical behavior therapy. *Cognitive Behavioral Practice*, *7*, 468–477.

Lynch, T. R., Morse, J. Q., Mendelson, T., & Robins, C. J. (2003). Dialectical behavior therapy for depressed older adults: A randomized pilot study. *The American Journal of Geriatric Psychiatry*, *11*(1), 33–45.

Mackin, R. S., Nelson, J. C., Delucchi, K., Raue, P., Byers, A., Barnes, D., ... Areán, P. A. (2014). Cognitive outcomes after psychotherapeutic interventions for major depression in older adults with executive dysfunction. *The American Journal of Geriatric Psychiatry*, *22*(12), 1496–14503.

McGirr, A., Dombrovski, A. Y., Butters, M. A., Clark, L., & Szanto, K. (2012). Deterministic learning and attempted suicide among older depressed individuals: Cognitive assessment using the Wisconsin Card Sorting Task. *Journal of Psychiatric Research*, *46*(2), 226–232. Available from https://doi.org/10.1016/j.jpsychires.2011.10.001.

Miller, M., Azrael, D., & Hemenway, D. (2004). The epidemiology of case fatality rates for suicide in the northeast. *Annals of Emergency Medicine*, *43*(6), 723–730.

Myung, W., Han, C., Fava, M., Mischoulon, D., Papakostas, G., Heo, J.-Y., ... Jeon, H. (2016). Reduced frontal-subcortical white matter connectivity in association with suicidal ideation in major depressive disorder. *Translational Psychiatry*, *6*(e835), 1–8.

O'Connor, R. C. (2011). Towards an integrated motivational-volitional model of suicidal behavior. In R. C. O'Connor, S. Platt, & J. Gordon (Eds.), *International handbook of suicide prevention: research,policy, and practice* (1st ed., pp. 181–198). London: John Wiley & Sons, Ltd.

Pu, S., Nakagome, K., Yamada, T., Yokoyama, K., Matsumura, H., Yamada, S., ... Kaneko, K. (2015). Suicidal ideation is associated with reduced prefrontal activation during a verbal fluency task in patients with major depressive disorder. *Journal of Affective Disorders*, *181*, 9–17.

Richard-Devantoy, S., Szanto, K., Butters, M. A., Kalkus, J., & Dombrovski, A. Y. (2015). Cognitive inhibition in older high-lethality suicide attempters. *International Journal of Geriatric Psychiatry*, *30*(3), 274–283. Available from https://doi.org/10.1002/gps.4138.

Ruocco, A. C. (2005). The neuropsychology of borderline personality disorder: A meta-analysis and review. *Psychiatry Research*, *137*(3), 191–202.

Spicer, R. S., & Miller, T. R. (2000). Suicide acts in 8 states: Incidence and case fatality rates by demographics and method. *American Journal of Public Health*, *90*(12), 1885–1891.

Stanley, I. H., Hom, M. A., Rogers, M. L., Hagan, C. R., & Joiner, T. E., Jr. (2016). Understanding suicide among older adults: A review of psychological and sociological theories of suicide. *Aging & Mental Health*, *20*(2), 113–122.

Stuart, S., & Robertson, M. (2003). *Interpersonal psychotherapy: A clinician's guide*. London: Arnold.

Szanto, K., Mulsant, B., Houck, P., Dew, A., & Reynolds, C., III (2003). Occurrence and course of suicidality during short-term treatment of late-life depression. *JAMA Psychiatry*, *60*(6), 610–617.

Szücs, A., Szanto, K., Aubry, J.-M., & Dombrovski, A. (2018). Personality and suicidal behavior in old age: A systematic literature review. *Frontiers in Psychiatry*, *9*(128).

Tully, P. J., & Baker, R. A. (2012). Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: A contemporary and practical review. *Journal of Geriatric Cardiology*, *9*(2), 197–208.

Turvey, C., Conwell, Y., Jones, M., Phillips, C., Simonsick, E., Pearson, J., & Wallace, R. (2002). Risk factors for late-life suicide: A prospective, community-based study. *The American Journal of Geriatric Psychiatry*, *10*(4), 398–406.

Unützer, J., Tang, L., Oishi, S., Katon, W., Williams, J. W., Hunkeler, E., … IMPACT Investigators. (2006). Reducing suicidal ideation in depressed older primary care patients. *Journal of the American Geriatrics Society*, *54*(10), 1550–1556.

van Heeringen, K., Bijttebier, S., Desmyter, S., Vervaet, M., & Baeken, C. (2014). Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. *Frontiers in Human Neuroscience*, *8*, 824.

van Heeringen, K., Wu, G.-R., Vervaet, M., Vanderhasselt, M.-A., & Baeken, C. (2017). Decreased resting state metabolic activity in frontopolar and parietal brain regions is associated with suicide plans in depressed individuals. *Journal of Psychiatric Research*, *84*, 243–248.

Van Orden, K., & Conwell, Y. (2011). Suicides in late life. *Current Psychiatry Reports*, *13*(3), 234–241.

Van Orden, K., Cukrowicz, K., Witte, T., & Joiner, T. (2011). Thwarted belongingness and perceived burdensomeness: Construct validity and psychometric properties of the Interpersonal Needs Questionnaire. *Psychological Assessment*, *24*(1), 197–215.

Van Orden, K. A., O'Riley, A. A., Simning, A., Podgorski, C., Richardson, T. M., & Conwell, Y. (2015). Passive suicide ideation: An indicator of risk among older adults seeking aging services? *The Gerontologist*, *55*(6), 972–980.

Van Orden, K. A., Witte, T. K., Cukrowicz, K. C., Braithwaite, S., Selby, E. A., & Joiner, T. E. (2010). The Interpersonal Theory of Suicide. *Psychological Review*, *117*(2), 575–600. Available from https://doi.org/10.1037/a0018697.

Woodford, R., Spittal, M. J., Milner, A., McGill, K., Kapur, N., Pirkis, J., … Carter, G. (2017). Accuracy of clinician predictions of future self-harm: A systematic review and meta-analysis of predictive studies. *Suicide and Life-Threatening Behavior*, *49*(1), 23–40. Available from https://doi.org/10.1111/sltb.12395.

World Health Organization. (2018). *World health statistics 2018: Monitoring health for the SDGs, sustainable development goals*. Geneva: World Health Organization.

Wyart, M., Jaussent, I., Ritchie, K., Abbar, M., Jollant, F., & Courtet, P. (2016). Iowa gambling task performance in elderly persons with a lifetime history of suicidal acts. *The American Journal of Geriatric Psychiatry*, *24*(5), 399–406. Available from https://doi.org/10.1016/j.jagp.2015.12.007.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*(1), 37–49.

Chapter 11

Anxiety and its disorders in old age

Sherry A. Beaudreau[1,2,3], Christine E. Gould[2,4], Susan Sharp Kolderup[5] and Nehjla Mashal[1,2]

[1]*Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States,* [2]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States,* [3]*School of Psychology, University of Queensland, Brisbane, QLD, Australia,* [4]*Geriatric Research Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, United States,* [5]*Home Based Primary Care, Memphis VA Medical Center, Memphis, TN, United States*

Anxiety and depression are the most common forms of emotional disturbance found in geriatric practice.

M.L. Riccitelli

Introduction

Riccitelli's statement regarding the clinical importance of anxiety and depression in older patients appeared in the July 1964 edition of the *Journal of the American Geriatrics Society*, in a review titled, "Modern Concepts in the Management of Anxiety and Depression in the Aged and Infirm." The author describes pharmacological management of anxiety symptoms occurring alongside depression in older patients. This acknowledgment of anxiety as a critical issue for the clinical care of older adults 50 years ago is remarkable given that the field of geriatrics dates back only a decade prior to the publication of Riccitelli's article. The present state of the field in geriatrics has a much firmer grasp on the prevalence and public health impact of anxiety disorders in older populations, with anxiety understood as an issue in its own right, regardless of cooccurring depression. Epidemiologic and clinic data to date fully support Riccitelli's supposition that anxiety is common based on evidence that anxiety disorders are among the most common psychiatric issues in older individuals. In fact, anxiety disorders are now known to be *the* most common class of mental health diagnoses in older adults, exceeding depressive disorders (Kessler et al., 2005).

This chapter will first provide an overview of the scope and public health impact of anxiety disorders. Then, it will describe the types of anxiety disorders often encountered in older adults, as well as the methods of assessing and treating anxiety in those 65 and older. Although the understanding of anxiety disorders in older adults lags behind the rich and extensive empirical work in younger populations with anxiety, scientific strides in late-life anxiety over the past two decades have been narrowing this gap in several ways. First, mental health investigations increasingly assess anxiety in addition to depression in older cohorts. Anxiety assessment measures have also been validated in older populations with geriatric anxiety measures under development. Finally, anxiety treatment research with older individuals has grown from clinical case reports and pilot studies to randomized control trials (Beaudreau & Pachana, 2016). This work, however, has unearthed challenges and limitations of current evidence-based therapies. This chapter summarizes what is known in each of these areas with regard to late-life anxiety and offers recommendations for both clinicians and researchers in geriatrics.

Overview

The American Psychiatric Association (APA, 2013) broadly characterizes anxiety disorders as engendering two primary components: fear and anxiety. Fear refers to the "emotional response to real or perceived threat" and anxiety as "the anticipation of future threat" (p. 189; APA, 2013). These disorders encompass a number of different chronic mental health diagnoses characterized by physical arousal, apprehensive thoughts or worry, and anxious feelings (APA, 2013). Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition (DSM-5) has broad applicability and is

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00011-9

used in practice to diagnose anxiety and other psychiatric disorders across the life span. Thus diagnoses occur by applying the same criteria to both younger and older adults. Data regarding altered diagnostic criteria for anxiety disorders in older compared with younger adults are limited or nonexistent. Regardless, clinicians should take extra care to determine that a symptom is not solely accounted for by a medical or cognitive issue when diagnosing older patients.

Estimates of anxiety disorders vary from 1.2% to 15% in older adults living in the community (Bryant, Jackson, & Ames, 2008) and 3.2% to 20% in older individuals in residential settings (Creighton, Davison, & Kissane, 2016). Subsyndromal anxiety, defined as clinically significant anxiety that does not meet criteria for a diagnosis, has been documented as 15%−52% in community-dwelling older adults, with strikingly similar prevalence estimates for subsyndromal anxiety among older adults in medical settings (Bryant et al., 2008). The lifetime prevalence of anxiety disorders (e.g., social phobia, generalized anxiety disorder, GAD) is higher in younger than older age groups (Gum, King-Kallimanis, & Kohn, 2009; Kessler et al., 2005). It is unclear if this occurs because the diagnostic criteria are less relevant to older adults due to selective mortality or if this reflects a true age-related difference. The high rates of subsyndromal anxiety among older persons could be one indication that anxiety symptoms attenuate over time. Alternatively, the clinical import of subsyndromal cases may warrant reconsideration of fewer symptoms needed to meet criteria for an anxiety disorder in older persons. Life span longitudinal studies are needed to determine why these rates differ by age cohorts and whether the rates will differ in future older adult cohorts.

Anxiety disorders can range from mild-to-severe symptom frequency and severity, which can also be mildly to severely debilitating to older adults in terms of functional ability (Miloyan, Byrne, & Pachana, 2015; Corna et al., 2007). More recently, having an anxiety disorder has also been shown to predict an increased risk of developing cognitive disorders such as dementia (Petkus et al., 2016). There is also some evidence that anxiety could be a risk factor for mortality (Ostir & Goodwin, 2006). Given these risk factors, understanding how anxiety affects older adults and how it is best assessed and treated are paramount to providers of older patients.

Anxiety disorders

Similar to younger individuals, those DSM-5 anxiety disorders most common in older adults include specific phobia, GAD, social anxiety disorder, panic disorder, and agoraphobia (Kessler et al., 2005). Although observed less often, other relevant anxiety diagnoses in older adults include substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder. We only briefly discuss selective mutism and separation anxiety, recently moved from the childhood disorders to the anxiety disorders, due to minimal available information regarding their manifestation in older persons. This section reviews the definition of these specific anxiety disorders and their prevalence rates in older adults. Age-related concerns and issues that have been suggested to increase the risk of anxiety disorders in older adults are also addressed. Obsessive-compulsive and related disorders and trauma-and stressor-related disorders are not discussed here because they are no longer included under DSM-5 anxiety disorders.

Common anxiety disorders

Specific phobia

Specific phobias are among the most common disorders in late life, yet little research has been conducted with older adults suffering from this disorder. A specific phobia, or unreasonable fear or anxiety of a specific situation or object, results in individuals actively attempting to avoid the specific situation or the experience of intense fear or anxiety if they have to confront the situation. Lifetime prevalence estimates of specific phobia are 7.5% among older adults aged 60 and older (Kessler et al., 2005). The 12-month prevalence is 4.7% among those 65 and older (Gum et al., 2009). Older adults tend to express specific phobias related to natural environments and fear of falling (Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010). Specific phobias in older adults also cooccur with medical problems such as chronic obstructive pulmonary disease (COPD, APA, 2013). As a result, the anxiety symptoms related to specific phobias may be mistakenly diagnosed as symptoms of a medical condition as opposed to a specific phobia.

Social anxiety disorder

Social anxiety disorder is also common in older adulthood, but similar to specific phobia, has received relatively little attention in empirical investigations. This disorder is characterized by fear in social situations in which individuals

believe others will evaluate them negatively. Anxiety in social situations could be particularly problematic in older adults who rely on others for activities of daily living. Lifetime prevalence estimates of social anxiety disorders in older adults range from 4.9% (Cairney et al., 2007) to 6.6% (Kessler et al., 2005) with a 12-month prevalence of 2.3% in those 65 and older (Gum et al., 2009). While social anxiety disorder is not well studied in older adults, it appears that social anxiety disorders in older adults have similar characteristics in younger adults (Cairney et al., 2007). However, older adults might feel anxious about different types of social situations such as forgetting information in front of other people (Ciliberti, Gould, Smith, Chorney, & Edelstein, 2011).

The longitudinal course of social anxiety in older adults differs from that of younger adults. In a general population sample of older adults ($N = 612$), nine participants met DSM criteria for social anxiety at baseline, and only one continued to meet DSM criteria 5 years later. Additionally, among participants who did not have social anxiety disorder at baseline ($n = 603$), 2.0% ($n = 12$) met DSM criteria for social anxiety disorder during follow-up (Karlsson et al., 2010). These findings are suggestive of social anxiety disorder being more chronic in younger than in older adults (Karlsson et al., 2010). Alternatively, this could indicate that the clinical course of social anxiety disorder fluctuates appreciably over time, warranting careful notation of social anxiety symptoms that do not meet full DSM-5 criteria in older individuals.

Generalized anxiety disorder

Of all the anxiety disorders, GAD has been most studied in older adults. The lifetime prevalence of GAD among older adults is 3.6% in those aged 60 and older (Kessler, Ormel, Demler, & Stang, 2003) with a 12-month prevalence of 1.2% in those aged 65 and older (Gum et al., 2009). GAD is characterized by excessive and uncontrollable worry about the anticipation of negative events (APA, 2013). In older adults with GAD, these symptoms are distressing and interfere significantly with their daily living. They are also typically accompanied by physical symptoms such as muscle tension and feeling easily fatigued (APA, 2013). Older adults with GAD often worry about a number of daily problems. Specifically, older adults appear to worry more about their health and potential burden on others (Lenze et al., 2001) and less about school, work, and interpersonal relationships than younger adults (Wuthrich, Johnco, & Wetherell, 2015).

Older adults with GAD, but also true of other anxiety disorders, may mistakenly identify their physical symptoms of anxiety as a somatic or medical problem (Wolitzky-Taylor et al., 2010). As a result, many older adults report these symptoms to their primary care provider as opposed to a provider in a specialty mental health clinic (APA, 2010). The overlap between medical conditions and GAD is vital to understand because GAD symptoms can mimic physical health problems and vice versa. For example, medical problems (e.g., hyperthyroidism), substance use (e.g., alcohol, caffeine), and certain medications for medical problems (e.g., diabetes, high blood pressure) can produce similar physical symptoms to GAD (APA, 2013). It is recommended to review the results of the patient's previous physical examination, along with conducting a clinical interview that includes the patient's medical and personal history (Gould, Beaudreau, & Huh, 2013). Certainly, this combined medical and psychiatric determination as part of the assessment process should also be implemented with other anxiety symptoms or disorders.

Panic disorder

Panic disorder is defined as unexpected and recurrent panic attacks. More specifically, panic disorder includes an episode of anxiety in which physical (e.g., paresthesia, pounding heart, or sweating) and cognitive (e.g., fear of losing control or fear of dying) symptoms occur. Panic attacks often peak within a couple of minutes, a criterion for panic disorder. Though not a requirement for panic disorder, panic attacks can also be followed by worry about having another panic attack, changes in panic attack related behaviors, or both (APA, 2013). Panic disorder appears to be relatively uncommon among older adults with a lifetime prevalence of 2.0% among those aged 60 and older (Kessler et al., 2005), and 12-month prevalence of 0.7% among those aged 65 and older (Gum et al., 2009). In older adults, panic disorder may be related to recent stressful life events or medical problems such as tachycardia, stomach ulcers (Chou, 2010), or COPD (Brenes, 2003). Panic disorder symptoms have been reported as more intense in the general population of adults as compared to older adults with a late age of onset of panic disorder (Sheikh, Swales, Carlson, & Lindley, 2004). The lower intensity of symptoms in panic disorder with a late age of onset may be due to an attenuated autonomic response in older adults (Mohlman et al., 2004). Despite less intense panic attacks in older adults, one study of older adults found that panic disorder was related to functional impairment in daily living (Corna et al., 2007) and likely has a negative effect on their overall quality of life. Panic disorder in persons of all ages can occur with and without agoraphobia (APA, 2013). Agoraphobia can also appear on its own without panic in older and younger persons alike (APA, 2013).

Agoraphobia

The central features of agoraphobia are intense fear and anxiety in situations or places such as public transportation, being outside of the home, and being in enclosed places. The distress may occur in the anticipation of the event or during the actual event. Individuals with agoraphobia actively try to avoid the given situation or place. The distress is related to the belief that it may be difficult to escape or to receive help in the given situation (APA, 2013). The lifetime prevalence of agoraphobia without panic in those aged 60 and older is estimated to be 1.0% (Kessler et al., 2005), with the 12-month prevalence of agoraphobia without panic estimated at 0% in those aged 65 and older—indicating that agoraphobia without panic is rare, though possible, in older adults (Gum et al., 2009). While the clinical features of agoraphobia appear consistent and chronic across a lifetime, the types of places and situations that cause fear may be different as individuals age. Older adults most often fear standing in lines, along with being in open spaces and shops (Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2010).

Anxiety disorders due to substances, medications, or medical conditions

In situations in which an older adult's significant anxiety or panic attacks occur solely in the context of a substance, medication, or the physiological effect of a medical condition, the appropriate diagnosis may be substance/medication-induced anxiety disorder or anxiety disorder due to another medical condition. The high prevalence rates of multimorbidity in older adults, especially those with elevated anxiety, can make the differential diagnosis between an anxiety disorder or anxiety disorder due to substance or medical condition challenging (Gould, O'Hara, Goldstein, & Beaudreau, 2016). Data based on the general population suggest that substance/medication-induced anxiety disorders are uncommon in all age groups (Grant et al., 2004). Epidemiological research (Kessler et al., 2005) has found specific medical conditions (e.g., hypertension, arthritis) are related to increased anxiety; however, it remains uncertain if the anxiety disorders in this study occurred due to medical conditions.

A variety of substances and medications that older adults consume may produce anxiety or panic attacks that develop shortly after consumption, during withdrawal, or during intoxication. For example, medications such as steroidal drugs to treat asthma, antiparkinsonian medications, and thyroid preparations could cause a medication-induced anxiety disorder. Features of medication-induced anxiety disorder may include heart palpitations, insomnia, dizziness, and nervousness. In addition, specific substances, such as alcohol, can cause anxiety or panic attacks during both intoxication and withdrawal. A number of medical conditions common in older adults may also cause anxiety or panic attacks, including congestive heart failure, COPD, and hypothyroidism (APA, 2013).

Other specified anxiety disorder/unspecified anxiety disorder

The essential features of other specified anxiety disorder and unspecified anxiety disorder are anxiety that causes clinically significant impairment and distress but does not fully meet criteria for an anxiety disorder. The diagnosis of other specified anxiety disorder might be used when the clinician has identified a specific type of anxiety (e.g., generalized anxiety, panic) affecting the older adult, but the symptom severity does not meet DSM-5 diagnostic criteria. Examples of other specified anxiety disorders in older adults include limited symptom panic attacks, generalized anxiety not occurring on more days than not, and cultural concepts (e.g., ataque de nervios, khyâl cap) that cause significant anxiety symptoms (APA, 2013). A diagnosis of unspecified anxiety disorder may be more appropriate if the symptoms are not clearly linked to a specific anxiety disorder designation and there is insufficient information to draw further diagnostic conclusions. The prevalence of specified and unspecified anxiety disorders in older adults is unknown.

It is estimated that as many as one in five older adults experience anxiety symptoms that do not meet diagnostic criteria for an anxiety disorder (Himmelfarb & Murrell, 1984). Some of these individuals would likely meet current criteria for other specified anxiety disorder or unspecified anxiety disorder based on the clinical significance of symptoms. Others with subsyndromal anxiety might not have functional impairment or distress, but these individuals could potentially be at risk for later development of more impairing symptoms for an anxiety disorder diagnosis (Karsten, Nolen, Penninx, & Hartman, 2011). The severity of self-reported anxiety symptoms did not show a clear association with disability in older participants in the Netherlands Study of Depression and Anxiety; however, the report of mild-to-severe self-reported anxiety was associated with more disability than reporting none to minimal symptoms (Karsten et al., 2011). Subthreshold anxiety has been shown to contribute to disability among older adults in at least one other study as well (Miloyan, Byrne, & Pachana, 2015). Thus while the presence of an anxiety disorder is important to ascertain, anxiety symptom severity is equally important to determine in older patients.

Less common anxiety disorders

Largely unknown is the prevalence and functional impact of two other anxiety disorders that recently moved from childhood disorders to anxiety disorders more generally that can occur across the life span: selective mutism and separation anxiety disorder (SAD). The essential features of selective mutism are constant refusal to speak in select social situations in spite of speaking in other situations. This would not include inability to speak due to age-related neurological disorders that lead to memory impairment, as with many dementias and particularly in the advanced stages of dementing disorders. Selective mutism disorder is often diagnosed in younger children; the longitudinal course of the disorder is unknown (APA, 2013). Though selective mutism has not been examined among older adults, in part due to previous conceptualizations that assumed that it resolved in adolescence, further understanding regarding its course in older adulthood may be possible now that it is included under anxiety disorders without the age restriction of childhood, which would allow its inclusion in epidemiological and clinical studies of older individuals.

SAD refers to developmentally excessive fear, anxiety, and avoidant behaviors upon separation from key attachment figures. Previously, an onset prior to 18 years of age was required, but the DSM-5 now recognizes that SAD onset can occur at any age, including in late life (Manicavasagar et al., 2010). No studies to date, however, have been conducted on SAD in older adults. National Comorbidity Survey Replication (a United States household survey) data suggest that a substantial portion (77.5%) of adults, aged 18 years and older with SAD, have an onset in adulthood (Shear, Jin, Ruscio, Walters, & Kessler, 2006). Of those adults with child-onset SAD, only 36.1% had SAD that continued into adulthood (Shear et al., 2006).

When diagnosing older patients, it is necessary to be able to distinguish between SAD and other mental health disorders, such as panic disorder, by determining if their anxiety is related to their main attachment figures or to something else (Rochester & Baldwin, 2015). Based on clinical observation, older adults with SAD's main attachment figures often include their significant other, caregiver, or adult children. The significant impact on their functioning is likely to result from fear that harm or death will occur to their attachment figures, anxiety related to being separated from others, and avoidance of being alone. SAD should be differentiated from reasonable concerns about attachment figures, as with older adults who may be primary caregivers or supports for a very old parent (e.g., in their 80s or 90s) with failing health or cognitive issues.

Similar to adults (APA, 2013), older adults with SAD will likely be fearful of situations (i.e., traveling alone, car accidents, burglaries) that may be perceived as presenting harm to their attachment figures or themselves. Some older adults could also desire to constantly know the location of their attachment figures and attempt to keep in constant touch with them. They may exhibit anxiety related to becoming lost and fearful that they will be separated from their attachment figures permanently. These symptoms often cause significant distress in areas of functioning to the older adult with SAD in their social and occupational life and likely do not affect them as much in their family environment.

In summary, DSM-5 anxiety disorders include those both common and rare in older individuals, with most research slanted toward GAD or subthreshold issues when it is conducted with older adults. This next section discusses anxiety that occurs in the context of neurocognitive disorders, termed "neuropsychiatric anxiety," and how it plays an increasingly important role in the overall understanding and context of late-life anxiety disorders.

Anxiety in the context of neurocognitive disorders

A neurocognitive disorder is defined as cognitive impairment, not due to normal aging and ranging from mild to severe (APA, 2013). These disorders can be due to an underlying neurological process such as Alzheimer's disease (AD), vascular insults, or some other factors, but the majority occurs due to AD (APA, 2013). It is estimated that approximately five to eight out of 100 individuals aged 60 years and older have major neurocognitive impairment, also called dementia (World Health Organization, 2015). Because dementia is a prevalent disability among older adults (World Health Organization, 2015), and anxiety is quite common among older adults with dementia (Starkstein, Jorge, Petracca, & Robinson, 2007; Zhao et al., 2016), it is important to understand the interrelationship between anxiety and dementia.

In their critical review, Seignourel, Kunik, Snow, Wilson, and Stanley (2008) observed anxiety symptoms and disorders as more common for certain types of dementias and among individuals of certain ethnic and racial backgrounds. In particular, they found that the presence of anxiety symptoms generally occur more often in vascular dementia than in AD. Further, among individuals with dementia, anxiety disorders were noted as more prevalent among those who were Asian and Latino compared with African American and Caucasian. Sex and education did not appear to be related to anxiety in individuals with dementia.

Recent evidence implicates anxiety as an independent risk factor for new cases of dementia. Dementia-free individuals from the Swedish Twin Study who reported higher state anxiety during a baseline assessment had a nearly 50% increased risk of developing dementia over a 28-year span (Petkus et al., 2016). This held even after adjustment for depressive symptoms. Consistent with this finding, Petkus and colleagues found that a report of elevated anxiety at any assessment time point was also associated with incident dementia. The authors postulate several biological explanations for the increased dementia risk in anxious older adults, as well as the possibility that insight about cognitive problems could explain the appearance of anxiety prior to dementia.

The cooccurrence of anxiety in dementia has critical implications for clinicians working with such individuals. First, older adults recently diagnosed with mild neurocognitive impairments may experience anxiety related to how they will inform their significant others about their diagnosis, who will care for them, and fear related to when their disorder will progress. As their dementia progresses, they may experience disorientation and confusion, which could increase their anxiety. Due to similarities between anxiety disorders and neurocognitive disorder symptoms, it is difficult to determine if there is a causal or indirect relationship between these disorders (Petkus et al., 2016; Seignourel et al., 2008). In a study of 552 patients with a likely diagnosis of AD, 26% reported excessive worry or anxiety in the past 6 months (Starkstein, Jorge, Petracca, & Robinson, 2007). This investigation found that excessive worry and anxiety was significantly associated with respiratory symptoms, increased fears, muscle tension, restlessness, and irritability. Interestingly, they found that sleep disturbance, difficulty concentrating, and fatigue were not associated with excessive worry and anxiety. Future research will likely continue to determine if anxiety is a direct effect of dementia or another mental health disorder such as GAD, depression with anxiety, or anxiety disorder due to another medical condition.

As investigations in this area continue to refine our understanding of anxiety and cognitive impairment, it will be enlightening to see if there are cognitive profiles or variants of anxiety disorders that can be used to identify different subgroups. Most notably, Butters and colleagues (2004) have determined that more than half of older adults with major depressive disorders also have marked executive dysfunction, meaning significant impairment in cognitive abilities such as planning, organizing, and decision-making. Evidence points to specific domains of executive function, mainly inhibitory ability, as potentially reduced or impaired in the presence of anxiety (Beaudreau, MacKay-Brandt, & Reynolds, 2013). However, this association between lower inhibitory ability and elevated anxiety may be lessened by the presence of elevated worry (Beaudreau et al., 2017). Further, evidence to date has not supported global deficits in executive functioning with older adults with elevated anxiety symptoms or anxiety disorders (Beaudreau & O'Hara, 2008, 2009) that have been found in late-life depression.

Diagnostic challenges

Even without co-occurring neurocognitive disorders, anxiety disorders can be challenging to diagnosis in older individuals. More specifically, as noted in Riccitelli's review (1964), it can be difficult to distinguish between normative variations in mental health symptoms and symptoms that warrant treatment. The main distinction Riccitelli makes is whether the symptoms are in excess or are absent during certain stressors. Nevertheless, determining whether the response or behavior occurs in excess can be quite challenging. For example, imagine an older patient who indicates that they have not left the house lately due to urinary incontinence. This could be due to agoraphobia with or without panic, social anxiety with fear of embarrassment related to having an "accident" in front of others, or depending on the extent of the urinary incontinence and the extent to which the patient is not leaving the house, this could be a normal reaction.

In other examples, following a recent move to an assisted living facility after being in one's home for 40 years, an older adult might report that she cannot stop thinking about how she wishes she was still back in her old home. In the case of an older adult with a history of stroke, they may state that "my speech has been slurred since having a stroke and I am avoiding seeing my old friends because I feel self-conscious." This reaction could be normative in that the older adult may "limit phone conversations because they are frustrated" and "still see friends each week for lunch," or the reaction could suggest the presence of an anxiety disorder (e.g., "I have not seen my friends in over 6 months due to my fear of making a fool of myself"). The next section describes the process of anxiety assessment with older persons and the measures with the best validation for use with this population.

Assessment of anxiety in older adults

Careful assessment of anxiety symptoms and their course facilitates the identification of late-life anxiety disorders while also navigating the diagnostic challenges discussed above. Clinicians should employ a multimodal approach to anxiety

assessment with older adults. Information about specific anxiety symptoms experienced and the course of those symptoms could be collected from multiple sources including the medical record, objective measures, a spouse or caregiver, the clinician's own observations, and from the patient. To begin, a review of the patient's current medications, medical problems, progress notes, and discharge summaries in the medical record could help the clinician ascertain whether the patient is taking medications that may cause anxiety in older adults. Next, the clinician can assess if the patient has developed new medical conditions that cause or exacerbate anxiety (e.g., heart arrhythmia) or is experiencing a worsening of current conditions (e.g., COPD). Objective measures include physiological measures such as blood pressure, heart rate, and variability, and skin conductance that can be used when available. Clinician observations are particularly important in cases where the self-reported symptoms do not match behavioral observations (e.g., an older adult denies anxiety but avoids activities). These observations can factor into assessments including questions asked during the interviews discussed below. Since many anxiety symptoms are not observable, semistructured interviews and paper-and-pencil questionnaires are both essential to the assessment of symptom frequency and severity by drawing on the patient's experience and caregiver's perception (when applicable).

Semistructured interviews may be used to assess for the presence of anxiety disorders, the severity of anxiety disorders, or both. The Structured Clinical Interview for DSM-5 Disorders (SCID-5; First, Williams, Karg, & Spitzer, 2015) and Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998) assess a myriad of psychiatric illnesses including anxiety disorders. The Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2014) can be used to assess the presence of anxiety and other disorders, as well as severity of those disorders using an eight-point rating scale. These semistructured interviews (SCID-5, M.I.N.I., and ADIS-5) have been used in published research with older adults, with adequate-to-excellent inter-rater reliability in the assessment of anxiety disorders in this population. Specifically, for the SCID-IV, the reliability coefficient (ICC) was 0.75 for anxiety disorders (Ivan et al., 2014), indicative of adequate or fair reliability with older adults. The ADIS-IV coefficient (kappa) was 0.85 (Diefenbach, Tolin, Meunier, & Gilliam, 2009), suggesting good reliability. The M.I.N.I. has good ($k = 0.88$ for simple phobia) to excellent ($k = 0.98$ for GAD) reliability (Sheehan et al., 1998). Limitations to using these semistructured interviews include the lengthy duration and the need for extensive interviewer training for the SCID-5 and ADIS-5 in particular.

The Hamilton Anxiety Scale (HARS or HAM-A; Hamilton, 1959) is a clinician-rated interview that assesses the severity of 14 anxiety symptoms using a five-point rating scale. Recent evaluations of the HARS have yielded excellent inter-rater reliability (ks = 0.95−0.96; Brenes, Danhauer, Lyles, Hogan, & Miller, 2015; Ivan et al., 2014) using the Structured Interview Guide developed by Shear and colleagues (2001) to help guide interviewers. Despite the excellent reliability, the HARS focuses mostly on somatic anxiety items and has limited assessment of worry, which may have yielded low convergent validity coefficients with other measures of anxiety (rs = 0.25−0.56; Leentjens et al., 2011).

Self-report measures of anxiety may provide the clinician an estimate of the severity of anxiety symptoms. Here we focus our discussion on general measures of anxiety and provide a general overview of four measures and their psychometric properties: a measure of anxiety (Beck Anxiety Inventory, BAI), a measure of worry (Penn State Worry Questionnaire), and two geriatric anxiety measures (Geriatric Anxiety Inventory (GAI), Geriatric Anxiety Scale (GAS)). Older adult specific measures of fear, social anxiety, and worry exist but are not discussed here. The interested reader is referred to Bower and Wetherell (2015) for further information.

One of the most often used self-report measures of anxiety is the BAI (Beck, Epstein, Brown, & Steer, 1988). The BAI measures symptom severity in the past week of 21 items using a four-point scale ranging from 0 (Not at all) to 3 (Severely). More than half of the BAI items assess physical symptoms, which raises concerns about using this measure with older adults who may have comorbid medical conditions (Wetherell & Gatz, 2005). Studies have demonstrated evidence of convergent validity with other measures of anxiety ($rs = 0.32-0.73$), but weak evidence of discriminant validity with measures of depression (e.g., Wetherell & Gatz, 2005). A recent study found that the BAI has good internal consistency with older adult samples (mean $\alpha = 0.86$, 95% CI [0.82, 0.86]; Therrien & Hunsley, 2013).

The Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) measures "trait worry" or an individual's propensity to worry using 16 items and a five-point scale ranging from 1 (Not at all typical) to 5 (Very typical). The PSWQ has been used to assess worry in older adults and was found to have good internal consistency (mean $\alpha = 0.90$, 95% CI [0.84, 0.94]; Therrien & Hunsley, 2013). The measure also demonstrates evidence of convergent validity with other measures of anxiety ($rs = 0.29-0.79$; Diefenbach et al., 2009). A limitation to using the PSWQ with older adults is the inclusion of reverse-scored items or items that assess the absence of symptoms rather than the presence of symptoms. Hopko and colleagues (2003) found that the reverse-scored items may confuse older adults. To address their concern, Hopko and colleagues removed the eight reverse-scored items to create an abbreviated version of the PSQW (PSWQ-A). The PSWQ-A has been validated with older adults (e.g., Diefenbach et al., 2009) and has been used in treatment studies (e.g., Brenes et al., 2015).

The GAI (Pachana et al., 2007) assesses the presence of anxiety in the past week using 20 items with a dichotomous (agree/disagree) response. In contrast with the BAI, the GAI focuses on worry symptoms in addition to some somatic items. Evidence of convergent validity with other measures of anxiety (rs = 0.28−0.71; Gould et al., 2014; Yochim, Mueller, June, & Segal, 2010) has been found, as well as evidence of discriminant validity with depression (r = 0.74; Yochim et al., 2010). This inventory also has cross-national support as a psychometrically valid unidimensional measure of anxiety in older adults (Molde et al., 2019). GAI developers (Byrne & Pachana, 2011) created a five-item version of the GAI, which had poor-to-good internal consistency (α = 0.58−0.84; Gerolimatos, Gregg, & Edelstein, 2013; Johnco, Knight, Tadic, & Wuthrich, 2015).

The GAS (Segal, June, Payne, Coolidge, & Yochim, 2010) assesses anxiety symptom severity during the past week using 30 items scored on a four-point scale ranging from 0 (Not at all) to 3 (All of the time). A unique aspect of the GAS is the inclusion of three subscales (affective, cognitive, and somatic anxiety), which may be useful to some researchers and clinicians. A 10-item version of the GAS was developed and initial psychometric properties were documented (Mueller et al., 2015). Researchers found good internal consistency for the long (α = 0.93; Segal et al., 2010) and short forms (α = 0.89; Mueller et al., 2015). Similar to the other measures, the GAS has evidence of convergent validity with measures of anxiety (rs = 0.57−0.60; Gould et al., 2014; Segal et al., 2010; Yochim et al., 2010), but limited evidence of discriminant validity with measures of depression.

In addition to assessing anxiety symptoms via interview or self-report measures, the clinician should assess cognitive functioning using a brief cognitive assessment or select cognitive measures that assess domains often impaired in late-life anxiety (e.g., executive functioning, memory). This information will help guide diagnosis and treatment. Should cognitive impairment be detected, the clinician can use measures such as the Anxiety in Cognitive Impairment and Dementia scales (Gerolimatos et al., 2015), the Neuropsychiatric Inventory (Cummings, 1997), or the Rating Anxiety in Dementia Scale (Shankar, Walker, Frost, & Orrell, 1999; Snow et al., 2012).

The assessment of anxiety requires careful measurement of not only anxiety symptom severity but also the consideration of medical disorders and cognitive functioning. A thorough anxiety assessment may help identify which treatment approach to take.

Treatment approaches

Cognitive behavioral therapy

Treatment studies on late-life anxiety have primarily focused on GAD and the most studied psychosocial intervention has been cognitive behavioral therapy (CBT). CBT has shown efficacy for GAD in older patients, but it appears to be less effective among older adults with GAD relative to their younger anxious counterparts (Ayers, Sorrell, Thorp, & Wetherell, 2007). Moreover, in a meta-analysis, standalone CBT and CBT with relaxation training demonstrated no additive benefit over relaxation training alone for older adults with late-life anxiety (largely GAD) (Thorp et al., 2009). The authors noted that this conclusion is limited given the heterogeneity of control conditions (active controls, placebo, waitlist control, or treatment as usual).

Based on meta-analytic review, other researchers have also found moderate effect sizes for CBT and for medication in the treatment of GAD in older adults (Gonçalves & Byrne, 2012). Again, several limitations in gauging the effect of CBT in late-life anxiety have been identified, including differing response criteria, control condition, and attrition rates across studies. CBT does not outperform active control conditions such as structured discussion groups (Wetherell, Gatz, Craske, & Peterson, 2003) or enhanced usual care (Stanley et al., 2009). Gonçalves and Byrne (2012) also noted that outcome measures used in the reviewed trials were not developed and normed for older adults. This is problematic because these measures may not be as sensitive to change or may have limited validity in older adults.

Gould, Coulson, and Howard (2012) found similar results in their meta-analysis and meta-regression of CBT for late-life anxiety that overwhelmingly focused on patients with GAD but also included studies of older adults with agoraphobia, panic disorder, social phobia, and anxiety disorder not otherwise specified (NOS; i.e., other specified anxiety disorder or unspecified anxiety disorder using DSM-5). CBT was significantly but modestly more effective at reducing anxiety symptoms than treatment as usual or a waiting list control. The difference between CBT versus an active control, however, was a small effect and not statistically significant. At 6-month (but not 3 or 12 months) posttreatment, CBT was significantly but modestly more effective at reducing anxiety symptoms when compared with an active control condition. Moreover, CBT was significantly but modestly more effective at reducing depression symptoms than treatment as usual or a waitlist. This suggests that treatment aimed at attenuating anxiety can also reduce depressive symptoms, though the effect may be small.

More recently, CBT delivered by telephone (CBT-T) has been explored as an option to counter issues some older adults might have with transportation, physical mobility, or both. Relative to an information-only comparison group, telephone-delivered CBT for older adults with GAD, panic disorder, or anxiety disorder NOS produced meaningful symptom reduction on measures of worry, trait anxiety, and insomnia; worry reductions were maintained 6 months posttreatment (Brenes et al., 2012). CBT-T has also outperformed telephone-delivered supportive therapy in a group of older adults with GAD (Brenes et al., 2015). In particular, participants in the CBT-T condition evidenced greater reductions in worry and depression symptoms after 4 months than those in the telephone-administered supportive therapy comparison (Brenes et al., 2015).

Further, Internet-delivered CBT (iCBT) is also being explored with regard to treating late-life anxiety (Dear et al., 2015). The iCBT consists of an 8-week online treatment course and brief weekly contact with a clinical psychologist via telephone or secure email. Older adults (60 years or older) selected for this study were treatment-seeking with self-reported elevated anxiety. When compared against the waitlist control, participants in iCBT evidenced lower anxiety and depression scores; these gains were maintained 3 and 12 months posttreatment. This preliminary evidence is encouraging for the potential for distance methods (telephone or Internet) to teach a skills-based treatment such as CBT for older adults suffering from anxiety.

Despite this predominant focus on GAD in the late-life treatment literature (Ayers et al., 2007), other anxiety disorders have begun to receive attention. Hendriks, Kampman, Keijsers, Hoogduin, and Voshaar (2014) examined CBT for panic with agoraphobia in younger and older (60 +) adults. Generally, the two age groups had similar outcomes, though older adults ($N = 29$) had lower attrition rates (6% vs 22%) and a greater reduction of agoraphobic avoidance relative to their younger counterparts ($N = 119$). Further, in a separate investigation, Hendriks et al. (2010) found that paroxetine and CBT were effective in the treatment of panic disorder in older patients relative to a waitlist control condition. Thus preliminary evidence suggests that CBT might be an effective treatment for late-life panic disorder with or without agoraphobia, with a need for randomized controlled trials (RCTs) to examine this further.

In addition to panic disorder, CBT has also been applied to fear of falling in older adults with exposure-based CBT (Jayasinghe et al., 2014; Wetherell et al., 2016). One such protocol targets older adults with fear of falling or posttraumatic stress disorder (PTSD) or subdiagnostic PTSD due to a traumatic falling within rehabilitation or outpatient settings (Jayasinghe et al., 2014). Outcome data for this specific protocol are not yet published, but a similar exposure-based CBT protocol called the Activity, Balance, Learning, and Exposure (ABLE) treatment program has demonstrated feasibility for treating excessive fear of falling (Wetherell et al., 2016). After participating in ABLE, most of the 10 older patients with excessive fear of falling reported reductions in fear and fall-related avoidance. As with panic disorder, RCTs are also needed to determine the extent to which CBT is efficacious for fear of falling. Another important direction for further developing treatments for late-life anxiety, particularly CBT, is the determination of factors associated with treatment outcome for anxiety and worry symptom severity. In a secondary analysis of a 10-session RCT of CBT for late-life GAD ($N = 150$; Stanley et al., 2014), Hundt et al. (2014) found predictors of anxiety and worry outcomes consistent with those found in the younger adults, namely lower symptom severity at baseline and treatment compliance. Investigators have also begun to examine outcome measures that are less susceptible to response demands such as attentional bias (Mohlman, Price, & Vietri, 2013) and moderators of treatment such as executive skills (Mohlman, 2013), and cognitive flexibility (Johnco, Wuthrich, & Rapee, 2014). Identification of other factors such as demographic variables (age, education, and marital status), medical and psychiatric comorbidity, and other cognitive, biological, or genetic factors could also deepen the understanding of treatment decision-making for anxious older adults.

To summarize, most of the work in CBT demonstrates an effect, though given the small effects, more RCTs or exploration of new approaches are needed. Of all the components of CBT, a meta-analysis and review support the behavioral component of CBT (i.e., relaxation skills). Thus some researchers have been developing relaxation protocols for late-life anxiety with the added component of scalability for use in different technological formats. To this end, Gould and colleagues recently developed video-delivered relaxation with coach support for late-life anxiety with promising initial support (Gould et al., 2017, 2019; Zapata et al., 2018).

Other psychotherapeutic approaches

Other psychotherapies for late-life anxiety have been examined, primarily within clinical case studies and pilot investigations. These other approaches include acceptance and commitment therapy (ACT), mindfulness-based stress reduction (MBSR), and problem-solving therapy (PST). Adjuncts to augment treatment, such as CBT plus cognitive training for anxiety-related psychiatric disorders (i.e., hoarding disorder), also have empirical support and will be discussed.

While CBT aims to change thoughts and behaviors directly, the purported third wave of cognitive-behavioral treatment approaches, such as ACT, seeks to increase acceptance of maladaptive thoughts and negative feelings rather than confront and change them. Wetherell and colleagues (2011) conducted a preliminary investigation of feasibility of ACT ($n = 7$), also comparing it with a CBT group ($n = 9$), in older adults with GAD. Not only did the study support the feasibility of ACT for late-life anxiety as evidenced by the lack of drop-outs from the ACT condition, but participants also reported significant reductions in worry and depressive symptoms at posttreatment. CBT did not lead to significant reductions in worry and had more drop-outs ($n = 4$) than ACT ($n = 0$); however, those completing CBT had significant reductions in anxiety and depression. The authors conclude that this pilot support warrants an RCT with ACT for GAD in older adults, particularly given the promising reductions in worry after ACT but not on CBT.

Moreover, the use of mindfulness strategies, such as meditation and yoga, in the context of an MBSR manualized protocol has demonstrated effects on reducing worry and depression and improved immediate memory performance in older adults with elevated anxiety or depression and memory complaints in an RCT (Wetherell et al., 2017). These two approaches, ACT and MBSR, appear to have the potential to decrease worry in anxious older adults. RCTs of ACT and MBSR for late-life anxiety would be useful to determine if that can yield larger treatment effect sizes than modestly effective CBT for late-life anxiety.

Another possible direction for late-life anxiety treatment research will be to examine PST. PST, a type of CBT intervention, teaches patients a systematic and thoughtful approach to dealing with everyday problems (D'Zurilla & Nezu, 2006). More recent conceptualizations of PST also teach emotion regulation skills (Nezu, Nezu, & D'Zurilla, 2012). PST has strong evidence for reducing depression and lowering disability in older adults with depression (Areán, Hegel, Vannoy, Fan, & Unuzter, 2008) and depression with executive dysfunction (Kiosses & Alexopoulos, 2014). Given the possibility that poorer executive control in late-life anxiety limits treatment gains in some older adults, a treatment that works in individuals with those cognitive deficits and anxiety could be an excellent option for some. PST has shown an effect in reducing anxiety in middle-aged adults with GAD (Provencher, Dugas, & Ladouceur, 2004) and in preventing GAD in patients recovering from stroke (Mikami et al., 2014). Case studies of PST for older adults with GAD suggest the potential for PST as a viable treatment for reducing anxiety to be explored in future RCTs (Beaudreau, Gould, Mashal, Huh, & Fairchild, 2019). While PST for late-life depression tends to focus almost exclusively on problem-solving skills, contemporary PST that also teaches stress reduction techniques, with a flexible selection of those techniques the patient wishes to use, might be critical for anxious older adults with significant worry, particularly as expected in GAD.

Finally, cognitive rehabilitation to augment psychotherapy deserves further empirical investigation. The finding of executive function deficits in hoarding disorder, an anxiety-related psychiatric disorder, has led to one pilot study of CBT with pretreatment cognitive rehabilitation (Ayers et al., 2014). This approach of adding cognitive rehabilitation doubled the previously reported effect size for CBT for hoarding disorders (Ayers, Wetherell, Golshan, & Saxena, 2011). A similar model could be argued for older adults with GAD or other anxiety disorders, who might also have executive dysfunction, although no such studies have been conducted at the time of this writing.

Conclusion

The growing evidence base in late-life anxiety has revealed a substantial need in several areas. First, as the DSM continues to incorporate empirical data to inform psychiatric diagnostic categories and their criteria, modifications, or caveats to those categories might slowly be introduced as relevant to older patients. Second, psychometric validation or creation of geriatric normed measures will lead to better late-life anxiety assessments, although adequate measures are currently available. Third, the development of evidence-based treatments will be a challenge, but use of new approaches or augmentation of existing ones using cognitive rehabilitation could optimize effects. Further delineation of the complex psychiatric, medical and cognitive comorbidities present in anxiety in older adults, as well as the unique phenomenological features of anxiety disorders in the latter part of the life span, will serve to launch late-life anxiety into a new era of empirical understanding.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. Washington, DC: American Psychiatric Publication.

American Psychological Association. (2010). *Psychology and aging: Addressing mental health needs of older adults.*. Washington, DC: Author. Retrieved from <http://www.apa.org/pi/aging/resources/guides/aging.pdf>.

Areán, P., Hegel, M., Vannoy, S., Fan, M. Y., & Unuzter, J. (2008). Effectiveness of problem-solving therapy for older, primary care patients with depression: Results from the IMPACT project. *Gerontologist*, *48*(3), 311–323.

Ayers, C. R., Saxena, S., Espejo, E., Twamley, E. W., Granholm, E., & Wetherell, J. L. (2014). Novel treatment for geriatric hoarding disorder: An open trial of cognitive rehabilitation paired with behavior therapy. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *22*(3), 248–252.

Ayers, C., Sorrell, J., Thorp, S., & Wetherell, J. L. (2007). Evidence-based psychological treatments for late-life anxiety. *Psychology and Aging*, *22*(1), 8–17.

Ayers, C. R., Wetherell, J. L., Golshan, S., & Saxena, S. (2011). Cognitive-behavioral therapy for geriatric compulsive hoarding. *Behaviour Research and Therapy*, *49*(10), 689–694.

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *American Journal of Geriatric Psychiatry*, *16*(10), 790–803, 2008.

Beaudreau, S. A., & O'Hara, R. (2009). The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging*, *24*(2), 507–512. Available from: https://doi.org/10.1037/a0016035.

Beaudreau, S. A., Gould, C. E., Mashal, N. M., Huh, J. T. W., & Fairchild, J. K. (2019). Application of problem solving therapy for late-life anxiety. *Cognitive and Behavioral Practice.*, *26*, 381–394.

Beaudreau, S. A., Hantke, N. C., Mashal, N., Gould, C. E., Henderson, V. W., & O'Hara, R. (2017). Unlocking neurocognitive substrates of late-life affective symptoms using the research domain criteria: Worry is an essential dimension. *Frontiers in Aging Neuroscience*, *9*, 380.

Beaudreau, S. A., MacKay-Brandt, A., & Reynolds, J. (2013). Application of a cognitive neuroscience perspective of cognitive control to late-life anxiety. *Journal of Anxiety Disorders*, *27*(6), 559–566.

Beaudreau, S. A., & Pachana, N. (2016). New directions in alleviating anxiety in older adults: Applications, modifications, and innovations. *Clinical Gerontologist*, *40*(3), 139–140.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897.

Bower, E. S., & Wetherell, J. L. (2015). Late-life anxiety disorders. In P. A. Lichtenberg, & B. T. Mast (Eds.), *APA handbook of clinical geropsychology: Vol. 2. Assessment, Treatment, and Issues of Later Life*. Washington, DC: American Psychological Association.

Brenes, G. A. (2003). Anxiety and chronic obstructive pulmonary disease: Prevalence, impact, and treatment psychosomatic medicine. *Psychosomatic Medicine*, *65*(6), 963–970.

Brenes, G. A., Danhauer, S. C., Lyles, M. F., Hogan, P. E., & Miller, M. E. (2015). Telephone-delivered cognitive behavioral therapy and telephone-delivered nondirective supportive therapy for rural older adults with generalized anxiety disorder: A randomized clinical trial. *JAMA Psychiatry*, *72*(10), 1012–1020.

Brenes, G. A., Miller, M., Williamson, J., McCall, W., Knudson, M., & Stanley, M. (2012). A randomized controlled trial of telephone-delivered cognitive-behavioral therapy for late-life anxiety disorders. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *20*(8), 707–716.

Brown, T. A., & Barlow, D. H. (2014). *Anxiety and related disorders interview schedule for DSM-5 (ADIS-5)*. New York: Oxford University Press.

Bryant, C., Jackson, H., & Ames, D. (2008). The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *Journal of Affective Disorders*, *109*(3), 233–250.

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H., & Becker, J. T. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry*, *61*(6), 587–595.

Byrne, G. J., & Pachana, N. A. (2011). Development and validation of a short form of the Geriatric Anxiety Inventory—the GAI-SF. *International Psychogeriatrics*, *23*, 125–131.

Cairney, J., McCabe, L., Veldhuizen, S., Corna, L. M., Streiner, D., & Herrmann, N. (2007). Epidemiology of social phobia in later life. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *15*(3), 224–233.

Chou, K. L. (2010). Panic disorder in older adults: Evidence from the national epidemiologic survey on alcohol and related conditions. *International Journal of Geriatric Psychiatry*, *25*(8), 822–832.

Ciliberti, C., Gould, C., Smith, M., Chorney, D., & Edelstein, B. (2011). A preliminary investigation of developmentally sensitive items for the assessment of social anxiety in late life. *Journal of Anxiety Disorders*, *25*(5), 686–689.

Corna, L. M., Cairney, J., Herrmann, N., Veldhuizen, S., McCabe, L., & Streiner, D. (2007). Panic disorder in later life: Results from a national survey of Canadians. *International Psychogeriatrics*, *19*(6), 1084–1096.

Creighton, A. S., Davison, T. E., & Kissane, D. W. (2016). The prevalence of anxiety among older adults in nursing homes and other residential aged care facilities: A systematic review. *International Journal of Geriatric Psychiatry*, *31*(6), 555–566.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*, *48*, S10–S16.

Cummings, J. L., & Masterman, D. L. (1999). Depression in patients with Parkinson's disease. *International Journal of Geriatric Psychiatry*, *14*, 711–718.

Dear, B. F., Zou, J. B., Ali, S., Lorian, C. N., Johnston, L., Sheehan, J., … … Titov, N. (2015). Clinical and cost-effectiveness of therapist-guided Internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety: A randomized controlled trial. *Behavior Therapy*, *46*(2), 206–217.

Diefenbach, G. J., Tolin, D. F., Meunier, S. A., & Gilliam, C. M. (2009). Assessment of anxiety in older home care recipients. *The Gerontologist*, *49*(2), 141–153.

D'Zurilla, T. J., & Nezu, A. M. (2006). *Problem-solving therapy: A positive approach to clinical intervention* (3rd ed.). New York: Springer.

First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). *Structured clinical interview for DSM-5 disorders*. Arlington, VA: American Psychiatric Publishing.

Gerolimatos, L. A., Gregg, J. J., & Edelstein, B. A. (2013). Assessment of anxiety in long-term care: examination of the Geriatric Anxiety Inventory (GAI) and its short form. *International Psychogeriatrics*, *25*(9), 1533−1542. Available from: https://doi.org/10.1017/S1041610213000847.

Gerolimatos, L. A., Ciliberti, C. M., Gregg, J. J., Nazem, S., Bamonti, P. M., Cavanagh, C. E., & Edelstein, B. A. (2015). Development and preliminary evaluation of the anxiety in cognitive impairment and dementia (ACID) scales. *International Psychogeriatrics*, *27*(11), 1825−1838.

Gonçalves, D. C., & Byrne, G. J. (2012). Interventions for generalized anxiety disorder in older adults: Systematic review and meta-analysis. *Journal of Anxiety Disorders*, *26*(1), 1−11.

Gould, C. E., Beaudreau, S. A., & Huh, J. T. (2013). A Veterans' Health Administration imperative: Recommendations for detecting anxiety in older adults. *Federal Practitioner*, *30*(8), 35−42.

Gould, R. L., Coulson, M. C., & Howard, R. J. (2012). Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *Journal of the American Geriatrics Society*, *60*(2), 218−229.

Gould, C. E., Kok, B. C., Ma, V. K., Wetherell, J. L., Sudheimer, K., & Beaudreau, S. A. (2019). Video-delivered relaxation intervention reduces late-life anxiety: A pilot randomized controlled trial. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *27*(5), 514−525.

Gould, C. E., O'Hara, R., Goldstein, M., & Beaudreau, S. A. (2016). Multimorbidity is associated with anxiety in older adults in the Health and Retirement Study. *International Journal of Geriatric Psychiatry*, *31*(10), 1105−1115.

Gould, C. E., Segal, D. L., Yochim, B. P., Pachana, N. A., Byrne, G. J., & Beaudreau, S. A. (2014). Measuring anxiety in late life: A psychometric examination of the Geriatric Anxiety Inventory and Geriatric Anxiety Scale. *Journal of Anxiety Disorders*, *28*(8), 804−811.

Gould, C. E., Zapata, A. M. L., Bruce, J., Bereknyei Merrell, S., Wetherell, J. L., O'Hara, R., … Beaudreau, S. A. (2017). Development of a video-delivered relaxation treatment of late-life anxiety for older Veterans. *International Psychogeriatrics*, *29*(10), 1−13.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., & Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry*, *61*(8), 807−816.

Gum, A. M., King-Kallimanis, B., & Kohn, R. (2009). Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the National Comorbidity Survey: Replication. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *17*, 769−781.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Psychiatry*, *32*(1), 50−55. Available from: https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

Hendriks, G. J., Kampman, M., Keijsers, G. P., Hoogduin, C. A., & Voshaar, R. C. O. (2014). Cognitive-behavioral therapy for panic disorder with agoraphobia in older people: A comparison with younger patients. *Depression and Anxiety*, *31*(8), 669−677.

Hendriks, G. J., Keijsers, G. P. J., Kampman, M., Oude Voshaar, R. C., Verbraak, M. J. P. M., Broekman, T. G., & Hoogduin, C. A. L. (2010). A randomized controlled study of paroxetine and cognitive-behavioural therapy for late-life panic disorder. *Acta Psychiatrica Scandinavica*, *122*(1), 11−19.

Himmelfarb, S., & Murrell, S. A. (1984). The prevalence and correlates of anxiety symptoms in older adults. *Journal of Psychology*, *116*(2d half), 159−167.

Hopko, D. R., Reas, D. L., Beck, J. G., Stanley, M. A., Wetherell, J. L., Novy, D. M., & Averill, P. M. (2003). Assessing worry in older adults: Confirmatory factor analysis of the Penn State Worry Questionnaire and psychometric properties of an abbreviated model. *Psychological Assessment*, *15*(2), 173−183.

Hundt, N. E., Amspoker, A. B., Kraus-Schuman, C., Cully, J. A., Rhoades, H., Kunik, M. E., & Stanley, M. A. (2014). Predictors of CBT outcome in older adults with GAD. *Journal of Anxiety Disorders*, *28*(8), 845−850.

Ivan, M. C., Amspoker, A. B., Nadorff, M. R., Kunik, M. E., Cully, J. A., Wilson, N., & Stanley, M. A. (2014). Alcohol use, anxiety, and insomnia in older adults with generalized anxiety disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *22*(9), 875−883.

Jayasinghe, N., Sparks, M. A., Kato, K., Wilbur, K., Ganz, S. B., Chiaramonte, G. R., … … Evans, A. T. (2014). Exposure-based CBT for older adults after fall injury: Description of a manualized, time-limited intervention for anxiety. *Cognitive and Behavioral Practice*, *21*(4), 432−445.

Johnco, C., Knight, A., Tadic, D., & Wuthrich, V. M. (2015). Psychometric properties of the Geriatric Anxiety Inventory (GAI) and its short-form (GAI-SF) in a clinical and non-clinical sample of older adults. *International Psychogeriatrics*, *27*, 1089−1097.

Johnco, C., Wuthrich, V. M., & Rapee, R. M. (2014). The influence of cognitive flexibility on treatment outcome and cognitive restructuring skill acquisition during cognitive behavioural treatment for anxiety and depression in older adults: Results of a pilot study. *Behaviour Research and Therapy*, *57*, 55−64.

Karlsson, B., Sigstrom, R., Waern, M., Ostling, S., Gustafson, D., & Skoog, I. (2010). The prognosis and incidence of social phobia in an elderly population: A 5-year follow-up. *Acta Psychiatrica Scandinavica*, *122*(1), 4−10.

Karsten, J., Nolen, W. A., Penninx, B. W. J. H., & Hartman, C. A. (2011). Subthreshold anxiety better defined by symptom self-report than by diagnostic interview. *Journal of Affective Disorders*, *129*(1), 236−243.

Kessler, R. C., Ormel, J., Demler, O., & Stang, P. E. (2003). Comorbid mental disorders account for the role impairment of commonly occurring chronic physical disorders: Results from the National Comorbidity Survey. *Journal of Occupational and Environmental Medicine*, *45*(12), 1257–1266.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602.

Kiosses, D. N., & Alexopoulos, G. (2014). Problem-solving therapy in the elderly. *Current Treatment Options in Psychiatry*, *1*(1), 15–26.

Leentjens, A. F. G., Dujardin, K., Marsh, L., Richard, I. H., Starkstein, S. E., & Martinez-Martin, P. (2011). Anxiety rating scales in Parkinson's disease: A validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. *Movement Disorders*, *26*(3), 407–415.

Lenze, E. J., Rogers, J. C., Martire, L. M., Mulsant, B. H., Rollman, B. L., & Dew, M. A. (2001). The association of late-life depression and anxiety with physical disability: A review of the literature and prospectus for future research. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *9*(2), 113–135.

Manicavasagar, V., Marnane, C., Pini, S., Abelli, M., Rees, S., & Eapen, V. (2010). Adult separation anxiety disorder: A disorder comes of age. *Current Psychiatry Reports*, *12*(4), 290–297.

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, *28*(6), 487–495.

Mikami, K., Jorge, R. E., Moser, D. J., Arndt, S., Jang, M., Solodkin, A., & Robinson, R. G. (2014). Prevention of post-stroke generalized anxiety disorder, using escitalopram or problem-solving therapy. *Journal of Neuropsychiatry and Clinical Neurosciences*, *26*(4), 323–328.

Miloyan, B., Byrne, G. J., & Pachana, N. A. (2015). Threshold and subthreshold generalized anxiety disorder in later life. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *23*(6), 633–641.

Mohlman, J., de Jesus, M., Gorenstein, E. E., Kleber, M., Gorman, J. M., & Papp, L. A. (2004). Distinguishing generalized anxiety disorder, panic disorder, and mixed anxiety states in older treatment-seeking adults. *Journal of Anxiety Disorders*, *18*(3), 275–290.

Mohlman, J. (2013). Executive skills in older adults with GAD: Relations with clinical variables and CBT outcome. *Journal of Anxiety Disorders*, *27*(1), 131–139.

Mohlman, J., Bryant, C., Lenze, E. J., Stanley, M. A., Gum, A., Flint, A., & Craske, M. G. (2012). Improving recognition of late life anxiety disorders in diagnostic and statistical manual of mental disorders, fifth edition: Observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. *International Journal of Geriatric Psychiatry*, *27*(6), 549–556.

Mohlman, J., Price, R. B., & Vietri, J. (2013). Attentional bias in older adults: Effects of generalized anxiety disorder and cognitive behavior therapy. *Journal of Anxiety Disorders*, *27*(6), 585–591.

Molde, H., Nordhus, I.-A., Torshiem, T., Engedal, K., Bendixen, A. B., Byrne, G. J., & Pachana, N. A. (2019). A cross-national analysis of the psychometric properties of the Geriatric Anxiety Inventory (GAI). *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *Epub available online*.

Mueller, A. E., Segal, D. L., Gavett, B., Marty, M. A., Yochim, B., June, A., & Coolidge, F. L. (2015). Geriatric Anxiety Scale: item response theory analysis, differential item functioning, and creation of a ten-item short form (GAS-10). *International Psychogeriatrics*, *27*(7), 1099–1111. Available from: https://doi.org/10.1017/S1041610214000210.

Nezu, A. M., Nezu, C. M., & D'Zurilla, T. J. (2012). *Problem-solving therapy: A treatment manual*. New York: Springer Publishing.

Ostir, G. V., & Goodwin, J. S. (2006). High anxiety is associated with an increased risk of death in an older tri-ethnic population. *Journal of Clinical Epidemiology*, *59*(5), 534–540.

Pachana, N. A., Byrne, G. J., Siddle, H., Koloski, N., Harley, E., & Arnold, E. (2007). Development and validation of the Geriatric Anxiety Inventory. *International Psychogeriatrics*, *19*(01), 103–114.

Petkus, A. J., Reynolds, C. A., Wetherell, J. L., Kremen, W. S., Pedersen, N. L., & Gatz, M. (2016). Anxiety is associated with increased risk of dementia in older Swedish twins. *Alzheimer's & Dementia*, *12*(4), 399–406. Available from: https://doi.org/10.1016/j.jalz.2015.09.008.

Provencher, M. D., Dugas, M. J., & Ladouceur, R. (2004). Efficacy of problem-solving training and cognitive exposure in the treatment of generalized anxiety disorder: A case replication series. *Cognitive and Behavioral Practice*, *11*, 404–414.

Rochester, J., & Baldwin, D. S. (2015). Adult separation anxiety disorder: Accepted but little understood. *Human Psychopharmacology: Clinical & Experimental*, *30*(1), 1–3.

Segal, D. L., June, A., Payne, M., Coolidge, F. L., & Yochim, B. (2010). Development and initial validation of a self-report assessment tool for anxiety among older adults: the Geriatric Anxiety Scale. *Journal of Anxiety Disorders*, *24*(7), 709–714. Available from: https://doi.org/10.1016/j.janxdis.2010.05.002.

Seignourel, P. J., Kunik, M. E., Snow, L., Wilson, N., & Stanley, M. (2008). Anxiety in dementia: A critical review. *Clinical Psychology Review*, *28*(7), 1071–1082.

Shankar, K. K., Walker, M., Frost, D., & Orrell, M. W. (1999). The development of a valid and reliable scale for rating anxiety in dementia (RAID). *Aging & Mental Health*, *3*(1), 39–49.

Shear, K., Jin, R., Ruscio, A. M., Walters, E. E., & Kessler, R. C. (2006). Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication. *The American Journal of Psychiatry*, *163*(6), 1074–1083.

Shear, M. K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W., & Frank, D. M. (2001). Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depression and Anxiety*, *13*(4), 166–178.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*, 22–33.

Sheikh, J. I., Swales, P. J., Carlson, E. B., & Lindley, S. E. (2004). Aging and panic disorder: Phenomenology, comorbidity, and risk factors. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *12*(1), 102–109.

Snow, A. L., Huddleston, C., Robinson, C., Kunik, M. E., Bush, A. L., Wilson, N., & Stanley, M. A. (2012). Psychometric properties of a structured interview guide for the rating for anxiety in dementia. *Aging & Mental Health*, *16*(5), 592–602.

Stanley, M., Wilson, N., Amspoker, A., Kraus-Schuman, C., Wagener, P., Calleo, J., & Kunik, M. (2014). Lay providers can deliver effective cognitive behavior therapy for older adults with generalized anxiety disorder: A randomized trial. *Depression and Anxiety*, *31*(5), 391–401.

Stanley, M. A., Wilson, N. L., Novy, D. M., Rhoades, H. M., Wagener, P. D., Greisinger, A. J., … Kunik, M. E. (2009). Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care: A randomized clinical trial. *JAMA*, *301*(14), 1460–1467.

Starkstein, S. E., Jorge, R., Petracca, G., & Robinson, R. G. (2007). The construct of generalized anxiety disorder in Alzheimer disease. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *15*(1), 42–49.

Therrien, Z., & Hunsley, J. (2013). Assessment of anxiety in older adults: Reliability generalization meta-analysis of commonly used measures. *Clinical Gerontologist*, *36*(3), 171–194.

Thorp, S. R., Ayers, C. R., Nuevo, R., Stoddard, J. A., Sorrell, J. T., & Wetherell, J. L. (2009). Meta-analysis comparing different behavioral treatments for late-life anxiety. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *17*(2), 105–115. Available from: https://doi.org/10.1097/JGP.0b013e31818b3f7e.

Wetherell, J. L., & Gatz, M. (2005). The Beck Anxiety Inventory in older adults with generalized anxiety disorder. *Journal of Psychopathology and Behavioral Assessment*, *27*(1), 17–24.

Wetherell, J., Gatz, M., Craske, M., & Peterson, L. (2003). Treatment of generalized anxiety disorder in older adults. *Journal of Consulting and Clinical Psychology*, *71*(1), 31–40.

Wetherell, J. L., Johnson, K., Chang, D., Ward, S. R., Bower, E. S., Merz, C., & Petkus, A. J. (2016). Activity, balance, learning, and exposure (ABLE): a new intervention for fear of falling. *International Journal of Geriatric Psychiatry*, *31*(7), 791–798. Available from: https://doi.org/10.1002/gps.4393.

Wetherell, J. L., Hershey, T., Hickman, S., Tate, S. R., Dixon, D., Bower, E. S., & Lenze, E. J. (2017). Mindfulness-based stress reduction for older adults with stress disorders and neurocognitive difficulties: A randomized controlled trial. *Journal of Clinical Psychiatry*, *78*(7), e734–e743. Available from: https://doi.org/10.4088/JCP.16m10947.

Wetherell, J. L., Liu, L., Patterson, T. L., Afari, N., Ayers, C. R., Thorp, S. R., … Petkus, A. J. (2011). Acceptance and commitment therapy for generalized anxiety disorder in older adults: A preliminary report. *Behavior Therapy*, *42*(1), 127–134.

Wittchen, H. U., Gloster, A. T., Beesdo-Baum, K., Fava, G. A., & Craske, M. G. (2010). Agoraphobia: A review of the diagnostic classificatory position and criteria. *Depression and Anxiety*, *27*(2), 113–133.

Wolitzky-Taylor, K. B., Castriotta, N., Lenze, E. J., Stanley, M. A., & Craske, M. G. (2010). Anxiety disorders in older adults: A comprehensive review. *Depression and Anxiety*, *27*(2), 190–211.

World Health Organization. (2015). *Dementia*. World Health Organization. Retrieved December 17, 2015. http://www.who.int/mediacentre/factsheets/fs362/en/.

Wuthrich, V. M., Johnco, C. J., & Wetherell, J. L. (2015). Differences in anxiety and depression symptoms: Comparison between older and younger clinical samples. *International Psychogeriatrics*, *27*(9), 1–10.

Yochim, B. P., Mueller, A. E., June, A., & Segal, D. L. (2010). Psychometric properties of the Geriatric Anxiety Scale: Comparison to the Beck Anxiety Inventory and Geriatric Anxiety Inventory. *The Clinical Gerontologist*, *34*(1), 21–33.

Zapata, A. M. L., Beaudreau, S. A., O'Hara, R., Bereknyei Merrell, S., Bruce, J., Garrison-Diehn, C., & Gould, C. E. (2018). Information-seeking about anxiety and perceptions about technology to teach coping skills in older veterans. *Clinical Gerontologist*, *41*(4), 346–356. Available from: https://doi.org/10.1080/07317115.2017.1359716.

Zhao, Q., Wang, H., Jiang, T., Tan, M., Tan, L., Xu, W., & Yu, J. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*, *190*, 264–271.

Further reading

Hendriks, G. J., Oude Voshaar, R. C., Keijsers, G. P. J., Hoogduin, C. A. L., & Van Balkom, A. J. L. M. (2008). Cognitive-behavioural therapy for late-life anxiety disorders: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *117*(6), 403–411.

Hofmann, S. G., & Smits, J. A. (2008). Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. *The Journal of Clinical Psychiatry*, *69*(4), 621.

Wetherell, J., Petkus, A., White, K., Nguyen, H., Kornblith, S., Andreescu, C., & Lenze, E. (2013). Antidepressant medication augmented with cognitive-behavioral therapy for generalized anxiety disorder in older adults. *The American Journal of Psychiatry*, *170*(7), 782–789.

Chapter 12

Bipolar disorders in older adults

Laura Hein[1], Annemiek Dols[2] and Lisa T. Eyler[1,3]

[1]Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States, [2]Department of Psychiatry, Amsterdam UMC, Location Vrije Universiteit Medical Center, Amsterdam, The Netherlands, [3]Desert Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, United States

Introduction/epidemiology

Bipolar disorder (BD) is a serious mental illness affecting up to 1% of the elderly population (Hirschfeld et al., 2003; Kessler et al., 2005; Unutzer, Simon, Pabiniak, Bond, & Katon, 1998). As the population ages and awareness surrounding BD increases, the prevalence of this illness in older adults is expected to rise (Almeida & Fenner, 2002). The population of people aged 65 years and older is predicted to increase to about 1 billion people by 2030 and to around 1.6 billion by 2050 (Wan He & Kowal, 2016). Currently, approximately one-quarter of individuals living with BD are older adults (Sajatovic et al., 2005) and by 2030, it is expected that this number will double (Jeste et al., 1999). Increases in the number of OABD patients and improved awareness surrounding this illness have led to a growth in the number of individuals seeking health services for this disorder (Sajatovic et al., 2015), pointing to the importance of offering specialized services for this population. However, researchers are just beginning to unravel the complexities of serious mental illness in the elderly. Older-age bipolar disorder (OABD) has traditionally been defined as those with BD aged 60 and older; however, the International Society for Bipolar Disorder Task Force has recommended this criterion be lowered to include those age 50 and older so that a life span approach can be taken to studying OABD (Sajatovic et al., 2015).

There appear to be unique clinical features of OABD compared to younger individuals with the disorder (Table 12.1). OABD patients may be at an increased risk for stressful life events such as changes related to housing, careers, familial roles, and finances (Chen, Dols, Rej, & Sajatovic, 2017; Yassa, Nair, & Iskandar, 1988). In addition, elderly patients with BD may experience worse functioning, which may be related to cognitive impairments that those with OABD experience (Chen et al., 2017). Namely, OABD populations may face challenges in functional domains such as communication, physical activity, mobility, household tasks, recreational and social activities, and perceived social support (Chen et al., 2017).

Historically, the management of OABD has been guided by studies with mixed age groups (Sajatovic et al., 2015); however, with the number of older adults living with BD on the rise, there is an increased need for research specifically targeting the OABD population. Studies have found that outcomes for OABD are improved when patients are treated by specialized geriatric teams as opposed to generalized psychiatrists (Abdul-Hamid, Lewis-Cole, Holloway, & Silverman, 2015), suggesting that there is also a need for increased research specific to the diagnosis and treatment of OABD patients, as the current guidelines for caring for this population are inadequate (Dols et al., 2016; Sajatovic et al., 2015). Additionally, geriatric psychiatric care will need to be delivered not solely by specialists but also in the primary care setting, as the need for proper care and treatment of older populations will continue to increase.

Approximately 3% of people living in nursing homes and 17% of older patients in psychiatric emergency departments have a diagnosis of BD (Depp & Jeste, 2004; Depp et al., 2005). In addition, 8%–10% of elderly patients admitted to psychiatric inpatient facilities and 6% of patients visiting outpatient psychiatric facilities have a diagnosis of BD (Depp & Jeste, 2004). Furthermore, 6% of older psychiatric inpatients are found to have late-life mania (Dols, Kupka, et al., 2014; Kessing, 2006). Late-life mania includes late-onset bipolar disorder (LOBD), the conversion of depression to BD during old age, and secondary mania, which may occur due to illness or the use of prescription medications

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00012-0

TABLE 12.1 Characteristics of bipolar disorder in older versus younger populations.

	Bipolar in older adults	Bipolar in younger adults
Prevalence	Lower	Higher
Comorbidity with physical illness	Higher	Lower
Ratio of prevalence in females: males	2:1	1:1
Psychosocial events	More	Less
Cognitive dysfunction	Higher	Lower
Symptoms of mania and depression	Similar	Similar
Prevalence of depressive episodes	Higher	Lower
Severity of depressive episodes	Lower	Higher
Antidepressant use	Higher	Lower
Secondary mania	Higher	Lower
Family history of mood disorder	Lower	Higher
Prevalence of psychotic features in mania	Lower	Higher
Substance use disorders	Lower	Higher
Personality disorders	Lower	Higher
Attention deficit hyperactivity disorders	Lower	Higher

(Kessing, 2006). Females with OABD outweigh males by a ratio of 2:1, which may be explained by the fact that females often live longer than males (Depp & Jeste, 2004).

Early versus late-onset

A distinction can be made between OABD who had a typical age of onset of BD and have grown old with the disorder, called early-onset bipolar disorder (EOBD), and BD that first presents in late life and is referred to as LOBD. EOBD has been found to be related to having a family history of mood disorders (Schurhoff et al., 2000). In LOBD, a manic episode may present during old age after depressive episodes are experienced in early life (converter) (Depp et al., 2004; Sajatovic & Kessling, 2010). Alternatively, LOBD may be associated with changes in or diseases of the brain during old age (Depp et al., 2004; Sajatovic & Kessling, 2010). While several studies have defined LOBD as BD initially presenting in individuals aged 50 and older (Depp et al., 2004; Vasudev & Thomas, 2010), the Older-Age Bipolar Disorder Task Force recommends the definition to include those aged 40 and above (Sajatovic et al., 2015).

While some studies have found that those with LOBD do not respond well to treatment and are at a high risk for cognitive decline, others have found that individuals with LOBD may in fact recover more quickly than those with EOBD (Oostervink, Boomsma, & Nolen, 2009; Oostervink, Nolen, & Kok, 2015; Sajatovic et al., 2005; Wylie et al., 1999). A meta-analysis by Joslyn, Hawes, Hunt, and Mitchell (2016) found that those with EOBD were more likely to delay seeking treatment, had higher odds of anxiety and substance use disorders, and had more severe depression than those with LOBD. However, those with EOBD and LOBD did not differ in their rates of mixed episodes, rapid cycling, or psychotic symptoms. Studies should focus on differences in the course of illness based on disorder onset.

Secondary mania

Medical conditions can contribute to the presentation of mania in individuals without a mood disorder history, which is referred to as "secondary mania" (Krauthammer & Klerman, 1978; Van Gerpen, Johnson, & Winstead, 1999). Secondary mania is most common among older adults due to the fact that medical conditions contributing to this phenomenon are more common amongst this age group. Secondary mania can arise as a result of brain tumors, various medications, strokes, and traumatic brain injury, as well as from a number of diseases such as HIV, meningitis, epilepsy, encephalitis, and Parkinson's disease (Van Gerpen et al., 1999). In addition, hypothyroidism, Cushing's

syndrome, Addison's disease, and deficiencies in niacin and B12 may also contribute to symptoms of mania (Van Gerpen et al., 1999). With similarities in the presentation of bipolar mania and frontal inhibition, it can be difficult to distinguish between the two; however, a family history of mood disorder, elevated mood, and a decreased need for sleep may help to identify bipolar mania (Dols & Beekman, 2018; Krauthammer & Klerman, 1978).

Clinical presentation

OABD is characterized as a chronic condition with recurrent mood episodes (Chen et al., 2017). There is limited evidence that the severity of BD in OABD patients may increase over time, with each new episode increasing the risk of recurrence (Angst & Preisig, 1995; Kessing, 1998). However, the rate of hospitalization due to recurrence appears to decrease as patients age (Kessing, Hansen, & Andersen, 2004). Studies have found that symptoms of mania and depression are similar in older and younger adults with BD (Almeida & Fenner, 2002; Kessing, 2006) as well as between individuals with EOBD and LOBD (Depp et al., 2004). However, some studies have found that those with OABD have a higher prevalence of depressive episodes (Kessing, 2006), a lower severity of depressive symptoms, and a higher rate of antidepressant use (Chen et al., 2017). Additionally, older adults with BD may have a lower prevalence of psychotic features during mania (Chen et al., 2017; Ernst & Goldberg, 2004; Kessing, 2006; Schurhoff et al., 2000) as well as a decreased severity of manic symptoms (Chen et al., 2017). Mood episodes can be triggered by a variety of factors such as life stressors, physical illness, and prescription medications such as steroids (Chen et al., 2017), but a more autonomous course with recurrences has also been described (Dols et al., 2017).

Approximately one in five patients with OABD experiences rapid cycling, which is defined as four or more depressive or manic episodes in 1 year (Al Jurdi et al., 2008; Chen et al., 2017; Oostervink et al., 2009). While the rate of misdiagnosis of BD tends to decrease with age, the issue of misclassification of this illness persists in OABD (Kessing, 2005).

Suicide

Studies have demonstrated that the highest rate of completed suicide occurs in patients with BD under the age of 35, suggesting a decline in lethality of suicidal behavior with age (Tsai, Kuo, Chen, & Lee, 2002). Although there have been no studies specifically assessing the rate of suicide in OABD patients with LOBD, meta-analyses and systematic review papers have indicated that later age of onset of BD is associated with a decreased number of suicide attempts (Schaffer et al., 2015); it is possible, however, that OABD patients represent a survivor cohort (Depp & Jeste, 2004). A review paper by the International Society for Bipolar Disorders Task Force found that the number of suicide attempts in BD was also correlated with psychiatric comorbidities such as substance and alcohol use disorders, cluster B personality disorders including borderline personality disorder, and anxiety disorders (Schaffer et al., 2015). In addition, suicide attempts were higher in those whose most recent or current episode was characterized by depressive polarity, and in individuals with a first-degree relative that had completed suicide (Schaffer et al., 2015). While the number of suicide attempts has been found to be higher in females, the rate of completed suicides is higher in men (Schaffer et al., 2015). Importantly, the risk of both suicide attempts and completed suicide has been found to be higher in those with a family history of suicide (Schaffer et al., 2015). Additional research is needed to better understand the risk factors and rate of suicide in OABD populations.

Psychiatric comorbidity

In individuals with BD, psychiatric conditions such as anxiety or substance abuse disorders may exist as comorbid conditions or symptoms of BD itself (McElroy et al., 2001). Among OABD, the comorbidity of eating disorders, attention deficit hyperactivity disorders, and personality disorders is lower than it is for younger adults with BD (Krishnan, 2005), while the prevalence of alcohol and substance use disorders amongst OABD patients is substantial (Dols, Rhebergen, et al., 2014; Lala & Sajatovic, 2012).

Physical health

Persons with BD have two to three times higher morbidity and mortality rates compared to the general population (Vancampfort et al., 2016). The diagnosis of BD is often in tandem with other comorbidities, and patients are rarely treated for bipolar symptomatology alone. One study found that the average life expectancy of individuals living with

BD was reduced by 10 years (Westman et al., 2013), and common causes of premature death amongst OABD populations include pneumonia, accidents, suicide, and disorders of the digestive tract (Chen et al., 2017). On average, individuals with BD have been found to have three to four physical comorbidities (Lala & Sajatovic, 2012; Tsai et al., 2009), and 86.3% of patients aged 65 and older with mania had a medical comorbidity (Lehmann & Rabins, 2006). However, the prevalence of these physical ailments is similar to those reported in individuals without BD (Lala & Sajatovic, 2012). Rise, Haro, and Gjervan (2016) conducted a literature review addressing comorbidities in patients with BD from 2012 to 2015 and found the most common physical comorbidities including cancer, diabetes mellitus, thyroid disorders, hypertension, viral hepatitis, and Parkinson's disease. In addition, arthritis and cardiovascular and respiratory diseases have also been found to be common (Lala & Sajatovic, 2012; Tsai et al., 2009). Elderly individuals with BD were also found to be at a higher risk for cardiovascular and respiratory conditions as well as endocrinological abnormalities (Rise et al., 2016). The prevalence of medical comorbidities amongst OABD population increases with age, leading to the concurrent use of multiple medications (Dols, Rhebergen, et al., 2014).

Cerebrovascular disease

Individuals with LOBD are found to be at an increased risk for cerebrovascular disease compared to those with EOBD (Sajatovic et al., 2015). There is radiological evidence that most older-age individuals living with BD have cardiovascular disease (Sajatovic et al., 2015). Longitudinal research studies should be conducted in order to better understand how risks associated with BD and cerebrovascular disease may be reduced through lifestyle factors such as increasing physical activity and reducing smoking (Sajatovic et al., 2015).

Obesity

Obesity is one of the most prevalent comorbidities in OABD, independently predicting the number of new onset medical conditions and increasing the risk of new medical conditions (Goldstein, Schaffer, Wang, & Blanco, 2015; Rise et al., 2016). Even in patients who are not taking pharmaceuticals associated with metabolic syndrome, the issue of overweight persists (Torrent et al., 2008). In patients with BD, this may be due to a multitude of causes; for example, lithium may contribute to undetected hypothyroidism, polydipsia which may lead to the consumption of sugary drinks, increased appetite or food consumption associated with improvements in mood symptoms, and decreased metabolic rate (Torrent et al., 2008). One European study found that older adults with BD and schizophrenia and healthy controls had a similar prevalence of metabolic syndrome (Konz et al., 2016), with rates that remained stable after 5 years of follow-up (de Louw et al., 2019); however these results should be interpreted with caution, as older adults with severe mental illness may represent a healthy survivor cohort.

Sedentary behaviors lead to health complications such as cardiovascular disease, type II diabetes, and a reduced life span (Vancampfort et al., 2016). Despite being an important issue, little research has been conducted on sedentary behavior and BD. Studies have largely focused on physical exercise in efforts to reduce cardiovascular comorbidities. These studies that have begun to address sedentary behavior in BD have often relied on self-report questionnaires, which may overestimate the amount of physical exercise in patients with BD. It has also been reported that sedentary behaviors differ regionally, with patients from North American studies averaging less physical activity than their European counterparts (Vancampfort et al., 2016). Future research should explore the role of obesity and sedentary behaviors in OABD patients with more reliable measures.

Cognition

Approximately one-half of euthymic OABD have some degree of cognitive impairment, particularly with regard to processing speed, memory, fluency, cognitive flexibility, and attention (Gildengers et al., 2004; Schaffer et al., 2015; Schouws et al., 2009; Schouws, Stek, Comijs, Dols, & Beekman, 2012). Because cognitive deficits are strongly linked to functional outcomes in BD (Burdick, Goldberg, & Harrow, 2010; Orhan et al., 2018), these deficits are important to recognize and address. However, there is a dearth of data about cognition in OABD relative to what is known about these deficits in younger patients with BD. In a review of the assessments included in studies of OABD, only 30% of investigations included a battery of neurocognitive tests that would help specify the pattern of deficits across domains (Rej et al., 2018). The domains and tests varied widely, and almost none included measures of social cognition, despite their importance to functional outcomes in younger BD patients (Ospina et al., 2018). Furthermore, while there is a growing interest in cognitive rehabilitation strategies applied to patients with

schizophrenia and younger people with BD, such cognitive enhancement interventions have not been tested in OABD (Harvey, Wingo, Burdick, & Baldessarini, 2010).

Slightly more attention has been placed on understanding the course of cognitive deficits across the life span in BD. It has been suggested that there may be accelerated cognitive decline, perhaps secondary to neuroprogression over the course of the disorder, but this remains a hotly contested topic (Sajatovic et al., 2015). Cross-sectional studies assessing populations of older compared to younger BD have found evidence of cognitive dysfunction in OABD (Young, Murphy, Heo, Schulberg, & Alexopoulos, 2006). Prospective longitudinal studies have been relatively rare and generally fail to demonstrate a more rapid decline in cognitive function with age in BD compared to nonpsychiatric samples (Schouws, Comijs, Dols, Beekman, & Stek, 2016). For example, a recent study (Sanchez-Morla et al., 2018) followed a group of 99 bipolar patients and 40 healthy controls over a period of 5 years and found no overall evidence for more rapid cognitive decline in the patient group. Those with a higher number of manic episodes and mania-related hospitalizations, however, showed greater decreases in neurocognitive composite index scores (Sanchez-Morla et al., 2018). This study seems to suggest that subgroups of patients may be at risk for accelerated cognitive decline, at least over a 5-year span. It may take longer than 5 years for neuroprogression to be demonstrated more broadly, however (Sanchez-Morla et al., 2018). Accelerated longitudinal designs, which recruit patients at a range of starting ages and follow each for a limited time, allow for longer-term trajectories to be inferred statistically and could be employed to better understand cognitive decline in BD (Thompson et al., 2013).

A further issue in understanding the course of cognitive function in BD is whether there is a heightened risk for dementia, such as Alzheimer's disease. One study found that having a diagnosis of BD increases the risk of dementia, with every new affective episode increasing this risk further (Kessing et al., 2004). However, there are still many limitations to this work as the research remains in its early stages with a lack of concordance between results. According to the cognitive reserve hypothesis, higher occupational and educational attainment, as well as a higher IQ may serve as protective factors against dementia (Stern, 2002), thereby allowing the brain to maintain a level of functioning regardless of assault. Cognitive reserve may be reduced in people with OABD, and in combination with vascular diseases may also lead to cognitive dysfunction and accelerated aging (Sajatovic et al., 2015).

Brain abnormalities

Neuroimaging has served as a useful tool to better understand biological and structural changes as well as symptoms in OABD (Sajatovic et al., 2015). Neuroanatomical abnormalities in the gray and white matter of OABD have been found in studies using magnetic resonance imaging (MRI) (Hahn, Lim, & Lee, 2014). Some of these abnormalities, such as reduced caudate volume and increased white matter hyperintensities, have been shown to be worse in LOBD compared to EOBD (Hahn et al., 2014). While there have been a limited number of published studies using structural MRI and diffusion tensor imaging in OABD, only a few have utilized magnetic spectroscopy to examine brain chemistry, and no published studies of OABD have utilized functional MRI (Rej et al., 2018).

Like in the realm of cognition, researchers have also been interested in understanding the course of brain aging in BD across the adult life span. Given that brain structures generally shrink and abnormalities of the white matter generally increase with age among nonpsychiatric samples, it is of interest to ask whether brain abnormalities observed in OABD are the result of premature or accelerated aging, and whether there is evidence of neuroprogression. As illustrated in Fig. 12.1, a premature aging course is one in which brain abnormalities are longstanding (perhaps arising before adulthood) and change in the same way with age as in nonpsychiatric samples. An accelerated or

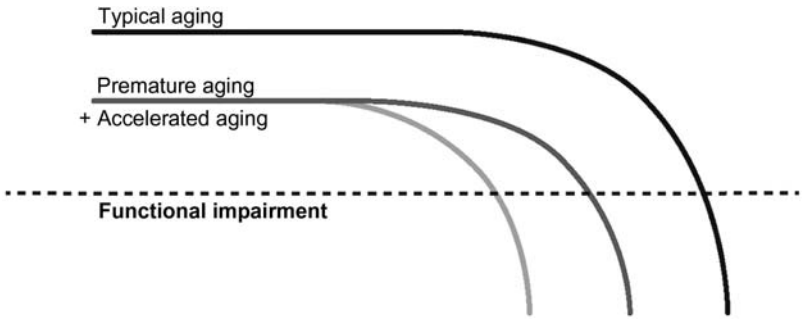


FIGURE 12.1 Comparing brain trajectories: Typical aging, premature aging, and accelerated aging.

TABLE 12.2 Evidence required to support hypotheses of neuroprogression, premature brain aging, and accelerated brain aging.

Neuroprogression	• At any age, those with greater chronicity have worse brains • At any age, accumulation of episodes leads to worsening brain abnormalities over time • This is true even after controlling for chronicity-associated factors
Premature brain aging	• Regardless of duration, brains look older than predicted by chronological age
Accelerated brain aging	• Regardless of duration, brains decline more rapidly than normal

neuroprogressive course has the additional feature of an increased rate of change with age. In each case, a hypothetical threshold for functional impairment due to these brain abnormalities in BD would be reached at an earlier age than in typical aging.

It is controversial whether there is premature or accelerated brain aging in BD. Studies have noted that young adult patients with BD have white matter abnormalities that resemble those seen in nonpsychiatric older adult samples (Mahon, Burdick, & Szeszko, 2010). Also, consistent with the shrinkage and thinning associated with typical aging, reductions in subcortical and cortical size have been observed in very large, and predominantly nonelderly, BD samples (Hibar et al., 2016; Hibar et al., 2018). One powerful technique for directly examining premature aging is to look at "predicted brain age discrepancy" or "brain age gap." In such studies, machine learning is first applied to structural MRI images to find the combination of brain features that best predicts chronological age within a nonpsychiatric sample. Then, the algorithm is applied to people with BD to see whether their predicted brain age exceeds their actual age (Cole, Marioni, Harris, & Deary, 2019). Initial studies have not found strong evidence for advanced brain age in BD within mixed-age samples (Hajek et al., 2019; Nenadic, Dietzek, Langbein, Sauer, & Gaser, 2017; Shahab et al., 2018).

Longitudinal studies of brain changes are scarce in BD, but are necessary in order to observe accelerated aging or neuroprogression relative to the declines seen in typical aging. A review of these studies (Lim et al., 2013) concluded that there is "loss of gray matter volume in prefrontal and anterior cingulate cortex and the subgenual region, with less consistent findings in temporal and subcortical regions." Unfortunately, most studies have only examined change over 1−2 years. Some have suggested that more precipitous brain changes in BD than in nonpsychiatric samples could be evidence of neuroprogression, meaning that brain abnormalities accumulate the longer one experiences symptoms of the disorder. As detailed in Table 12.2, to verify neuroprogression, one would need to see associations with chronicity factors and, ideally, longitudinal studies that track the course of symptoms and link accumulation of chronicity variables (e.g., number of hospitalizations or mood episodes) to observed brain declines within each individual. It is also important that variables such as head injury or smoking, which might accumulate in concert with other indicators of chronicity, are controlled for in such analyses. So far, there have not been any prospective studies conducted over a long enough timeframe to test whether those patients who experience a more deleterious course of illness also show a steeper rate of decline, so the neuroprogression hypothesis has yet to be fully tested.

Neuroimaging can also be used as a tool to help understand the potential neuroprotective effects of psychotropic medications. For example, the use of lithium has been found to have neuroprotective effects and its long-term use is associated with increased volume of the hippocampus (Hajek, Cullis, et al., 2012; Hajek, Kopecek, Hoschl, & Alda, 2012) and gray matter (Moore, Bebchuk, Wilds, Chen, & Manji, 2000) as well as decreased microstructural abnormalities in the white matter (Macritchie et al., 2010). However, one study using lithium-7 magnetic resonance spectroscopy (MRS) found that in OABD, increased lithium levels in the brain were associated with executive dysfunction and increased symptoms of depression (Forester et al., 2009).

Clinical care

Treating patients with BD is a complicated and personalized process, particularly given that the research on BD and aging is still in a nascent stage. Difficulties arise in addressing bipolar symptoms in addition to other psychiatric and physical comorbidities. Approximately one-third of individuals living with BD are taking at least six medications (Dols, Rhebergen, et al., 2014). Physiological changes in older adults place those with OABD at a higher risk for adverse reactions to medications (Ghose & Aging, 1991). This is exacerbated by the fact that comorbid medical conditions are common in older adults with BD, and the use of multiple medications among with these physiological changes may change the way in which mood stabilizers affect, and are metabolized and excreted by, the body (Ghose & Aging, 1991).

With the concurrent use of multiple medications, older-age individuals with BD should be seen by physicians up to four times a year to assess for medication side effects and complications and to screen for new medical conditions and cerebrovascular disease, which are consistently found in older patients with BD (Ng et al., 2009; Sajatovic et al., 2015). Research remains limited in elucidating the effects of medications in older populations and long-term use of antipsychotics, lithium, and other mood stabilizers (Sajatovic et al., 2015). In addition, metabolic syndrome should be screened for in patients taking antipsychotics (Ng et al., 2009). Future research should take a longitudinal approach to assessing the long-term effects of medications and combinations of therapies that can help in symptom reduction (i.e., exercise, mindfulness, etc.).

Psychiatric medications

Little research has been conducted on the pharmacological treatment of OABD, largely due to the fact that this age group is at high risk of medical complications (Dols & Beekman, 2018). Despite the limited evidence available regarding the treatment of OABD, medications remain the most common treatment modality.

Lithium remains the most common pharmaceutical treatment for BD as it can effectively reduce manic and depressive episodes and also seems to have neuroprotective properties (Sajatovic et al., 2015). Most studies investigating the side effects of psychotropic medications in older-age patients with BD have involved small sample sizes and utilized a cross-sectional approach; therefore strong evidence regarding this topic is limited (Sajatovic et al., 2015). Renal issues associated with the long-term use of lithium have been indicated but have not yet been confirmed by prospective longitudinal studies (Rej, Abitbol, Looper, & Segal, 2013). The risk of renal disease in geriatric patients taking lithium is increased for those taking angiotensin-converting enzyme inhibitors, diuretics, and high levels of lithium (Ghose & Aging, 1991), as well as those with renal dysfunction associated with age (Head & Dening, 1998), high blood pressure, and diabetes (Coresh et al., 2007).

One study utilizing a Delphi survey determined there to be consensus among world experts regarding the use of lithium as the first line monotherapy maintenance treatment drug in OABD populations (Shulman et al., 2005). In addition, olanzapine, quetiapine, valproate, and lamotrigine were agreed upon as recommended second-line maintenance drugs in this group (Shulman et al., 2005).

During the survey, the team of experts was also asked to report the therapeutic doses of lithium recommended by their local laboratories (Shulman et al., 2005). These doses were found to be higher than the recommended range agreed upon by the experts, which was 0.4−0.8 mmol/L for patients aged 60−79, and 0.4−0.7 mmol/L for patients 80 and above (Shulman et al., 2005). This may be due to the fact that the laboratories did not provide separate recommendations for the therapeutic dosage based on age; this being said, efforts should be made to ensure that the recommended therapeutic dosage is informed by consensus expert opinion from this survey as well as clinical practice guidelines (Shulman et al., 2005) to prevent toxicity. No consensus was reached with regard to dosing lithium once versus twice per day (Shulman et al., 2005). The expert panel also agreed that every 3−6 months functioning of the kidneys, gait, tremor, and cognitive functioning should be evaluated to assess for symptoms of lithium toxicity (Shulman et al., 2005). Abnormal findings should not be confused with comorbid conditions such as gastrointestinal issues, dementia, or parkinsonism, as this can lead to the prescription of unnecessary additional medications referred to as a "prescribing cascade" (Shulman et al., 2005).

Bipolar depression is notoriously difficult to treat. Among OABD, there is some evidence that lithium, valproate, quetiapine, aripiprazole, and asenapine are effective treatment options in comparison to no-treatment groups (Sajatovic et al., 2015).

Only a single randomized controlled medication trial has been published on OABD; this study, GERI-BD, conducted by Young et al. (2017), found that both lithium and valproate were tolerated by and effective for the treatment of older-age adults with BD. Given that antipsychotics may lead to adverse consequences and increased risk of mortality, and that lithium may help to reduce the risk of suicide and dementia, findings from this study support the use of lithium in the treatment of older adults with BD (Young et al., 2017). Additional prospective randomized controlled trials are needed in order to better understand the use of psychotropic medications in OABD (Sajatovic et al., 2015).

Evidence supporting the effectiveness of antipsychotics in treating geriatric BD patients is limited. However, a meta-analysis by Cipriani et al. (2011) comparing the use of pharmacological drugs in adults with acute mania found antipsychotic medications to be more effective than mood stabilizers, with olanzapine, risperidone, and haloperidol being the most effective of these drugs. Benzodiazepines may also be useful for reducing agitation and improving sleep quality in the short term (Dols & Beekman, 2018).

Electroconvulsive therapy

Electroconvulsive therapy (ECT) may be a promising treatment modality to help treat both mania and depression in people with treatment-resistant BD (Sienaert, Lambrichts, Dols, & De Fruyt, 2013; Versiani, Cheniaux, & Landeira-Fernandez, 2011). Despite this fact, concerns regarding the cognitive side effects of ECT, stigma surrounding the use of this modality, and limited availability led to the underutilization of ECT (Wilkinson, Agbese, Leslie, & Rosenheck, 2018). While there have been no studies specifically assessing the use of electroconvulsive therapy in OABD, studies with older adults with unipolar depression and in younger BD patients indicate that ECT may be most effective during the manic, depressive, and mixed episodes (Stek, Wurff van der, Hoogendijk, & Beekman, 2003; Versiani et al., 2011). Furthermore, the use of ECT in older adults with BD may be most useful for patients with resistance to pharmaceutical drugs and a history of a positive response to ECT, those refusing fluids and foods, or individuals with severe suicidal thoughts (Greenberg & Kellner, 2005). The cognitive effects of ECT in OABD patients are largely unknown due to the limited number of high-quality studies on this topic. However, studies in older patients with unipolar depression treated with ECT have demonstrated that cognitive symptoms may improve due to improvements in focus and depressive mood symptoms (Obbels et al., 2018; Tielkes, Comijs, Verwijk, & Stek, 2008).

In recent years, the use of novel technologies for addressing treatment-resistant BD such as ketamine and transcranial magnetic stimulation (TMS) has gained attention. Two randomized controlled trials assessing the impact of ketamine on treatment-resistant bipolar depression in people aged 18−65 determined that those treated with ketamine experienced a significant reduction in depressive symptoms, and that the treatment was generally well tolerated by the subjects (Diazgranados et al., 2010; Lally et al., 2014). These effects were observed as early as 40 minutes posttreatment and as late as 14 days after the treatment (Diazgranados et al., 2010; Lally et al., 2014). Additional studies targeting OABD are needed in order to determine the effectiveness and tolerability of ketamine treatment amongst this age group.

Some studies have found repetitive TMS, referred to as rTMS, to be safe and effective for reducing symptoms of anxiety and depression in elderly patients with resistant unipolar and bipolar depression (Abraham et al., 2007; Desbeaumes Jodoin, Miron, & Lesperance, 2018). However, these studies were nonblinded, had no control group, and had a small sample size; therefore additional research is needed to discern the effectiveness and safety of this treatment modality in OABD.

Psychotherapy

Systematic studies assessing the use of psychotherapy in older-age adults with BD have been limited, and the use of psychotherapy in OABD has largely been guided by clinical experience or through studies involving mixed-age groups. A systematic review by Bartels et al. in 2009 found that older adults living with serious psychiatric illness receiving psychosocial interventions benefited from improvements in their quality of life (Bartels & Pratt, 2009). One study found that an intervention called HOPES, or "Helping Older People Experience Success", led to improved outcomes in social skills, recreation and leisure, functioning in the community, self-efficacy, and negative symptoms (Mueser et al., 2010).

Medication adherence programs may also contribute to psychosocial well-being in patients with OABD. One quasiexperimental study of a medication adherence skills training program in middle- and older-aged adults with BD, called the MAST-BD, found the program to be effective in improving adherence, depressive symptoms, and quality of life (Depp et al., 2007).

Another treatment modality which has been found to be effective in the management of BD is interpersonal and social rhythm therapy (IPSRT), which involves helping patients regulate routines of daily living related to eating sleeping, activity, and rest (Frank, Swartz, & Boland, 2007). Two randomized controlled trials have shown support for the use of IPSRT in patients under the age of 60−65, with those receiving IPSRT showing more regular social rhythms and increased interepisode recovery time (Frank et al., 2005), and individuals receiving intensive psychotherapy that included IPSRT being more likely to recover than those in the comparison conditions (Miklowitz et al., 2007). Given that sleep and circadian rhythms tend to change as patients age, the use of rhythm therapy should be tested in OABD populations.

Exercise and nutrition

Exercise is an important component of maintaining both physical and mental health in BD. As discussed in a review by Hearing et al. (2016) assessing the role of exercise in the treatment of mood disorders, open trials and retrospective

cohort pilot studies have found evidence that exercise may help to reduce psychiatric comorbidity, improve functioning and quality of life, and reduce depression, anxiety, pain, and stress in individuals with BD. A proof-of-concept pilot study involving mixed-age groups also found evidence that a three-part nutrition, exercise, and wellness intervention increased exercise, improved nutrition, improved functioning, and reduced symptoms of depression (Hearing et al., 2016; Sylvia et al., 2013). In addition, the intervention was determined to be both feasible and acceptable (Hearing et al., 2016; Sylvia et al., 2013). However, further research is needed to better understand the potential for exercise and nutrition interventions specifically in the management of OABD.

Limitations and future directions

As the population ages, the number of elderly individuals living with BD will continue to rise (Sajatovic et al., 2015). This demographic shift in the population calls for greater research on the management of BD across the life course (Sajatovic et al., 2015). In addition, further research is needed to better understand the etiology of EOBD versus LOBD and should approach the disorder in an integrated way that considers all comorbidities (Sajatovic et al., 2015).

Clinical trials for the treatment of OABD have been very limited (Sajatovic et al., 2015), perhaps due to the expense of such trials and feasibility of conducting them. In light of this, research should at least be conducted on existing therapies through the use of databases and case registries that contain sufficiently large samples of geriatric BD patients (Sajatovic et al., 2015). In addition, there is a potential role for global consortia in conducting prospective studies and trials with standardized measures relevant to OABD (Rej et al., 2018). For example, the Global Aging and Geriatric Experiments in Bipolar Disorder Database is a new multinational effort of the International Society for Bipolar Disorders, which is working to compile datasets from OABD research studies across the globe. This project will use existing data to examine clinical features of OABD and will provide a framework for future global collaborations.

More long-term longitudinal studies are needed to better understand cognitive and brain aging in BD, as well as what subgroups of patients might be at greater risk for accelerated declines. For instance, it has been suggested that aging-related biomarkers, such as peripheral inflammation, may be important predictors of cognitive and brain declines (Castano-Ramirez et al., 2018). Notably, OABD with higher levels of inflammatory markers has been shown to have smaller hippocampal and total gray matter volume (Tsai et al., 2019). It remains to be seen whether inflammation is a leading indicator for brain and cognitive declines, or whether antiinflammatory treatments might improve the quality of life for those aging with BD.

References

Abdul-Hamid, W. K., Lewis-Cole, K., Holloway, F., & Silverman, A. M. (2015). Comparision of how old age psychiatry and general adult psychiatry services meet the needs of elderly people with functional mental illness: Cross-sectional survey. *The British Journal of Psychiatry: the Journal of Mental Science*, *207*(5), 440–443. Available from https://doi.org/10.1192/bjp.bp.114.145706.

Abraham, G., Milev, R., Lazowski, L., Jokic, R., du Toit, R., & Lowe, A. (2007). Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression—An open label trial. *Neuropsychiatric Disease and Treatment*, *3*(6), 919–924.

Al Jurdi, R. K., Marangell, L. B., Petersen, N. J., Martinez, M., Gyulai, L., & Sajatovic, M. (2008). Prescription patterns of psychotropic medications in elderly compared with younger participants who achieved a "recovered" status in the systematic treatment enhancement program for bipolar disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *16*(11), 922–933. Available from https://doi.org/10.1097/JGP.0b013e318187135f.

Almeida, O. P., & Fenner, S. (2002). Bipolar disorder: Similarities and differences between patients with illness onset before and after 65 years of age. *International Psychogeriatrics*, *14*(3), 311–322.

Angst, J., & Preisig, M. (1995). Course of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. *Schweizer Archiv fur Neurologie und Psychiatrie (Zurich, Switzerland: 1985)*, *146*(1), 5–16.

Bartels, S. J., & Pratt, S. I. (2009). Psychosocial rehabilitation and quality of life for older adults with serious mental illness: Recent findings and future research directions. *Current Opinion in Psychiatry*, *22*(4), 381–385. Available from https://doi.org/10.1097/YCO.0b013e32832c9234.

Burdick, K. E., Goldberg, J. F., & Harrow, M. (2010). Neurocognitive dysfunction and psychosocial outcome in patients with bipolar I disorder at 15-year follow-up. *Acta Psychiatrica Scandinavica*, *122*(6), 499–506. Available from https://doi.org/10.1111/j.1600-0447.2010.01590.x.

Castano-Ramirez, O. M., Sepulveda-Arias, J. C., Duica, K., Diaz Zuluaga, A. M., Vargas, C., & Lopez-Jaramillo, C. (2018). Inflammatory markers in the staging of bipolar disorder: A systematic review of the literature. *Revista Colombiana de Psiquiatría*, *47*(2), 119–128. Available from https://doi.org/10.1016/j.rcp.2017.01.004.

Chen, P., Dols, A., Rej, S., & Sajatovic, M. (2017). Update on the epidemiology, diagnosis, and treatment of mania in older-age bipolar disorder. *Current Psychiatry Reports*, *19*(8), 46. Available from https://doi.org/10.1007/s11920-017-0804-8.

Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., ... Geddes, J. R. (2011). Comparative efficacy and acceptability of antimanic drugs in acute mania: A multiple-treatments meta-analysis. *Lancet*, *378*(9799), 1306−1315. Available from https://doi.org/10.1016/s0140-6736(11)60873-8.

Cole, J. H., Marioni, R. E., Harris, S. E., & Deary, I. J. (2019). Brain age and other bodily 'ages': Implications for neuropsychiatry. *Molecular Psychiatry*, *24*(2), 266−281. Available from https://doi.org/10.1038/s41380-018-0098-1.

Coresh, J., Selvin, E., Stevens, L. A., Manzi, J., Kusek, J. W., Eggers, P., ... Levey, A. S. (2007). Prevalence of chronic kidney disease in the United States. *JAMA*, *298*(17), 2038−2047. Available from https://doi.org/10.1001/jama.298.17.2038.

de Louw, E. J., Paans, N. P. G., Sonnenberg, C. M., Konz, H., Meesters, P. D., van Grootheest, D., ... Dols, A. (2019). Metabolic syndrome rates in older patients with severe mental illness after five years of follow-up and the association with mortality. *International Journal of Geriatric Psychiatry*, *34*(2), 333−336. Available from https://doi.org/10.1002/gps.5025.

Depp, C. A., & Jeste, D. V. (2004). Bipolar disorder in older adults: A critical review. *Bipolar Disorders*, *6*(5), 343−367. Available from https://doi.org/10.1111/j.1399-5618.2004.00139.x.

Depp, C. A., Jin, H., Mohamed, S., Kaskow, J., Moore, D. J., & Jeste, D. V. (2004). Bipolar disorder in middle-aged and elderly adults: Is age of onset important? *The Journal of Nervous and Mental Disease*, *192*(11), 796−799.

Depp, C. A., Lindamer, L. A., Folsom, D. P., Gilmer, T., Hough, R. L., Garcia, P., & Jeste, D. V. (2005). Differences in clinical features and mental health service use in bipolar disorder across the lifespan. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *13*(4), 290−298. Available from https://doi.org/10.1176/appi.ajgp.13.4.290.

Depp, C. A., Moore, D. J., Sitzer, D., Palmer, B. W., Eyler, L. T., Roesch, S., ... Jeste, D. V. (2007). Neurocognitive impairment in middle-aged and older adults with bipolar disorder: Comparison to schizophrenia and normal comparison subjects. *Journal of Affective Disorders*, *101*(1−3), 201−209. Available from https://doi.org/10.1016/j.jad.2006.11.022.

Desbeaumes Jodoin, V., Miron, J. P., & Lesperance, P. (2018). Safety and efficacy of accelerated repetitive transcranial magnetic stimulation protocol in elderly depressed unipolar and bipolar patients. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*. Available from https://doi.org/10.1016/j.jagp.2018.10.019.

Diazgranados, N., Ibrahim, L., Brutsche, N. E., Newberg, A., Kronstein, P., Khalife, S., ... Zarate, C. A., Jr. (2010). A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of General Psychiatry*, *67*(8), 793−802. Available from https://doi.org/10.1001/archgenpsychiatry.2010.90.

Dols, A., & Beekman, A. (2018). Older age bipolar disorder. *The Psychiatric Clinics of North America*, *41*(1), 95−110. Available from https://doi.org/10.1016/j.psc.2017.10.008.

Dols, A., Kessing, L. V., Strejilevich, S. A., Rej, S., Tsai, S. Y., Gildengers, A. G., ... Sajatovic, M. (2016). Do current national and international guidelines have specific recommendations for older adults with bipolar disorder? A brief report. *International Journal of Geriatric Psychiatry*, *31*(12), 1295−1300. Available from https://doi.org/10.1002/gps.4534.

Dols, A., Korten, N., Comijs, H., Schouws, S., van Dijk, M., Klumpers, U., ... Stek, M. (2017). The clinical course of late-life bipolar disorder, looking back and forward. *Bipolar Disorders*. Available from https://doi.org/10.1111/bdi.12586.

Dols, A., Kupka, R. W., van Lammeren, A., Beekman, A. T., Sajatovic, M., & Stek, M. L. (2014). The prevalence of late-life mania: A review. *Bipolar Disorders*, *16*(2), 113−118. Available from https://doi.org/10.1111/bdi.12104.

Dols, A., Rhebergen, D., Beekman, A., Kupka, R., Sajatovic, M., & Stek, M. L. (2014). Psychiatric and medical comorbidities: Results from a bipolar elderly cohort study. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *22*(11), 1066−1074. Available from https://doi.org/10.1016/j.jagp.2013.12.176.

Ernst, C. L., & Goldberg, J. F. (2004). Clinical features related to age at onset in bipolar disorder. *Journal of Affective Disorders*, *82*(1), 21−27. Available from https://doi.org/10.1016/j.jad.2003.10.002.

Forester, B. P., Streeter, C. C., Berlow, Y. A., Tian, H., Wardrop, M., Finn, C. T., ... Moore, C. M. (2009). Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: A lithium-7 magnetic resonance spectroscopy study. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *17*(1), 13−23. Available from https://doi.org/10.1097/JGP.0b013e318172b3d0.

Frank, E., Kupfer, D. J., Thase, M. E., Mallinger, A. G., Swartz, H. A., Fagiolini, A. M., ... Monk, T. (2005). Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry*, *62*(9), 996−1004. Available from https://doi.org/10.1001/archpsyc.62.9.996.

Frank, E., Swartz, H. A., & Boland, E. (2007). Interpersonal and social rhythm therapy: An intervention addressing rhythm dysregulation in bipolar disorder. *Dialogues in Clinical Neuroscience*, *9*(3), 325−332.

Ghose, K. (1991). The need for a review journal of drug use and the elderly. *Drugs & Aging*, *1*(1), 2−5. doi:10.2165/00002512-199101010-00002

Gildengers, A. G., Butters, M. A., Seligman, K., McShea, M., Miller, M. D., Mulsant, B. H., ... Reynolds, C. F., 3rd (2004). Cognitive functioning in late-life bipolar disorder. *The American Journal of Psychiatry*, *161*(4), 736−738. Available from https://doi.org/10.1176/appi.ajp.161.4.736.

Goldstein, B. I., Schaffer, A., Wang, S., & Blanco, C. (2015). Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. *The Journal of Clinical Psychiatry*, *76*(2), 163−169. Available from https://doi.org/10.4088/JCP.14m09300.

Greenberg, R. M., & Kellner, C. H. (2005). Electroconvulsive therapy: A selected review. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *13*(4), 268−281. Available from https://doi.org/10.1176/appi.ajgp.13.4.268.

Hahn, C., Lim, H. K., & Lee, C. U. (2014). Neuroimaging findings in late-onset schizophrenia and bipolar disorder. *Journal of Geriatric Psychiatry and Neurology*, *27*(1), 56−62. Available from https://doi.org/10.1177/0891988713516544.

Hajek, T., Cullis, J., Novak, T., Kopecek, M., Hoschl, C., Blagdon, R., ... Alda, M. (2012). Hippocampal volumes in bipolar disorders: Opposing effects of illness burden and lithium treatment. *Bipolar Disorders*, *14*(3), 261–270. Available from https://doi.org/10.1111/j.1399-5618.2012.01013.x.

Hajek, T., Franke, K., Kolenic, M., Capkova, J., Matejka, M., Propper, L., ... Alda, M. (2019). Brain age in early stages of bipolar disorders or schizophrenia. *Schizophrenia Bulletin*, *45*(1), 190–198. Available from https://doi.org/10.1093/schbul/sbx172.

Hajek, T., Kopecek, M., Hoschl, C., & Alda, M. (2012). Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: A meta-analysis. *Journal of Psychiatry & Neuroscience*, *37*(5), 333–343. Available from https://doi.org/10.1503/jpn.110143.

Harvey, P. D., Wingo, A. P., Burdick, K. E., & Baldessarini, R. J. (2010). Cognition and disability in bipolar disorder: Lessons from schizophrenia research. *Bipolar Disorders*, *12*(4), 364–375. Available from https://doi.org/10.1111/j.1399-5618.2010.00831.x.

Head, L., & Dening, T. (1998). Lithium in the over-65s: Who is taking it and who is monitoring it? A survey of older adults on lithium in the Cambridge Mental Health Services catchment area. *International Journal of Geriatric Psychiatry*, *13*(3), 164–171.

Hearing, C. M., Chang, W. C., Szuhany, K. L., Deckersbach, T., Nierenberg, A. A., & Sylvia, L. G. (2016). Physical exercise for treatment of mood disorders: A critical review. *Current Behavioral Neuroscience Reports*, *3*(4), 350–359. Available from https://doi.org/10.1007/s40473-016-0089-y.

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., ... Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular Psychiatry*, *23*(4), 932–942. Available from https://doi.org/10.1038/mp.2017.73.

Hibar, D. P., Westlye, L. T., van Erp, T. G., Rasmussen, J., Leonardo, C. D., Faskowitz, J., ... Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular Psychiatry*, *21*(12), 1710–1716. Available from https://doi.org/10.1038/mp.2015.227.

Hirschfeld, R. M., Calabrese, J. R., Weissman, M. M., Reed, M., Davies, M. A., Frye, M. A., ... Wagner, K. D. (2003). Screening for bipolar disorder in the community. *The Journal of Clinical Psychiatry*, *64*(1), 53–59.

Jeste, D. V., Alexopoulos, G. S., Bartels, S. J., Cummings, J. L., Gallo, J. J., Gottlieb, G. L., ... Lebowitz, B. D. (1999). Consensus statement on the upcoming crisis in geriatric mental health: Research agenda for the next 2 decades. *Archives of General Psychiatry*, *56*(9), 848–853.

Joslyn, C., Hawes, D. J., Hunt, C., & Mitchell, P. B. (2016). Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. *Bipolar Disorders*, *18*(5), 389–403. Available from https://doi.org/10.1111/bdi.12419.

Kessing, L. V. (1998). Recurrence in affective disorder. II. Effect of age and gender. *The British Journal of Psychiatry: the Journal of Mental Science*, *172*, 29–34.

Kessing, L. V. (2005). Diagnostic stability in bipolar disorder in clinical practise as according to ICD-10. *Journal of Affective Disorders*, *85*(3), 293–299. Available from https://doi.org/10.1016/j.jad.2004.11.001.

Kessing, L. V. (2006). Diagnostic subtypes of bipolar disorder in older versus younger adults. *Bipolar Disorders*, *8*(1), 56–64. Available from https://doi.org/10.1111/j.1399-5618.2006.00278.x.

Kessing, L. V., Hansen, M. G., & Andersen, P. K. (2004). Course of illness in depressive and bipolar disorders. Naturalistic study, 1994–1999. *The British Journal of Psychiatry: the Journal of Mental Science*, *185*, 372–377. Available from https://doi.org/10.1192/bjp.185.5.372.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602. Available from https://doi.org/10.1001/archpsyc.62.6.593.

Konz, H. W., Meesters, P. D., Paans, N. P. G., van Grootheest, D. S., Comijs, H. C., Stek, M. S., & Dols, A. (2016). [Screening for metabolic syndrome in older patients with severe mental illness]. *Tijdschrift voor Psychiatrie*, *58*(1), 61–66.

Krauthammer, C., & Klerman, G. L. (1978). Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. *Archives of General Psychiatry*, *35*(11), 1333–1339.

Krishnan, K. R. (2005). Psychiatric and medical comorbidities of bipolar disorder. *Psychosomatic Medicine*, *67*(1), 1–8. Available from https://doi.org/10.1097/01.psy.0000151489.36347.18.

Lala, S. V., & Sajatovic, M. (2012). Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: A literature review. *Journal of Geriatric Psychiatry and Neurology*, *25*(1), 20–25. Available from https://doi.org/10.1177/0891988712436683.

Lally, N., Nugent, A. C., Luckenbaugh, D. A., Ameli, R., Roiser, J. P., & Zarate, C. A. (2014). Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Translational Psychiatry*, *4*, e469. Available from https://doi.org/10.1038/tp.2014.105.

Lehmann, S. W., & Rabins, P. V. (2006). Factors related to hospitalization in elderly manic patients with early and late-onset bipolar disorder. *International Journal of Geriatric Psychiatry*, *21*(11), 1060–1064. Available from https://doi.org/10.1002/gps.1607.

Lim, C. S., Baldessarini, R. J., Vieta, E., Yucel, M., Bora, E., & Sim, K. (2013). Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence. *Neuroscience and Biobehavioral Reviews*, *37*(3), 418–435. Available from https://doi.org/10.1016/j.neubiorev.2013.01.003.

Macritchie, K. A., Lloyd, A. J., Bastin, M. E., Vasudev, K., Gallagher, P., Eyre, R., ... Young, A. H. (2010). White matter microstructural abnormalities in euthymic bipolar disorder. *The British Journal of Psychiatry: the Journal of Mental Science*, *196*(1), 52–58. Available from https://doi.org/10.1192/bjp.bp.108.058586.

Mahon, K., Burdick, K. E., & Szeszko, P. R. (2010). A role for white matter abnormalities in the pathophysiology of bipolar disorder. *Neuroscience and Biobehavioral Reviews*, *34*(4), 533–554. Available from https://doi.org/10.1016/j.neubiorev.2009.10.012.

McElroy, S. L., Altshuler, L. L., Suppes, T., Keck, P. E., Jr., Frye, M. A., Denicoff, K. D., ... Post, R. M. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *The American Journal of Psychiatry*, *158*(3), 420–426. Available from https://doi.org/10.1176/appi.ajp.158.3.420.

Miklowitz, D. J., Otto, M. W., Frank, E., Reilly-Harrington, N. A., Wisniewski, S. R., Kogan, J. N., … Sachs, G. S. (2007). Psychosocial treatments for bipolar depression: A 1-year randomized trial from the Systematic Treatment Enhancement Program. *Archives of General Psychiatry*, *64*(4), 419–426. Available from https://doi.org/10.1001/archpsyc.64.4.419.

Moore, G. J., Bebchuk, J. M., Wilds, I. B., Chen, G., & Manji, H. K. (2000). Lithium-induced increase in human brain grey matter. *Lancet*, *356* (9237), 1241–1242.

Mueser, K. T., Pratt, S. I., Bartels, S. J., Swain, K., Forester, B., Cather, C., & Feldman, J. (2010). Randomized trial of social rehabilitation and integrated health care for older people with severe mental illness. *Journal of Consulting and Clinical Psychology*, *78*(4), 561–573. Available from https://doi.org/10.1037/a0019629.

Nenadic, I., Dietzek, M., Langbein, K., Sauer, H., & Gaser, C. (2017). BrainAGE score indicates accelerated brain aging in schizophrenia, but not bipolar disorder. *Psychiatry Research: Neuroimaging*, *266*, 86–89. Available from https://doi.org/10.1016/j.pscychresns.2017.05.006.

Ng, F., Mammen, O. K., Wilting, I., Sachs, G. S., Ferrier, I. N., Cassidy, F., … Berk, M. (2009). The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disorders*, *11*(6), 559–595. Available from https://doi.org/10.1111/j.1399-5618.2009.00737.x.

Obbels, J., Verwijk, E., Vansteelandt, K., Dols, A., Bouckaert, F., Schouws, S., … Sienaert, P. (2018). Long-term neurocognitive functioning after electroconvulsive therapy in patients with late-life depression. *Acta Psychiatrica Scandinavica*, *138*(3), 223–231. Available from https://doi.org/10.1111/acps.12942.

Oostervink, F., Boomsma, M. M., & Nolen, W. A. (2009). Bipolar disorder in the elderly; different effects of age and of age of onset. *Journal of Affective Disorders*, *116*(3), 176–183. Available from https://doi.org/10.1016/j.jad.2008.11.012.

Oostervink, F., Nolen, W. A., & Kok, R. M. (2015). Two years' outcome of acute mania in bipolar disorder: Different effects of age and age of onset. *International Journal of Geriatric Psychiatry*, *30*(2), 201–209. Available from https://doi.org/10.1002/gps.4128.

Orhan, M., Korten, N., Stek, M., Comijs, H., Schouws, S., & Dols, A. (2018). The relationship between cognitive and social functioning in older patients with bipolar disorder. *Journal of Affective Disorders*, *240*, 177–182. Available from https://doi.org/10.1016/j.jad.2018.07.055.

Ospina, L. H., Nitzburg, G. C., Shanahan, M., Perez-Rodriguez, M. M., Larsen, E., Latifoglu, A., & Burdick, K. E. (2018). Social cognition moderates the relationship between neurocognition and community functioning in bipolar disorder. *Journal of Affective Disorders*, *235*, 7–14. Available from https://doi.org/10.1016/j.jad.2018.03.013.

Rej, S., Abitbol, R., Looper, K., & Segal, M. (2013). Chronic renal failure in lithium-using geriatric patients: Effects of lithium continuation versus discontinuation—a 60-month retrospective study. *International Journal of Geriatric Psychiatry*, *28*(5), 450–453. Available from https://doi.org/10.1002/gps.3841.

Rej, S., Quayle, W., Forester, B. P., Dols, A., Gatchel, J., Chen, P., … Eyler, L. T. (2018). Measurement tools for assessment of older age bipolar disorder: A systematic review of the recent global literature. *Bipolar Disorders*, *20*(4), 359–369. Available from https://doi.org/10.1111/bdi.12566.

Rise, I. V., Haro, J. M., & Gjervan, B. (2016). Clinical features, comorbidity, and cognitive impairment in elderly bipolar patients. *Neuropsychiatric Disease and Treatment*, *12*, 1203–1213. Available from https://doi.org/10.2147/ndt.S100843.

Sajatovic, M., Gyulai, L., Calabrese, J. R., Thompson, T. R., Wilson, B. G., White, R., & Evoniuk, G. (2005). Maintenance treatment outcomes in older patients with bipolar I disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *13*(4), 305–311. Available from https://doi.org/10.1176/appi.ajgp.13.4.305.

Sajatovic, M., & Kessling, L. (2010). Bipolar disorder in older adults: A critical review. In L. N. Yatham, & M. Maj (Eds.), *Bipolar disorder—Clinical and neurobiological foundations*. Singapore: Markono Print Media.

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., … Shulman, K. I. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disorders*, *17*(7), 689–704. Available from https://doi.org/10.1111/bdi.12331.

Sanchez-Morla, E. M., Lopez-Villarreal, A., Jimenez-Lopez, E., Aparicio, A. I., Martinez-Vizcaino, V., Roberto, R. J., … Santos, J. L. (2018). Impact of number of episodes on neurocognitive trajectory in bipolar disorder patients: A 5-year follow-up study. *Psychological Medicine*, *49*, 1299–1307. Available from https://doi.org/10.1017/s0033291718001885.

Schaffer, A., Isometsa, E. T., Tondo, L., Moreno, D. H., Turecki, G., Reis, C., … Yatham, L. N. (2015). International Society for Bipolar Disorders Task Force on Suicide: Meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disorders*, *17*(1), 1–16. Available from https://doi.org/10.1111/bdi.12271.

Schouws, S. N., Comijs, H. C., Dols, A., Beekman, A. T., & Stek, M. L. (2016). Five-year follow-up of cognitive impairment in older adults with bipolar disorder. *Bipolar Disorders*, *18*(2), 148–154. Available from https://doi.org/10.1111/bdi.12374.

Schouws, S. N., Comijs, H. C., Stek, M. L., Dekker, J., Oostervink, F., Naarding, P., … Beekman, A. T. (2009). Cognitive impairment in early and late bipolar disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *17*(6), 508–515. Available from https://doi.org/10.1097/JGP.0b013e31819e2d50.

Schouws, S. N., Stek, M. L., Comijs, H. C., Dols, A., & Beekman, A. T. (2012). Cognitive decline in elderly bipolar disorder patients: A follow-up study. *Bipolar Disorders*, *14*(7), 749–755. Available from https://doi.org/10.1111/bdi.12000.

Schurhoff, F., Bellivier, F., Jouvent, R., Mouren-Simeoni, M. C., Bouvard, M., Allilaire, J. F., & Leboyer, M. (2000). Early and late onset bipolar disorders: Two different forms of manic-depressive illness? *Journal of Affective Disorders*, *58*(3), 215–221.

Shahab, S., Mulsant, B. H., Levesque, M. L., Calarco, N., Nazeri, A., Wheeler, A. L., … Voineskos, A. N. (2018). Brain structure, cognition, and brain age in schizophrenia, bipolar disorder, and healthy controls. *Neuropsychopharmacology*. Available from https://doi.org/10.1038/s41386-018-0298-z.

Shulman, K. I., Sykora, K., Gill, S., Mamdani, M., Bronskill, S., Wodchis, W. P., ... Rochon, P. (2005). Incidence of delirium in older adults newly prescribed lithium or valproate: A population-based cohort study. *The Journal of Clinical Psychiatry*, *66*(4), 424–427.

Sienaert, P., Lambrichts, L., Dols, A., & De Fruyt, J. (2013). Evidence-based treatment strategies for treatment-resistant bipolar depression: A systematic review. *Bipolar Disorders*, *15*(1), 61–69. Available from https://doi.org/10.1111/bdi.12026.

Stek, M. L., Wurff van der, F. F. B., Hoogendijk, W. J. G., & Beekman, A. T. F. (2003). Electroconvulsive therapy for the depressed elderly. *Cochrane Database of Systematic Reviews* (2). Available from https://doi.org/10.1002/14651858.CD003593, CD003593.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460.

Sylvia, L. G., Salcedo, S., Bernstein, E. E., Baek, J. H., Nierenberg, A. A., & Deckersbach, T. (2013). Nutrition, exercise, and wellness treatment in bipolar disorder: Proof of concept for a consolidated intervention. *International Journal of Bipolar Disorders*, *1*(1), 24. Available from https://doi.org/10.1186/2194-7511-1-24.

Thompson, W. K., Savla, G. N., Vahia, I. V., Depp, C. A., O'Hara, R., Jeste, D. V., & Palmer, B. W. (2013). Characterizing trajectories of cognitive functioning in older adults with schizophrenia: Does method matter? *Schizophrenia Research*, *143*(1), 90–96. Available from https://doi.org/10.1016/j.schres.2012.10.033.

Tielkes, C. E., Comijs, H. C., Verwijk, E., & Stek, M. L. (2008). The effects of ECT on cognitive functioning in the elderly: A review. *International Journal of Geriatric Psychiatry*, *23*(8), 789–795. Available from https://doi.org/10.1002/gps.1989.

Torrent, C., Amann, B., Sanchez-Moreno, J., Colom, F., Reinares, M., Comes, M., ... Vieta, E. (2008). Weight gain in bipolar disorder: Pharmacological treatment as a contributing factor. *Acta Psychiatrica Scandinavica*, *118*(1), 4–18. Available from https://doi.org/10.1111/j.1600-0447.2008.01204.x.

Tsai, S. Y., Gildengers, A. G., Hsu, J. L., Chung, K. H., Chen, P. H., & Huang, Y. J. (2019). Inflammation associated with volume reduction in the gray matter and hippocampus of older patients with bipolar disorder. *Journal of Affective Disorders*, *244*, 60–66. Available from https://doi.org/10.1016/j.jad.2018.10.093.

Tsai, S. Y., Kuo, C. J., Chen, C. C., & Lee, H. C. (2002). Risk factors for completed suicide in bipolar disorder. *The Journal of Clinical Psychiatry*, *63*(6), 469–476.

Tsai, S. Y., Kuo, C. J., Chung, K. H., Huang, Y. L., Lee, H. C., & Chen, C. C. (2009). Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *17*(12), 1004–1011. Available from https://doi.org/10.1097/JGP.0b013e3181b7ef2a.

Unutzer, J., Simon, G., Pabiniak, C., Bond, K., & Katon, W. (1998). The treated prevalence of bipolar disorder in a large staff-model HMO. *Psychiatric Services (Washington, D.C.)*, *49*(8), 1072–1078. Available from https://doi.org/10.1176/ps.49.8.1072.

Vancampfort, D., Stubbs, B., Sienaert, P., Wyckaert, S., De Hert, M., Soundy, A., & Probst, M. (2016). A comparison of physical fitness in patients with bipolar disorder, schizophrenia and healthy controls. *Disability and Rehabilitation*, *38*(20), 2047–2051. Available from https://doi.org/10.3109/09638288.2015.1114037.

Van Gerpen, M. W., Johnson, J. E., & Winstead, D. K. (1999). Mania in the geriatric patient population: A review of the literature. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *7*(3), 188–202.

Vasudev, A., & Thomas, A. (2010). Bipolar disorder' in the elderly: What's in a name? *Maturitas*, *66*(3), 231–235. Available from https://doi.org/10.1016/j.maturitas.2010.02.013.

Versiani, M., Cheniaux, E., & Landeira-Fernandez, J. (2011). Efficacy and safety of electroconvulsive therapy in the treatment of bipolar disorder: A systematic review. *The Journal of ECT*, *27*(2), 153–164. Available from https://doi.org/10.1097/YCT.0b013e3181e6332e.

W. He, D. Goodkind, & P.R. Kowal (2016). *U.S. Census Bureau, International, Population Reports. An Aging World: 2015*. Washington, DC: U.S. Government Publishing Office.

Westman, J., Hallgren, J., Wahlbeck, K., Erlinge, D., Alfredsson, L., & Osby, U. (2013). Cardiovascular mortality in bipolar disorder: A population-based cohort study in Sweden. *BMJ Open*, *3*(4). Available from https://doi.org/10.1136/bmjopen-2012-002373.

Wilkinson, S. T., Agbese, E., Leslie, D. L., & Rosenheck, R. A. (2018). Identifying recipients of electroconvulsive therapy: Data from privately insured Americans. *Psychiatric Services (Washington, D.C.)*, *69*(5), 542–548. Available from https://doi.org/10.1176/appi.ps.201700364.

Wylie, M. E., Mulsant, B. H., Pollock, B. G., Sweet, R. A., Zubenko, G. S., Begley, A. E., ... Kupfer, D. J. (1999). Age at onset in geriatric bipolar disorder. Effects on clinical presentation and treatment outcomes in an inpatient sample. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *7*(1), 77–83.

Yassa, R., Nair, N. P., & Iskandar, H. (1988). Late-onset bipolar disorder. *The Psychiatric Clinics of North America*, *11*(1), 117–131.

Young, R. C., Mulsant, B. H., Sajatovic, M., Gildengers, A. G., Gyulai, L., Al Jurdi, R. K., ... Alexopoulos, G. S. (2017). GERI-BD: A randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. *The American Journal of Psychiatry*, *174*(11), 1086–1093. Available from https://doi.org/10.1176/appi.ajp.2017.15050657.

Young, R. C., Murphy, C. F., Heo, M., Schulberg, H. C., & Alexopoulos, G. S. (2006). Cognitive impairment in bipolar disorder in old age: Literature review and findings in manic patients. *Journal of Affective Disorders*, *92*(1), 125–131. Available from https://doi.org/10.1016/j.jad.2005.12.042.

This page intentionally left blank

Chapter 13

Positive Psychiatry and successful aging in people with schizophrenia

Dilip V. Jeste[1,2,3], **Ryan Van Patten**[1,2] **and Ellen E. Lee**[1,2]

[1]Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States, [2]Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States, [3]Department of Neurosciences, University of California San Diego School of Medicine, La Jolla, CA, United States

Introduction

The discipline of psychiatry has long been associated with symptom alleviation and management in people with various forms of psychopathology. This approach is appropriate, as individuals afflicted with mental illnesses endure a tremendous amount of pain and suffering, not to mention the downstream societal burden in the form of lost wages and expanding health care costs. However, the traditional model of psychiatry is incomplete, as it fails to adequately attend to the opposite end of the mental health continuum—namely, strength-based positive psychosocial characteristics (PPCs) such as optimism, resilience, wisdom, personal mastery, coping self-efficacy, spirituality, and religiosity. These traits are at the core of the subdiscipline of positive psychiatry and are thought to mediate the movement toward improved mental health outcomes, including constructs such as well-being, low perceived stress, posttraumatic growth, recovery, and prevention of psychopathology. Importantly, empirical data have supported this perspective, as PPCs have repeatedly been associated with healthy biomarker levels and reduced mortality (Diener & Chan, 2011; Lee, Lavretsky, Renn, & Arean, 2018; Rasmussen, Scheier, & Greenhouse, 2009). Moreover, a focus on PPCs is consistent with the viewpoint of the World Health Organization (WHO), which has long advocated for a conceptualization of overall health that extends beyond symptom alleviation and absence of illness, to a state of enhanced biological, psychological, and social well-being (World Health Organization, 2018).

Commensurate with the WHO framework, the positive psychiatry movement aims to assess and therapeutically target PPCs, thereby expanding on individual strengths, (1) to provide a direct buffer against the symptoms of psychiatric disorders and (2) to maximize well-being and quality of life when clinical symptoms are persistent and treatment-resistant, such as is frequently the case in severe mental illness. Specifically, *positive psychiatry* can be defined as "the science and practice of psychiatry that seeks to understand and promote well-being through assessment and interventions aimed at enhancing behavioral and mental wellness" (Jeste, Palmer, Rettew, & Boardman, 2015, p. 676). With this in mind, the purpose of the current chapter is to provide a conceptual overview of the literature on positive psychiatry, with a focus on current evidence in a particularly severe, persistent, and treatment-resistant illness—schizophrenia.

Historical background of positive psychiatry

In 1675, Isaac Newton famously stated, "If I have seen further than others, it is by standing on the shoulders of Giants." Similar to every other field of inquiry, positive psychiatry has been shaped by the theories and ideas of those who came before it. In the early 20th century, the psychologist/physician William James advocated for the notion of a "mind-cure," conceptualized as the purported restorative powers of positive emotions and beliefs (Froh, 2004). Unfortunately, James' notions did not develop intellectual momentum at the time and it was not until about 50 years later that the mind cure was expanded and extended by Abraham Maslow and colleagues in the form of Humanistic Psychology (Maslow, 1971). Maslow contended that measuring and cultivating overall health and creativity was the best approach to improving outcomes in people with mental illnesses. However, in spite of its influence on present-day clinical

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00013-2

psychology, Humanistic Psychology was not the most direct predecessor of positive psychiatry. Instead, in the late 1990s, Martin Seligman and his colleagues advanced the epistemological precursor to positive psychiatry with the positive psychology movement (Seligman & Csikszentmihalyi, 2000). Like positive psychiatry, positive psychology aims to maximize well-being through increased scientific attention to PPCs; however, unlike positive psychiatry, which focuses on wellness in individuals afflicted with mental illnesses, positive psychology is geared toward improving outcomes in the physically, cognitively, and emotionally healthy/normative population. Moreover, while psychiatrists are trained as physicians, with a strong background in biology and disease pathophysiology, psychologists develop extensive knowledge in psychometric assessment and human behavior. Consequently, these two subdisciplines are related but distinct and complementary rather than competitive. As an area of inquiry, positive psychiatry is still in its infancy, and although there have been a number of recent efforts to advance the overall concepts and clinical recommendations (Eglit, Palmer, & Jeste, 2018; Jeste & Palmer, 2015; Jeste et al., 2015; Jeste, Palmer, & Saks, 2017), current empirical data on PPCs and positive mental health outcomes in people with schizophrenia remain scarce.

Schizophrenia

Schizophrenia is a multifaceted neurodevelopmental disorder with cognitive, emotional, physical, and functional sequelae. Frequently, subtle signs of the illness are evident in childhood and adolescence, with severe psychiatric symptoms often manifesting in adolescence or early adulthood. Schizophrenia is also associated with accelerated physical aging (Jeste, Wolkowitz, & Palmer, 2011) such that people with schizophrenia die 15−20 years earlier than people without the disorder. Our recent review of the literature showed that the mortality gap between people with schizophrenia and general population has increased by 30% since the 1970s (Lee, Martin, Tu, Palmer, & Jeste, 2018; Lee, Liu, et al., 2018). Importantly, suicide and accidents are not the primary explanation for this large discrepancy; instead, it is due primarily to earlier onset of the same age-related chronic disease processes that affect nonpsychiatric samples (e.g., cardiovascular disease, metabolic dysregulation). Fortunately, however, in contrast with physical aging, cognitive and psychosocial aging in schizophrenia do not appear to be accelerated relative to the general population. Cognitive abilities are negatively impacted from a young age in people who ultimately develop schizophrenia (often before the disorder itself is recognized), but the slope of decline from adulthood to older adulthood is comparable to the slope of decline in healthy older adults (Heaton et al., 2001). Moreover, psychosocial aging in this population is associated with improvements in functioning (e.g., fewer relapses and enhanced overall mental health), and there are a number of useful interventions for people with schizophrenia of all ages, including antipsychotic pharmacotherapy and cognitive behavioral therapy (CBT), among others (see below). Consequently, older adults with schizophrenia contend with a variety of physical ailments and residual psychiatric symptoms, but their level of everyday functioning need not decline.

Assessment in positive psychiatry

Positive psychiatry does not minimize or ignore the suffering of people with mental illnesses. Moreover, it is not a naïve, feel-good pseudoscience that views the world through rose-colored glasses. Instead, it is an evidence-based approach to understanding psychopathology and improving the lives of psychiatric patients by objectively measuring and then enhancing PPCs. Indeed, all aspects of the assessment process are integral to positive psychiatry and both researchers and clinicians already have access to a large armamentarium of objective self-report inventories with excellent psychometric properties, in order to quantify the degree of various PPCs in their research participants and patients (Eglit et al., 2018).

Although the field of self-report measurement has been criticized due to both conscious (e.g., deliberate deception) and unconscious (e.g., impression management) biases in human introspection and subsequent reporting (see Chan, 2009 for a review), such criticisms apply more to the evaluation of some constructs than others. For example, self-reported historical behavior that may be stigmatized (e.g., alcohol use, sexual experiences) is quite susceptible to biased reporting (Del Boca & Darkes, 2003; Schroder, Carey, & Vanable, 2003). On the other hand, self-report inventories for recent subjective internal states such as happiness, optimism, well-being, and subjective recovery are fully appropriate, as these constructs are inherently tied to an individual's introspective feelings rather than an external biological or historical proxy (Eglit et al., 2018; Kukla, Lysaker, & Roe, 2014). As a concrete example, in order to determine someone's level of happiness, would it make more sense to collect cerebrospinal fluid and test for biomarkers of pathology, or to simply ask them about their current inner experiences? The answer is obvious.

In addition to the aforementioned self-report paper-pencil assessment measures, in which answers are severely constrained by limited response options, there have also been several impactful qualitative investigations of coping

strategies in people living with schizophrenia (Cohen & Berk, 1985; Corin, 1990, 1992). Compared to closed-ended multiple-choice inventories, this approach confers much more flexibility and autonomy to participants in the disclosing of their subjective experiences. For example, Shepherd and colleagues (2012) interviewed 32 older adults with schizophrenia about the longitudinal course of their symptom expression and their overall quality of life and wellness. Most participants endorsed trouble managing the initial symptom onset, leading to confusion and interpersonal isolation. However, the vast majority of these people bounced back later in life due to improved coping techniques, leading to attenuated symptoms and a higher level of functioning. Even more recently, Cohen and colleagues (2017) interviewed people with schizophrenia who had achieved a high degree of occupational attainment in spite of their illness. Participants reported utilizing a number of successful coping strategies, including maintaining a routine, cultivating spirituality, using recovery-oriented language, and focusing energy on school and work, thereby providing examples of positive psychiatry in practice. That is, these individuals were able to strive for and attain a greater level of wellness within their illness, through the use of adaptive coping strategies in the face of severe clinical symptoms.

Positive psychosocial characteristics

Prior reviews have fully delineated the current state of the literature on PPCs (Jeste & Palmer, 2015; Jeste et al., 2015). In the current chapter, we summarize the few investigations of PPCs in people with schizophrenia (primarily cross-sectional), with an eye toward future opportunities to advance this literature.

Van Patten and colleagues (2019) examined a three-dimensional wisdom framework (cognitive, affective, and reflective; Ardelt, 2003) in 65 adult outpatients with chronic psychotic disorders and 96 nonpsychiatric comparison participants. Reflective wisdom, representing personal insight and the ability to engage in perspective taking, was positively correlated with mental health across nine measures in people with schizophrenia. Moreover, the overall wisdom moderated the relationship between diagnosis (schizophrenia or control) and cognitive outcomes such that patients who were higher in wisdom performed better than those who were lower in wisdom. This suggests that reflective wisdom is integral to multiple aspects of mental health and that overall wisdom may mitigate the impact of schizophrenia on cognitive performance.

Palmer, Martin, Depp, Glorioso, and Jeste (2014) measured the construct of happiness in 72 outpatients with chronic schizophrenia and 64 healthy comparison participants. Although the control group earned higher average scores on the happiness scale compared to the schizophrenia group, the latter exhibited significant variability in happiness. Moreover, happiness was positively correlated with multiple additional PPCs (resilience, optimism, and mastery) and was negatively correlated with perceived stress. Overall, the authors concluded that it is possible to achieve happiness in severe mental illness and that this construct should be considered to be a prime therapeutic target in future interventions.

Lee , Martin, et al. (2018) assessed degree of resilience and mental and physical health in 114 people with schizophrenia and 101 comparison participants. Additionally, they also retrospectively measured childhood emotional abuse/neglect, physical abuse/neglect, and sexual abuse in the sample. Their most notable result was that resilience served a protective function against the negative mental and physical health effects of trauma and adversity. In contrast to those who were low in resilience, participants who were high in resilience did not report as many negative effects of childhood adverse events and their metabolic biomarker levels were comparable to controls who did not experience significant trauma. This suggests that resilience serves as a buffer against early and severe psychosocial stress in schizophrenia. The importance of this finding cannot be understated, given the greatly increased rates of abuse and neglect in this vulnerable population (Bendall, Jackson, Hulbert, & McGorry, 2007).

Johnson and colleagues (2010) recorded suicidal ideation, hopelessness, and positive self-appraisals in 77 individuals with psychotic disorders. Statistical analyses revealed that positive self-appraisals moderated the relationship between hopelessness (a predictor of self-harm) and suicidal ideation such that those patients who were high in hopelessness but who also possessed positive self-appraisals were significantly less likely to endorse suicidal ideation. Given high rates of suicide in people with schizophrenia (approximately 5%; Palmer, Pankratz, & Bostwick, 2005), the enhancement of PPCs capable of decreasing the probability of this event should be a top priority in future research and clinical intervention.

Kukla and colleagues (2014) measured subjective recovery—or perceptions and inner experiences related to meaning-making in the face of psychiatric illness—as well as clinical symptoms and quality of life in 68 veterans with psychotic disorders. The authors reported that subjective recovery mitigated the deleterious impact of positive psychotic symptoms on quality of life such that participants with high degrees of subjective recovery were nevertheless able to attain high levels of experiential and external quality of life. This finding is significant inasmuch as it shows that PPCs can facilitate positive outcomes in people with schizophrenia, even in the face of severe symptomatology.

Finally, religiosity and spirituality are more common in people with schizophrenia as compared to people without psychotic disorders (Huguelet, Mohr, Borras, Gillieron, & Brandt, 2006). This issue is complex and multifaceted, as such practices can have positive effects on health, but religious hallucinations/delusions can also play a central role in patients' clinical symptom profiles. With this in mind, Mohr, Brandt, Borras, Gilliéron, and Huguelet (2006) measured religiosity and spirituality in 115 outpatients with schizophrenia and related disorders using semistructured clinical interviews. In terms of the impact of these constructs on relevant outcomes, a small minority of participants described negative effects on wellness and mental health. However, 71% endorsed increased hope, purpose, and meaning, 54% reported attenuated psychotic symptomatology, 28% described more positive social interactions, and 33% indicated a lower risk of suicide related to increased religiosity and spirituality. Overall, many participants described the healing properties of religious practices and indicated that their faith helped them through their illness in ways that secular resources could not. After the completion of the 2006 study, the authors followed the same cohort of people for 3 years and reported on longitudinal predictive outcomes of religious coping (Mohr et al., 2011). Participants who engaged in healthy religious coping strategies and who valued spirituality experienced lower degrees of negative symptomatology and improved interpersonal functioning and quality of life.

Cognition

Although not typically a focus of positive psychiatry, neurocognition is integral to therapeutic outcomes in psychiatric disorders in general (Beaudreau, Rideaux, O'Hara, & Arean, 2015; Goodkind et al., 2016) and to the clinical profile of people with schizophrenia in particular. Indeed, a wealth of evidence has shown that people with schizophrenia often experience severe and persistent cognitive impairments across multiple domains, including attention/vigilance, processing speed, working memory, visual and verbal memory, and aspects of executive functioning (Keefe & Harvey, 2012), leading to significant functional deficits (Green, Kern, & Heaton, 2004). Findings showing cognitive impairment in schizophrenia have been repeated in hundreds of studies, across decades of research, and in a wide variety of different geographic locations around the world (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). However, there exists a subset of people with schizophrenia who are cognitively intact, with estimates ranging from 2% (Keefe, Eesley, & Poe, 2005) to 27% (Palmer et al., 1997). Given the close relationship between cognition and important outcomes such as quality of life (Mohamed et al., 2008), social problem-solving (Green, Kern, Braff, & Mintz, 2000), occupational and economic capacity (Keefe & Harvey, 2012), community functioning (Green et al., 2004), interpersonal interactions (Milev, Ho, Arndt, & Andreasen, 2005), and instrumental skills (Green et al., 2000), the ability to maintain intact cognitive abilities in the face of psychotic symptoms can certainly be conceptualized as a critical facet of positive psychiatry. To this end, several interventions have shown promise in improving cognitive outcomes in people with psychotic disorders. Twamley et al. (2017), Twamley, Savla, Zurhellen, Heaton, and Jeste (2008), and Twamley, Vella, Burton, Heaton, and Jeste (2012) have repeatedly reported on the efficacy of compensatory cognitive training (CCT) in schizophrenia, involving strategies to enhance attention, learning and memory, prospective memory, and aspects of executive functioning. Additionally, in a 2-year randomized controlled trial, Hogarty and colleagues (2004) and Eack et al. (2010) showed that a multimodal intervention approach—cognitive enhancement therapy—significantly improved cognitive performance and protected against gray matter loss. Clearly, cognition is amenable to improvement in schizophrenia and the literature strongly supports the existence of interventions capable of buffering against illness-mediated cognitive deficits (also see Etkin, Gyurak, & O'Hara, 2013).

Successful biopsychosocial aging

Chronological aging is associated with increases in both physical (Mittlemark et al., 1993) and cognitive (Small et al., 1997) ailments. However, in spite of these challenges, a large number of older adults exhibit so-called "successful aging" (Jeste, Depp, & Vahia, 2010; Jeste et al., 2013). This concept was originally conceptualized simply as the absence of significant disease burden, but—consistent with the positive psychiatry movement—more recent data suggest that the key factor in successful aging is not merely the absence of illness, but rather the overall psychological outlook of the individual (Jeste et al., 2010; Reichstadt, Depp, Palinkas, & Jeste, 2007). Indeed, the importance of emotional health in aging is exemplified by the positivity effect, which represents the tendency for older adults to experience a higher ratio of positive to negative emotions relative to younger adults (Mather & Carstensen, 2005). It is posited that a reduction in the tendency to experience unpleasant emotions, along with equivalent experience of pleasant emotions, drives the positivity effect. The construct is manifested in cognitive processes such as attention, where older adults utilize top-down processes to selectively and preferentially attend to positive rather than negative stimuli, and

memory, where they display a bias toward the recall of positive experiences. These cognitive strategies are utilized to elevate mood, despite declining cognitive resources, ultimately leading many older adults to embody successful aging.

In addition to a psychological basis for successful aging, there is also a wealth of neurobiological data as well. Specifically, contrary to traditional beliefs, neuroplasticity continues into old age (albeit to a lesser degree than in younger individuals), allowing for the possibility of new learning and adaptation in the context of sufficient environmental stimulation (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). Mechanisms underlying plasticity in older adults include neural compensation for age-related decline through the recruitment of additional brain circuits in the performance of tasks, dendritic arborization and synapse proliferation, increased vascularity, and a limited degree of neurogenesis (e.g., in the hippocampal dentate gyrus; Gage, 2002).

The presence of biopsychosocial processes underlying growth and well-being in old age is incredibly important for the field of schizophrenia research. It has been widely reported that a substantial proportion of people with schizophrenia experience symptom reduction as they age (Jeste et al., 2011), in spite of the fact that accelerated biological senescence often leads to early mortality (Crump, Winkleby, Sundquist, & Sundquist, 2013; Kirkpatrick, Messias, Harvey, Fernandez-Egea, & Bowie, 2008). On average, older adulthood in schizophrenia brings rapid declines in physical health, typical rates of decline in cognitive health (albeit with lower cognitive baselines), and improvements in emotional health (Jeste et al., 2011). The field of positive psychiatry is poised to address aging in schizophrenia by capitalizing on PPCs such as wisdom (Van Patten et al., 2019), resilience (Lee, Liu, et al., 2018; Lee, Martin, et al., 2018), happiness (Palmer et al., 2014), positive self-appraisals (Johnson et al., 2010), and subjective recovery (Kukla et al., 2014), in order to maximize quality and duration of life for people with schizophrenia.

Biology

Potential biomarkers of positive psychiatry

In addition to their effects on emotional and cognitive health, PPCs are closely related to physical health as well. Empirical evidence supports links between biomarkers and measures of positive psychiatry, including allostatic load, telomere length, inflammation, and genes, although the literature on the impact of these factors in people with schizophrenia is sparse.

Allostatic load. Allostatic load, or the cumulative toll on the body as it adapts to environmental stressors, has important implications for physical disease. For example, a sustained stress response (as measured by cortisol) can precipitate a series of changes that negatively impact neuroplasticity, resulting in a deleterious effect on cognitive functioning (McEwen, 1998). Indices of allostatic load have included measures related to cardiovascular function, metabolic regulation, immune function, and cortisol excretion/metabolism, including the following: blood pressure, heart rate, body mass index, waist-to-hip ratio, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, glycated hemoglobin (HbA1C), C-reactive protein, albumin, blood glucose dehydroepiandrosterone, epinephrine, norepinephrine, and cortisol (Seeman, McEwen, Rowe, & Singer, 2001; Viljoen & Claassen, 2017). Importantly, studies have shown that PPCs such as social support, optimism, hope, and personal mastery are associated with decreased allostatic load (Meeks et al., 2016; Wiley, Bei, Bower, & Stanton, 2017). Conversely, psychosocial stressors such as childhood abuse and neglect, as well as impaired sociability and low empathy, are associated with increased allostatic load (Laviola et al., 2017; Rogosch, Dackis, & Cicchetti, 2011).

Telomere length. Telomeres, or the noncoding sequences at the ends of chromosomes, protect vital genetic material from deterioration. The length of telomeres decreases with repeated cell divisions and is inversely associated with aging. Persons with low psychosocial resources (i.e., low social support, low optimism) and greater childhood adversity have increased telomerase activity and shorter telomere length (Zalli et al., 2014). On the other hand, persons with greater optimism and higher emotional intelligence have longer telomeres, even after controlling for age and gender (Schutte, Palanisamy, & McFarlane, 2016).

Inflammation and immune function. Inflammation and dysregulated immune function are also associated with PPCs. Children and adults with higher perceived self-efficacy (Breines et al., 2014; Caserta, Wyman, Wang, Moynihan, & O'Connor, 2011), optimism (Ikeda et al., 2011), empathy (Manczak, DeLongis, & Chen, 2016), spirituality (Seeman, Dubin, & Seeman, 2003), and engagement with pleasant activities (Mausbach, Harmell, Moore, & Chattillion, 2011) have less systemic inflammation (e.g., lower levels of pro-inflammatory cytokines, interleukin-6 and C-reactive protein). Additionally, high levels of personal mastery may be protective against the inflammatory consequences of chronic stress and exposure to trauma (Elliot, Mooney, Infurna, & Chapman, 2017; Mausbach, Aschbacher, et al., 2008;

Mausbach et al., 2007; Mausbach, von Kanel, et al., 2008). Finally, evidence shows that self-efficacy moderates the relationship between subjective stress and interleukin-6 levels among dementia caregivers (Mausbach et al., 2007).

Genetics and epigenetics. The genetic and epigenetic basis underlying PPCs is complex, often moderating the impact of environmental stressors on well-being. The literature is extensive and we provide a nonexhaustive sampling of the available evidence.

The rs53576 polymorphism of the oxytocin receptor gene (OXTR) modulates amygdala activation and is associated with social cognition, empathy, and optimism (Ebert & Brune, 2018; Huetter et al., 2016; Mosing, Zietsch, Shekar, Wright, & Martin, 2009; Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011). Relatedly, the T-allele carriers of the rs2268498 OXTR polymorphism have been found to have better implicit learning performance, which may play a key role in social functioning and link to higher self-reported empathy (Melchers et al., 2017). Adding to the OXTR literature, several studies also suggest that the vasopressin receptor genes are tied to prosociality and emotional empathy (Uzefovsky et al., 2015; Wu, Shang, & Su, 2015).

Genes linked with resilience have varied functions, from hypothalamic-pituitary-adrenal axis activity to neurotransmitter involvement (Feder, Nestler, & Charney, 2009; Waaktaar & Torgersen, 2012). Serotonin transporter gene polymorphisms have been shown to interact with childhood adversity, affecting (and potentially protecting against) the development of anxiety and affective disorders (Schiele et al., 2016). Genes related to the stress axis, such as the corticotropin-releasing hormone receptor 1, may influence cognitive and emotional empathy and thus vulnerability to the psychopathology associated with childhood adversity (Grimm et al., 2017).

The BDNF Val66Met polymorphism, thought to be a key modulator of illness in schizophrenia (Notaras, Hill, & van den Buuse, 2015), is associated with increased self-reported empathy (Davis' Interpersonal Reactivity Index; Taschereau-Dumouchel et al., 2016). Meanwhile, the Val158Met COMT polymorphism has been associated with worse social cognition in persons with schizophrenia (Tylec, Jeleniewicz, Mortimer, Bednarska-Makaruk, & Kucharska, 2017).

Clinical implications

Clearly, PPCs have implications for mental, cognitive, and physical health. For example, optimism, self-efficacy, and perceived social support play important roles in patients' adoption of behavioral interventions, as well as how they understand their medical illnesses (Bekke-Hansen, Weinman, Thastum, Thygesen, & Zachariae, 2014). As reviewed above, Lee and colleagues (2018) have shown that increased resilience in adulthood is associated with improved insulin resistance and glucose homeostasis in adults with childhood adversity, suggesting that resilience may buffer against the negative health effects of adversity. Similar work has found that children with better self-regulation of emotional and behavioral responses may be protected from the cognitive deficits associated with childhood poverty (Evans & Fuller-Rowell, 2013). Thus, PPCs may enable individuals to overcome the detrimental health effects associated with stress. PPCs may even contribute to increased longevity and reduced mortality, an outcome with significant implications for people with schizophrenia (Diener & Chan, 2011; Rasmussen et al., 2009). On an evolutionary level, it has been proposed that empathy improves species survival by promoting communal societies that confer protection for individuals, as well as allowing them to avoid social isolation/ostracism that could lead to a physiological stress response (Lahvis, 2016).

Overall psychosocial resources and specific behavioral interventions can improve psychological well-being and thus promote overall mental and physical health (McEwen & Getz, 2013). Mindfulness interventions have been shown to improve the body's physiological response to stress by promoting acceptance and nonreactivity toward potential stressors, thereby facilitating constructive reframing (Garland, Hanley, Baker, & Howard, 2017). Additionally, neuroimaging studies suggest that mindfulness enhances neurocircuitry associated with increased empathy and emotional processing (Hofmann, Grossman, & Hinton, 2011). Although there has been some historical concern about the possibility of meditation leading to symptom exacerbation (and potentially even an acute psychotic episode) in schizophrenia (Chadwick, 2014; Garden, 2007), a recent meta-analysis of 13 studies (468 patients) showed moderate positive effects of mindfulness interventions on negative symptoms in schizophrenia (Khoury, Lecomte, Gaudiano, & Paquin, 2013).

Similar to mindfulness, yoga-based treatments have been demonstrated to have a positive impact on self-regulation and psychological resilience (Sullivan et al., 2018). Ayurvedic intervention (which incorporates yoga, medication, diet, massage, didactic education, and self-reflective journaling) improves spirituality, self-compassion, and gratitude, and it reduces anxiety (Mills et al., 2016). One systematic review and meta-analysis of the impact of yoga on clinical outcomes in people with schizophrenia [five randomized clinical trials (RCTs)]; 337 patients showed moderate effect sizes for quality of life, but yoga interventions did not outperform an exercise treatment (Cramer, Lauche, Klose, Langhorst,

& Dobos, 2013). On the other hand, a different systematic review of the potential for yoga as an adjunct to conventional psychological treatments (three RCTs; 125 patients) reported lower psychotic symptomatology and improved quality of life compared to wait-list control and exercise interventions (Vancampfort et al., 2012).

A therapeutic approach that is related to but distinct from mindfulness and yoga is focused compassion training. Self-compassion meditation training has wide-ranging positive effects, including reducing anxiety and improving physiological responses to social stressors (Arch, Landy, & Brown, 2016). Compassion meditation has also been shown to decrease social stress−induced inflammation (Pace et al., 2009). Adding to the literature on compassion, increased spirituality is associated with improved depressive symptoms (Rickhi et al., 2015), decreased risk for mental disorders, and increased purpose in life, gratitude, and posttraumatic growth (Sharma et al., 2017). Moreover, as reviewed above, empirical evidence suggests that spirituality and religiosity can be protective in people with schizophrenia (Mohr et al., 2006, 2011).

Specific to people with psychotic disorders, Twamley and colleagues (2008, 2012, 2017) have demonstrated the effectiveness of CCT in improving cognition in schizophrenia (see *Cognition* section above). As part of a more traditional psychological intervention, Granholm et al. (2005, 2007), Granholm, Holden, Link, McQuaid, and Jeste (2013), and Granholm, Holden, Link, and McQuaid (2014) developed Cognitive Behavioral Social Skills Training (CBSST). CBSST capitalizes on the individual effectiveness of both CBT (Rector & Beck, 2001) and social skills training (Penn & Mueser, 1996), integrating the treatments together to target maladaptive thoughts and behaviors in the everyday interpersonal context. To date, CBSST has successfully increased insight, improved interpersonal skills, reduced negative symptoms (amotivation, asociality, and defeatist performance beliefs), and enhanced overall functional outcomes in people with schizophrenia (Granholm, Ben-Zeev, & Link, 2009; Granholm et al., 2005, 2013, 2014), with some effects lasting for at least 12 months (Granholm et al., 2007).

Limitations

Despite the clear economic and societal costs of poor health and the strong association between PPCs and health, clinical research and care in psychiatry remains focused on addressing DSM disorders. While most clinicians ask standard questions regarding symptomatology and functional deficits, there is rarely a deliberate assessment of PPCs. Moreover, the literature supporting positive psychiatry is growing, but there is still a need for more rigorous and well-powered RCTs testing PPC-focused interventions. To translate the experimental results to a clinical setting will require further study and a clear infrastructure to support such assessments and interventions.

An important *caveat* to the theory and practice of both positive psychiatry and positive psychology is the notion of "too much of a good thing." That is, the relationship between many psychological traits (including at least some PPCs) and overall functioning/well-being exists in a nonmonotonic inverted U shape. Enhancing these characteristics leads to functional improvements until a threshold is reached (the middle of the inverted U), at which point continued increases can have adverse consequences (Grant & Schwartz, 2011). For example, excessive optimism can precipitate risky medical and health-related choices, ultimately leading to negative outcomes (Milam, Richardson, Marks, Kemper, & McCutchan, 2004). Similarly, extreme happiness has been associated with a lack of attention to prophylactic health behaviors, leading to increased mortality (Martin et al., 2002).

In the context of the positive psychiatry movement, we must place these findings into the context of mental illness. Excessive PPCs are intuitively related to the symptom profile of some psychiatric disorders (e.g., bipolar disorder, narcissistic personality disorder). On the other hand, most individuals with schizophrenia are much more likely to reside on the left-hand side of the inverted U when it comes to PPCs reviewed in this chapter, including optimism, resilience, wisdom, happiness, personal mastery, and coping self-efficacy. Consequently, enhancing these traits will improve well-being in the vast majority of people with psychotic disorders.

Future directions

The future of positive psychiatry for persons with serious mental illnesses is promising. Rising costs, as well as challenges such as obesity and opioid epidemics, have overextended the health care system, limiting our ability to adequately treat a plethora of physical and mental illnesses. In response to this changing landscape, preventative medicine may be the most powerful and cost-reducing method for maximizing quality of life in the general population. A focus on enhancing overall wellness, and PPCs in particular, is consistent with a preventative medicine approach, as optimal degrees of positive traits can buffer against the negative impact of psychiatric disorders (Johnson et al., 2010; Kukla et al., 2014; Lee, Liu, et al., 2018; Lee, Martin, et al., 2018; Van Patten et al., 2019).

If adults all over the world were to drastically improve their diet, sleep, and daily cognitive, social, and physical activities, the incidence of heart disease, stroke, and certain cancers would quickly plummet. And yet, lifestyle interventions, especially in populations with serious mental illnesses, are some of the most difficult to implement and sustain. Rather than swallowing a pill, people must first alter their attitudes in order to usher in behavioral changes. As has been stated by neuroscientists, "the brain has its own drugstore," (Rendell & Anch, 2011). Unfortunately, however, many people underappreciate the power of changes in thinking styles and habitual behaviors on neural circuitry. Psychiatrists, clinical psychologists, and other mental health workers are uniquely suited to address these issues, given their theoretical knowledge of psychopathology and behavioral change interventions. With this in mind, we envision future positive psychiatry clinics, where patients would receive personalized strength-based assessments and interventions to bolster PPCs. Patients would recognize the true importance of PPCs, as well as the need to implement behavioral and cognitive changes in order to enhance PPCs. Clinicians would track patients' progress longitudinally and investigate the contribution of environmental stressors versus maladaptive internal schemas. Such clinics would promote wellness using a holistic, evidence-based approach and include training programs for clinicians to expand their competencies with respect to positive psychiatric evaluations.

Conclusion

Positive psychiatry is poised to revolutionize the assessment and treatment of people suffering from psychopathology, particularly those afflicted with severe mental illnesses. There already exists a wide array of psychometrically sound instruments to measure the core facets of positive psychiatry—PPCs. Utilizing many of these tests, researchers have assessed wisdom, happiness, resilience, positive self-appraisals, subjective recovery, and religion and spirituality in schizophrenia, and this literature suggests that PPCs serve as protective factors against the negative effects of illness on health and well-being. Moreover, in addition to traditional PPCs, cognition is closely tied to functional outcomes in schizophrenia and there are empirically supported interventions capable of enhancing cognition in this population. Finally, research in successful aging strongly suggests the potential for enhancement of PPCs in older adults, mediated by continued neuroplasticity. We believe that the future of positive psychiatry is bright and we look forward to its continued development and integration into the discipline of psychiatry more broadly.

References

Arch, J. J., Landy, L. N., & Brown, K. W. (2016). Predictors and moderators of biopsychological social stress responses following brief self-compassion meditation training. *Psychoneuroendocrinology*, *69*, 35−40. Available from https://doi.org/10.1016/j.psyneuen.2016.03.009.

Ardelt, M. (2003). Empirical assessment of a three-dimensional wisdom scale. *Research on Aging*, *25*(3), 275−324. Available from https://doi.org/10.1177/0164027503025003004.

Beaudreau, S. A., Rideaux, T., O'Hara, R., & Arean, P. (2015). Does cognition predict treatment response and remission in psychotherapy for late-life depression? *The American Journal of Geriatric Psychiatry*, *23*(2), 215−219. Available from https://doi.org/10.1016/j.jagp.2014.09.003.

Bekke-Hansen, S., Weinman, J., Thastum, M., Thygesen, K., & Zachariae, R. (2014). Psycho-social factors are important for the perception of disease in patients with acute coronary disease. *Heredity*, *3*, 1−4.

Bendall, S., Jackson, H. J., Hulbert, C. A., & McGorry, P. D. (2007). Childhood trauma and psychotic disorders: A systematic, critical review of the evidence. *Schizophrenia Bulletin*, *34*(3), 568−579. Available from https://doi.org/10.1093/schbul/sbm121.

Breines, J. G., Thoma, M. V., Gianferante, D., Hanlin, L., Chen, X., & Rohleder, N. (2014). Self-compassion as a predictor of interleukin-6 response to acute psychosocial stress. *Brain, Behavior, and Immunity*, *37*, 109−114. Available from https://doi.org/10.1016/j.bbi.2013.11.006.

Caserta, M. T., Wyman, P. A., Wang, H., Moynihan, J., & O'Connor, T. G. (2011). Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children. *Development and Psychopathology*, *23*(04), 1139−1147. Available from https://doi.org/10.1017/S0954579411000526.

Chadwick, P. (2014). Mindfulness for psychosis. *British Journal of Psychiatry*, *204*(05), 333−334. Available from https://doi.org/10.1192/bjp.bp.113.136044.

Chan, D. (2009). *So why ask me? Are self-report data really that bad?* New York, NY: Taylor & Francis Group.

Cohen, A. N., Hamilton, A. B., Saks, E. R., Glover, D. L., Glynn, S. M., Brekke, J. S., & Marder, S. R. (2017). How occupationally high-achieving individuals with a diagnosis of schizophrenia manage their symptoms. *Psychiatric Services*, *68*(4), 324−329. Available from https://doi.org/10.1176/appi.ps.201600031.

Cohen, C., & Berk, L. A. (1985). Personal coping styles of schizophrenia outpatients. *Psychiatric Services*, *36*(4), 407−410.

Corin, E. E. (1990). Facts and meaning in psychiatry. An anthropological approach to the lifeworld of schizophrenics. *Culture, Medicine, and Psychiatry*, *14*(2), 153−188.

Corin, E. E. (1992). Positive withdrawal and the quest for meaning: The reconstruction of experience among schizophrenics. *Psychiatry*, *55*(3), 266−278.

Cramer, H., Lauche, R., Klose, P., Langhorst, J., & Dobos, G. (2013). Yoga for schizophrenia: A systematic review and meta-analysis. *BMC Psychiatry*, *13*(1), 32. Available from https://doi.org/10.1186/1471-244X-13-32.

Crump, C., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: A Swedish national cohort study. *American Journal of Psychiatry*, *170*(3), 324–333. Available from https://doi.org/10.1176/appi.ajp.2012.12050599.

Del Boca, F. K., & Darkes, J. (2003). The validity of self-reports of alcohol consumption: State of the science and challenges for research. *Addiction*, *98*, 1–12.

Diener, E., & Chan, M. Y. (2011). Happy people live longer: Subjective well-being contributes to health and longevity: Health benefits of happiness. *Applied Psychology: Health and Well-Being*, *3*(1), 1–43. Available from https://doi.org/10.1111/j.1758-0854.2010.01045.x.

Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M. R., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: Results from a 2-year randomized controlled trial. *Archives of General Psychiatry*, *67*(7), 674. Available from https://doi.org/10.1001/archgenpsychiatry.2010.63.

Ebert, A., & Brune, M. (2018). Oxytocin and social cognition. *Current Topics in Behavioral Neurosciences*, *35*, 375–388.

Eglit, G. M. L., Palmer, B. W., & Jeste, D. V. (2018). Overview of measurement-based positive psychiatry. *Nordic Journal of Psychiatry*, *72*, 396–403.

Elliot, A. J., Mooney, C. J., Infurna, F. J., & Chapman, B. P. (2017). Associations of lifetime trauma and chronic stress with c-reactive protein in adults ages 50 years and older: Examining the moderating role of received control. *Psychosomatic Medicine*, *79*(6), 622–630.

Etkin, A., Gyurak, A., & O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Translational Research*, *15* (4), 419–429.

Evans, G. W., & Fuller-Rowell, T. E. (2013). Childhood poverty, chronic stress, and young adult working memory: The protective role of self-regulatory capacity. *Developmental Science*, *16*(5), 688–696.

Feder, A., Nestler, E. J., & Charney, D. S. (2009). Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience*, *10*(6), 446–457. Available from https://doi.org/10.1038/nrn2649.

Froh, J. J. (2004). The history of positive psychology: Truth be told. *NYS Psychologist*, *16*(3), 18–20.

Gage, F. H. (2002). Neurogenesis in the adult brain. *The Journal of Neuroscience*, *22*(3), 612–613.

Garden, M. (2007). Can meditation be bad for you? *The Humanist*, 22–27.

Garland, E.L., Hanley, A.W., Baker, A.K., & Howard, M.O. (2017). *Biobehavioral mechanisms of mindfulness as a treatment for chronic stress: An RDoC perspective*. Thousand Oaks, CA.

Goodkind, M. S., Gallagher-Thompson, D., Thompson, L. W., Kesler, S. R., Anker, L., Flournoy, J., ... O'Hara, R. M. (2016). The impact of executive function on response to cognitive behavioral therapy in late-life depression: Executive function and CBT response in late-life depression. *International Journal of Geriatric Psychiatry*, *31*(4), 334–339. Available from https://doi.org/10.1002/gps.4325.

Granholm, E., Ben-Zeev, D., & Link, P. C. (2009). Social disinterest attitudes and group cognitive-behavioral social skills training for functional disability in schizophrenia. *Schizophrenia Bulletin*, *35*(5), 874–883.

Granholm, E., Holden, J., Link, P. C., McQuaid, J. R., & Jeste, D. V. (2013). Randomized controlled trial of cognitive behavioral social skills training for older consumers with schizophrenia: Defeatist performance attitudes and functional outcome. *The American Journal of Geriatric Psychiatry*, *21*(3), 251–262.

Granholm, E., Holden, J., Link, P. C., & McQuaid, J. R. (2014). Randomized clinical trial of cognitive behavioral social skills training for schizophrenia: Improvement in functioning and experiential negative symptoms. *Journal of Consulting and Clinical Psychology*, *82*(6), 1173–1185.

Granholm, E., McQuaid, J. R., McClure, F. S., Auslander, L. A., Perivoliotis, D., Pedrelli, P., ... Jeste, D. V. (2005). A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. *American Journal of Psychiatry*, *162* (3), 520–529.

Granholm, E., McQuaid, J. R., McClure, F. S., Link, P. C., Perivoliotis, D., Gottlieb, J. D., ... Jeste, D. V. (2007). Randomized controlled trial of cognitive behavioral social skills training for older people with schizophrenia: 12-month follow-up. *Journal of Clinical Psychiatry*, *68*(5), 730–737.

Grant, A. M., & Schwartz, B. (2011). Too much of a good thing: The challenge and opportunity of the Inverted U. *Perspectives on Psychological Science*, *6*(1), 61–76. Available from https://doi.org/10.1177/1745691610393523.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the "right stuff"? *Schizophrenia Bulletin*, *26*(1), 119–136. Available from https://doi.org/10.1093/oxfordjournals.schbul.a033430.

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: Implications for MATRICS. *Schizophrenia Research*, *72*(1), 41–51. Available from https://doi.org/10.1016/j.schres.2004.09.009.

Grimm, S., Wirth, K., Fan, Y., Weigand, A., Gärtner, M., Feeser, M., ... Aust, S. (2017). The interaction of corticotropin-releasing hormone receptor gene and early life stress on emotional empathy. *Behavioural Brain Research*, *329*, 180–185. Available from https://doi.org/10.1016/j.bbr.2017.04.047.

Heaton, R. K., Gladsjo, J. A., Palmer, B. W., Kuck, J., Marcotte, T. D., & Jeste, D. V. (2001). Stability and course of neuropsychological deficits in schizophrenia. *Archives of General Psychiatry*, *58*(1), 24–32.

Hofmann, S. G., Grossman, P., & Hinton, D. E. (2011). Loving-kindness and compassion meditation: Potential for psychological interventions. *Clinical Psychology Review*, *31*(7), 1126–1132. Available from https://doi.org/10.1016/j.cpr.2011.07.003.

Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., & Zoretich, R. (2004). Cognitive enhancement therapy for schizophrenia: Effects of a 2-year randomized trial on cognition and behavior. *Archives of General Psychiatry*, *61*, 866–876.

Huetter, F. K., Bachmann, H. S., Reinders, A., Siffert, D., Stelmach, P., Knop, D., ... Siffert, W. (2016). Association of a common oxytocin receptor gene polymorphism with self-reported "empathic concern" in a large population of healthy volunteers. *PLoS One*, *11*(7), e0160059. Available from https://doi.org/10.1371/journal.pone.0160059.

Huguelet, P., Mohr, S., Borras, L., Gillieron, C., & Brandt, P.-Y. (2006). Spirituality and religious practices among outpatients with schizophrenia and their clinicians. *Psychiatric Services*, *57*(3), 366–372. Available from https://doi.org/10.1176/appi.ps.57.3.366.

Ikeda, A., Schwartz, J., Peters, J. L., Fang, S., Spiro, A., Sparrow, D., ... Kubzansky, L. D. (2011). Optimism in relation to inflammation and endothelial dysfunction in older men. *Psychosomatic Medicine*, *73*(8), 664–671.

Jeste, D. V., Depp, C. A., & Vahia, I. V. (2010). Successful cognitive and emotional aging. *World Psychiatry*, *9*(2), 78–84. Available from https://doi.org/10.1002/j.2051-5545.2010.tb00277.x.

Jeste, D. V., & Palmer, B. W. (2015). *Positive psychiatry: A clinical handbook*. Washington, DC: American Psychiatric Publishing.

Jeste, D. V., Palmer, B. W., Rettew, D. C., & Boardman, S. (2015). Positive psychiatry: Its time has come. *The Journal of Clinical Psychiatry*, *76*, 675–683. Available from https://doi.org/10.4088/JCP.14nr09599.

Jeste, D. V., Palmer, B. W., & Saks, E. R. (2017). Why we need positive psychiatry for schizophrenia and other psychotic disorders. *Schizophrenia Bulletin*, *43*(2), 227–229. Available from https://doi.org/10.1093/schbul/sbw184.

Jeste, D. V., Savla, G. N., Thompson, W. K., Vahia, I. V., Glorioso, D. K., Martin, A. S., ... Depp, C. A. (2013). Association between older age and more successful aging: Critical role of resilience and depression. *American Journal of Psychiatry*, *170*(2), 188–196. Available from https://doi.org/10.1176/appi.ajp.2012.12030386.

Jeste, D. V., Wolkowitz, O. M., & Palmer, B. W. (2011). Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophrenia Bulletin*, *37*(3), 451–455. Available from https://doi.org/10.1093/schbul/sbr026.

Johnson, J., Gooding, P. A., Wood, A. M., Taylor, P. J., Pratt, D., & Tarrier, N. (2010). Resilience to suicidal ideation in psychosis: Positive self-appraisals buffer the impact of hopelessness. *Behaviour Research and Therapy*, *48*(9), 883–889. Available from https://doi.org/10.1016/j.brat.2010.05.013.

Keefe, R. S. E., Eesley, C. E., & Poe, M. P. (2005). Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry*, *57*(6), 688–691. Available from https://doi.org/10.1016/j.biopsych.2005.01.003.

Keefe, R. S. E., & Harvey, P. D. (2012). Cognitive impairment in schizophrenia. In M. A. Geyer, & G. Gross (Eds.), *Novel antischizophrenia treatments* (Vol. 213, pp. 11–37). Berlin, Heidelberg: Springer. Available from https://doi.org/10.1007/978-3-642-25758-2_2.

Khoury, B., Lecomte, T., Gaudiano, B. A., & Paquin, K. (2013). Mindfulness interventions for psychosis: A meta-analysis. *Schizophrenia Research*, *150*(1), 176–184. Available from https://doi.org/10.1016/j.schres.2013.07.055.

Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E., & Bowie, C. R. (2008). Is schizophrenia a syndrome of accelerated aging? *Schizophrenia Bulletin*, *34*(6), 1024–1032. Available from https://doi.org/10.1093/schbul/sbm140.

Kukla, M., Lysaker, P. H., & Roe, D. (2014). Strong subjective recovery as a protective factor against the effects of positive symptoms on quality of life outcomes in schizophrenia. *Comprehensive Psychiatry*, *55*(6), 1363–1368. Available from https://doi.org/10.1016/j.comppsych.2014.04.022.

Lahvis, G. P. (2016). Social reward and empathy as proximal contributions to altruism: The camaraderie effect. In M. Wöhr, & S. Krach (Eds.), *Social behavior from rodents to humans* (Vol. 30, pp. 127–157). Cham: Springer. Available from https://doi.org/10.1007/7854_2016_449.

Laviola, G., Zoratto, F., Ingiosi, D., Carito, V., Huzard, D., Fiore, M., & Macrì, S. (2017). Low empathy-like behaviour in male mice associates with impaired sociability, emotional memory, physiological stress reactivity and variations in neurobiological regulations. *PLoS One*, *12*(12), e0188907. Available from https://doi.org/10.1371/journal.pone.0188907.

Lee, E. E., Lavretsky, H., Renn, B. N., & Arean, P. (2018). Positive psychiatry in geropsychiatric clinical practice: In schizophrenia, cognitive disorders, and affective disorders. *The American Journal of Geriatric Psychiatry*, *26*(3), 29–30.

Lee, E. E., Liu, J., Tu, X., Palmer, B. W., Eyler, L. T., & Jeste, D. V. (2018). A widening longevity gap between people with schizophrenia and general population: A literature review and call for action. Special Issue. *Schizophrenia Research*, *196*, 9–13.

Lee, E. E., Martin, A. S., Tu, X., Palmer, B. W., & Jeste, D. V. (2018). Childhood adversity and schizophrenia: The protective role of resilience in mental and physical health and metabolic markers. *The Journal of Clinical Psychiatry*, *79*(3). Available from https://doi.org/10.4088/JCP.17m11776, 17m11776.

Manczak, E. M., DeLongis, A., & Chen, E. (2016). Does empathy have a cost? Diverging psychological and physiological effects within families. *Health Psychology*, *35*(3), 211–218. Available from https://doi.org/10.1037/hea0000281.

Martin, L. R., Friedman, H. S., Tucker, J. S., Tomlinson-Keasey, C., Criqui, M. H., & Schqartz, J. E. (2002). A life course perspective on childhood cheerfulness and its relation to mortality risk. *Personality and Social Psychology Bulletin*, *28*, 1155–1165.

Maslow, A. H. (1971). *The farther reaches of human nature*. New York, NY: Arkana/Penguin Books.

Mather, M., & Carstensen, L. L. (2005). Aging and motivated cognition: The positivity effect in attention and memory. *Trends in Cognitive Sciences*, *9*(10), 496–502. Available from https://doi.org/10.1016/j.tics.2005.08.005.

Mausbach, B. T., Aschbacher, K., Mills, P. J., Roepke, S. K., von Känel, R., Patterson, T. L., ... Grant, I. (2008). A 5-year longitudinal study of the relationships between stress, coping, and immune cell β2-adrenergic receptor sensitivity. *Psychiatry Research*, *160*(3), 247–255. Available from https://doi.org/10.1016/j.psychres.2007.09.006.

Mausbach, B. T., Harmell, A. L., Moore, R. C., & Chattillion, E. A. (2011). Influence of caregiver burden on the association between daily fluctuations in pleasant activities and mood: A daily diary analysis. *Behaviour Research and Therapy*, *49*(1), 74–79. Available from https://doi.org/10.1016/j.brat.2010.11.004.

Mausbach, B. T., Patterson, T. L., Kanel, R. V., Mills, P. J., Dimsdale, J. E., Ancoli-Israel, S., & Grant, I. (2007). The attenuating effect of personal mastery on the relations between stress and Alzheimer caregiver health: A five-year longitudinal analysis. *Aging & Mental Health*, *11*(6), 637–644.

Mausbach, B. T., von Kanel, R., Patterson, T. L., Dimsdale, J. E., Depp, C. A., Aschbacher, K., ... Grant, I. (2008). The moderating effect of personal mastery and the relations between stress and Plasminogen Activator Inhibitor-1 (PAI-1) antigen. *Health Psychology*, *27*(2), 172–179.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33–44.

McEwen, B. S., & Getz, L. (2013). Lifetime experiences, the brain and personalized medicine: An integrative perspective. *Metabolism*, *62*, S20–S26. Available from https://doi.org/10.1016/j.metabol.2012.08.020.

Meeks, S., Van Haitsma, K., Mast, B. T., Arnold, S., Streim, J. E., Sephton, S., ... Rovine, M. (2016). Psychological and social resources relate to biomarkers of allostasis in newly admitted nursing home residents. *Aging & Mental Health*, *20*(1), 88–99. Available from https://doi.org/10.1080/13607863.2015.1072796.

Melchers, M., Montag, C., Markett, S., Niazy, N., Gross-Bolting, J., Zimmermann, J., & Reuter, M. (2017). The OXTR gene, implicit learning and social processing: Does empathy evolve from perceptual skills for details? *Behavioral Brain Research*, *329*, 35–40.

Milam, J. E., Richardson, J. L., Marks, G., Kemper, C. A., & McCutchan, A. J. (2004). The roles of dispositional optimism and pessimism in HIV disease progression. *Psychology and Health*, *19*, 167–181.

Milev, P., Ho, B.-C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *American Journal of Psychiatry*, *162*(3), 495–506. Available from https://doi.org/10.1176/appi.ajp.162.3.495.

Mills, P. J., Wilson, K. L., Pung, M. A., Weiss, L., Patel, S., Doraiswamy, P. M., ... Tanzi, R. E. (2016). The self-directed biological transformation initiative and well-being. *The Journal of Alternative and Complementary Medicine*, *22*(8), 627–634. Available from https://doi.org/10.1089/acm.2016.0002.

Mittlemark, M., Psaty, B. M., Rautaharju, P. M., Fried, L. P., Borhani, N. O., Tracy, R. P., & Kronmal, R. (1993). Prevalence of cardiovascular diseases among older adults: The cardiovascular health study. *American Journal of Epidemiology*, *137*(3), 311–317.

Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J. A., & Keefe, R. S. E. (2008). Relationship of cognition and psychopathology to functional impairment in schizophrenia. *American Journal of Psychiatry*, *165*(8), 978–987. Available from https://doi.org/10.1176/appi.ajp.2008.07111713.

Mohr, S., Brandt, P.-Y., Borras, L., Gilliéron, C., & Huguelet, P. (2006). Toward an integration of spirituality and religiousness into the psychosocial dimension of schizophrenia. *American Journal of Psychiatry*, *163*(11), 1952–1959.

Mohr, S., Perroud, N., Gillieron, C., Brandt, P.-Y., Rieben, I., Borras, L., & Huguelet, P. (2011). Spirituality and religiousness as predictive factors of outcome in schizophrenia and schizo-affective disorders. *Psychiatry Research*, *186*(2–3), 177–182. Available from https://doi.org/10.1016/j.psychres.2010.08.012.

Mosing, M. A., Zietsch, B. P., Shekar, S. N., Wright, M. J., & Martin, N. G. (2009). Genetic and environmental influences on optimism and its relationship to mental and self-rated health: A study of aging twins. *Behavior Genetics*, *39*(6), 597–604. Available from https://doi.org/10.1007/s10519-009-9287-7.

Notaras, M., Hill, R., & van den Buuse, M. (2015). A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. *Neuroscience & Biobehavioral Reviews*, *51*, 15–30. Available from https://doi.org/10.1016/j.neubiorev.2014.12.016.

Pace, T. W. W., Negi, L. T., Adame, D. D., Cole, S. P., Sivilli, T. I., Brown, T. D., ... Raison, C. L. (2009). Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology*, *34*(1), 87–98. Available from https://doi.org/10.1016/j.psyneuen.2008.08.011.

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A reexamination. *Archives of General Psychiatry*, *62*(3), 247. Available from https://doi.org/10.1001/archpsyc.62.3.247.

Palmer, B. W., Heaton, R. K., Kuck, J., Braff, D., Paulsen, J. S., Harris, M. J., & Jeste, D. V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology*, *11*(3), 437–446.

Palmer, B. W., Martin, A. S., Depp, C. A., Glorioso, D. K., & Jeste, D. V. (2014). Wellness within illness: Happiness in schizophrenia. *Schizophrenia Research*, *159*(1), 151–156. Available from https://doi.org/10.1016/j.schres.2014.07.027.

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience*, *28*(1), 377–401. Available from https://doi.org/10.1146/annurev.neuro.27.070203.144216.

Penn, D. L., & Mueser, K. T. (1996). Research update on the psychosocial treatment of schizophrenia. *The American Journal of Psychiatry*, *153*(5), 607–617.

Rasmussen, H. N., Scheier, M. F., & Greenhouse, J. B. (2009). Optimism and physical health: A meta-analytic review. *Annals of Behavioral Medicine*, *37*(3), 239–256. Available from https://doi.org/10.1007/s12160-009-9111-x.

Rector, N. A., & Beck, A. T. (2001). Cognitive behavioral therapy for schizophrenia: an empirical review. *The Journal of nervous and mental disease*, *189*(5), 278–287.

Reichstadt, J., Depp, C. A., Palinkas, L. A., & Jeste, D. V. (2007). Building blocks of successful aging: A focus group study of older adults' perceived contributors to successful aging. *The American Journal of Geriatric Psychiatry*, *15*(3), 194–201.

Rendell, S., & Anch, M. (2011). The brain's drugstore. *Annals of Psychotherapy and Integrative Health*, *14*(3), 52–64.

Rickhi, B., Kania-Richmond, A., Moritz, S., Cohen, J., Paccagnan, P., Dennis, C., ... Toews, J. (2015). Evaluation of a spirituality informed e-mental health tool as an intervention for major depressive disorder in adolescents and young adults—A randomized controlled pilot trial. *BMC Complementary and Alternative Medicine*, *15*(1), 450. Available from https://doi.org/10.1186/s12906-015-0968-x.

Rogosch, F. A., Dackis, M. N., & Cicchetti, D. (2011). Child maltreatment and allostatic load: Consequences for physical and mental health in children from low-income families. *Development and Psychopathology*, *23*(04), 1107–1124. Available from https://doi.org/10.1017/S0954579411000587.

Saphire-Bernstein, S., Way, B. M., Kim, H. S., Sherman, D. K., & Taylor, S. E. (2011). Oxytocin receptor gene (OXTR) is related to psychological resources. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(37), 15118−15122. Available from https://doi.org/10.1073/pnas.1113137108.

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42−50. Available from https://doi.org/10.1016/j.schres.2013.07.009.

Schiele, M. A., Ziegler, C., Holitschke, K., Schartner, C., Schmidt, B., Weber, H., … Domschke, K. (2016). Influence of 5-HTT variation, childhood trauma and self-efficacy on anxiety traits: A gene-environment-coping interaction study. *Journal of Neural Transmission*, *123*(8), 895−904. Available from https://doi.org/10.1007/s00702-016-1564-z.

Schroder, K. E. E., Carey, M. P., & Vanable, P. A. (2003). Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports. *Annals of Behavioral Medicine*, *26*(2), 104−123. Available from https://doi.org/10.1207/S15324796ABM2602_03.

Schutte, N. S., Palanisamy, S. K., & McFarlane, J. R. (2016). The relationship between positive psychological characteristics and longer telomeres. *Psychology and Health*, *31*(12), 1466−1480.

Seeman, T. E., Dubin, L. F., & Seeman, M. (2003). Religiosity/spirituality and health: A critical review of the evidence for biological pathways. *American Psychologist*, *58*(1), 53−63. Available from https://doi.org/10.1037/0003-066X.58.1.53.

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(8), 4770−4775. Available from https://doi.org/10.1073/pnas.081072698.

Seligman, M. E., & Csikszentmihalyi, M. (2000). *Positive psychology: An introduction*. American Psychological Association.

Sharma, V., Marin, D. B., Koenig, H. K., Feder, A., Iacoviello, B. M., Southwick, S. M., & Pietrzak, R. H. (2017). Religion, spirituality, and mental health of US military veterans: Results from the National Health and Resilience in Veterans Study. *Journal of Affective Disorders*, *217*, 197−204.

Shepherd, S., Depp, C. A., Harris, G., Halpain, M., Palinkas, L. A., & Jeste, D. V. (2012). Perspectives on schizophrenia over the lifespan: A qualitative study. *Schizophrenia Bulletin*, *38*(2), 295−303. Available from https://doi.org/10.1093/schbul/sbq075.

Small, G. W., Rabins, P. W., Barry, P. P., Buckholtz, N. S., DeKosky, S. T., Ferris, S. H., … Tune, L. E. (1997). Diagnosis and treatment of Alzheimer disease and related disorders. *Journal of the American Medical Association*, *278*(16), 1363−1371.

Sullivan, M. B., Erb, M., Schmalzl, L., Moonaz, S., Noggle Taylor, J., & Porges, S. W. (2018). Yoga therapy and polyvagal theory: The convergence of traditional wisdom and contemporary neuroscience for self-regulation and resilience. *Frontiers in Human Neuroscience*, *12*, 67. Available from https://doi.org/10.3389/fnhum.2018.00067.

Taschereau-Dumouchel, V., Hétu, S., Bagramian, A., Labrecque, A., Racine, M., Chagnon, Y. C., & Jackson, P. L. (2016). BDNF Val66Met polymorphism is associated with self-reported empathy. *PLoS One*, *11*(2), e0149911. Available from https://doi.org/10.1371/journal.pone.0149911.

Twamley, E. W., Savla, G. N., Zurhellen, C. H., Heaton, R. K., & Jeste, D. V. (2008). Development and pilot testing of a novel compensatory cognitive training intervention for people with psychosis. *American Journal of Psychiatric Rehabilitation*, *11*(2), 144−163.

Twamley, E. W., Thomas, K. R., Burton, C. Z., Vella, L., Jeste, D. V., Heaton, R. K., & McGurk, S. R. (2017). Compensatory cognitive training for people with severe mental illnesses in supported employment: A randomized controlled trial. *Schizophrenia Research*, *203*, 41−48.

Twamley, E. W., Vella, L., Burton, C. Z., Heaton, R. K., & Jeste, D. V. (2012). Compensatory cognitive training for psychosis: Effects in a randomized controlled trial. *The Journal of Clinical Psychiatry*, *73*(9), 1212−1219.

Tylec, A., Jeleniewicz, W., Mortimer, A., Bednarska-Makaruk, M., & Kucharska, K. (2017). Interaction between Val158Met catechol-O-methyltransferase polymorphism and social cognitive functioning in schizophrenia: Pilot study. *Annals of Human Genetics*, *81*(6), 267−275.

Uzefovsky, F., Shalev, I., Israel, S., Edelman, S., Raz, Y., Mankuta, D., … Ebstein, R. P. (2015). Oxytocin receptor and vasopressin receptor 1a genes are respectively associated with emotional and cognitive empathy. *Hormones and Behavior*, *67*, 60−65.

Vancampfort, D., Vansteelandt, K., Scheewe, T., Probst, M., Knapen, J., De Herdt, A., & De Hert, M. (2012). Yoga in schizophrenia: A systematic review of randomised controlled trials: Yoga in schizophrenia. *Acta Psychiatrica Scandinavica*, *126*(1), 12−20. Available from https://doi.org/10.1111/j.1600-0447.2012.01865.x.

Van Patten, R., Lee, E. E., Daly, R., Twamley, E. W., Tu, X. M., & Jeste, D. V. (2019). Assessment of 3-dimensional wisdom in schizophrenia: Associations with neuropsychological functions and physical and mental health. *Schizophrenia Research*, *208*, 360−369.

Viljoen, M., & Claassen, N. (2017). Allostatic load and heart rate variability as health risk indicators. *African Health Sciences*, *17*(2), 428. Available from https://doi.org/10.4314/ahs.v17i2.17.

Waaktaar, T., & Torgersen, S. (2012). Genetic and environmental causes of variation in trait resilience in young people. *Behavior Genetics*, *42*(3), 366−377. Available from https://doi.org/10.1007/s10519-011-9519-5.

World Health Organization. (2018). *WHO definition of health*. <https://www.who.int/about/mission/en/> Accessed 27.10.18.

Wiley, J. F., Bei, B., Bower, J. E., & Stanton, A. L. (2017). Relationship of psychosocial resources with allostatic load: A systematic review. *Psychosomatic Medicine*, *79*(3), 283−292. Available from https://doi.org/10.1097/PSY.0000000000000395.

Wu, N., Shang, S., & Su, Y. (2015). The arginine vasopressin V1b receptor gene and prosociality: Mediation role of emotional empathy. *PsyCh Journal*, *4*(3), 160−165.

Zalli, A., Carvalho, L. A., Lin, J., Hamer, M., Erusalimsky, J. D., Blackburn, E. H., & Steptoe, A. (2014). Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(12), 4519−4524. Available from https://doi.org/10.1073/pnas.1322145111.

Chapter 14

Alzheimer's disease and other neurocognitive disorders

Lucy Y. Wang, Beth Ann LaBardi, Murray A. Raskind and Elaine R. Peskind
Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States

Introduction

Alzheimer's disease (AD) and other neurocognitive disorders are one of the major classes of disorders we face in geriatric psychiatry. In the United States, Alzheimer's dementia is expected to reach record numbers; in 2025, the number of people with Alzheimer's dementia is projected to reach 7.1 million people, and by 2050, reach 13.8 million (Hebert, Weuve, Scherr, & Evans, 2013). Five out of six people with dementia will develop psychiatric symptoms during the course of their illness (Abraha et al., 2017). These psychiatric symptoms substantially impair quality of life for both patients and caregivers, and contribute significantly to health care costs. Given the number of patients and socioeconomic impact of these disorders, the specialty of geriatric psychiatry, whose core competencies include diagnosis and management of both cognitive and psychiatric symptoms of dementia, meets a substantial and growing need in health care.

This chapter provides a background on neurocognitive disorders, approaches to diagnosis, and management of several of the more problematic psychiatric complications of dementia. The scope of this topic is broad and the field's understanding of these disorders is constantly evolving, so the content of this chapter is not intended to be fully comprehensive. Rather, we present foundational information that is informative to current clinical practice. Also, several disorders that can cause dementia syndromes, such as HIV, drug and alcohol use, or traumatic brain injury are mentioned but not discussed in detail, as diagnosis and management for these disorders are best tailored to the specific causative agent or injury. Prion disease and Huntington's disease are also not reviewed in detail due to their rarity and disease-specific approach toward diagnosis and treatment. Discussed instead here are what many consider the four most common dementias, including dementia caused by AD, vascular disease, Lewy body disease, and frontotemporal lobar degeneration (FTLD). Finally, the latter part of this chapter focuses on psychiatric symptoms in dementia that frequently come to clinical attention, including apathy, agitation, psychosis, depression, and anxiety.

Terminology

The term "dementia" describes a syndrome of cognitive impairment affecting more than one cognitive domain that results in a significant decline in ability to function in day-to-day activities and live independently. Historically, there have been recognized multiple causes or subtypes of dementia, examples including neurodegenerative (e.g., AD), static (e.g., stroke), or reversible etiologies (e.g., HIV). Because of this heterogeneity, the term "dementia" often is an inadequate descriptor; for example, Alzheimer's dementia, being the most common and prototypical example of dementia, affects a different population and has a different clinical course than other forms such as dementia caused by HIV. Adding to this complexity is the more recent recognition of mild cognitive impairment (MCI), with cognitive impairment confirmed on objective neuropsychologic tests, but without significant functional decline. MCI usually, but not always, is an early presentation and precursor of dementia caused by neurodegenerative disorders.

Specialty workgroups have attempted to improve nomenclature around these disorders, but the language will likely continue to evolve as understanding of these disorders grows. For now, the diagnostic and statistical manual of mental disorders (DSM)-5 and other consensus diagnostic guidelines such as the National Institute of Aging and Alzheimer's

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00014-4

Association (NIA-AA) guidelines for AD, are the more widely accepted (American Psychiatric Association, 2013; McKhann et al., 2011). The DSM-5 promotes a categorical approach, first providing criteria for "major neurocognitive disorder" (synonymous with dementia) or "mild neurocognitive disorder" (synonymous with MCI). Specific criteria to aid in determining a certain etiology are then considered. This categorical approach provides room for clinical situations where the etiology is unknown or multifactorial and does not assume that mild neurocognitive disorder will necessarily progress to major neurocognitive disorder (e.g., traumatic brain injury, HIV) (Sachdev et al., 2014). Other diagnostic guidelines, such as the NIA-AA guidelines for AD, instead are disease-focused. For neurodegenerative conditions, the categories of preclinical disease, MCI, and dementia are recognized as simply stages of the same pathology, and progression to the next stages is expected. This diagnostic approach currently is the most widely accepted. It also promotes the goal of early detection, with the potential to intervene and slow down future progression.

For the purposes of this chapter, we use the terms dementia and MCI interchangeably with major and mild neurocognitive disorder. Dementia and MCI is the language more widely used in the literature and is more familiar to laypeople, but in clinical practice, DSM diagnoses are preferred by the psychiatric field. Another clarification to note is that, although in the past AD was used interchangeably with dementia, we are careful now to describe AD specifically as the disease pathology and Alzheimer's dementia as the clinical stage of this disease. Similar care in our terminology differentiating underlying disease versus stage of functional impairment is made for other disorders such as vascular disease, Lewy body disease, and FTLD.

General diagnostic approach

A dementia evaluation addresses four questions: (1) is there subjective impairment noticed by the individual or observed by a collateral informant, (2) is there objective evidence of cognitive impairment on testing, (3) is there functional decline, and (4) are symptoms caused by something other than dementia (e.g., delirium, substances, or other medical, neurological, or psychiatric disorders)? To answer these questions, the dementia workup includes obtaining history, cognitive screening, a physical exam, and appropriate laboratory studies and neuroimaging, described in further detail below (Knopman et al., 2001).

While specific criteria may differ between dementia subtypes, criteria generally require cognitive symptoms observed by the patients or those around them, and objective impairment found on cognitive testing. Cognitive testing can be performed using a screening measure, and commonly used measures include the Montreal Cognitive Assessment, the Mini-Mental State Exam (MMSE), and the St. Louis University Mental Status exam. A referral to a neuropsychologist is of benefit when a more thorough evaluation than can be achieved from a screening measure is warranted. Examples of such cases can include situations where a screening measure is not interpretable (e.g., very high or low educational level, language barriers), there are other contributing conditions (e.g., history of traumatic brain injury), or where cognitive screening results are not consistent with clinical history.

Laboratory studies typically include a complete blood count, chemistries, thyroid screen, and vitamin B12 level. If clinically relevant, a syphilis screen and HIV test can be added. Neuroimaging rules out neoplasm and hemorrhage while also assessing the presence of vascular disease. Brain magnetic resonance imaging (MRI) is standard and is the preferred approach, particularly if entertaining the possibility of vascular impairment; however, head computed tomography (CT) is still informative if a patient cannot tolerate an MRI or if an MRI is contraindicated. Finally, if clinically appropriate, other studies can include EEG, lumbar puncture, positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging, and genetic testing.

Fig. 14.1 summarizes an approach to diagnosis. When a nonneurodegenerative cause is ruled out, dementia or MCI caused by AD, vascular disease, Lewy body disease, or FTLD can be considered. Answering the question of whether cognitive symptoms have resulted in a decline in previous functioning informs whether the diagnosis is dementia, where changes negatively impact independence, or MCI where independence is not affected. If a dementia syndrome is present, criteria described in later sections of this chapter can guide diagnosis for a specific dementia subtype. Although a gross overgeneralization and with many exceptions, some key distinguishing features that can guide diagnosis include short-term memory loss in Alzheimer's dementia, evidence of cerebrovascular disease in vascular dementia, parkinsonism in dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), and early behavioral or language changes in frontotemporal dementia (FTD). If MCI, the diagnosis can be further described as amnestic or nonamnestic MCI; alternatively, specifying the likely underlying etiology to the MCI diagnosis is appropriate (e.g., MCI due to AD) (Petersen, 2016). It has been conceptualized that amnestic MCI is caused by AD and in some cases cerebrovascular disease, and nonamnestic MCI is caused by not only AD and vascular disease, but also Lewy body disease and FTLD.

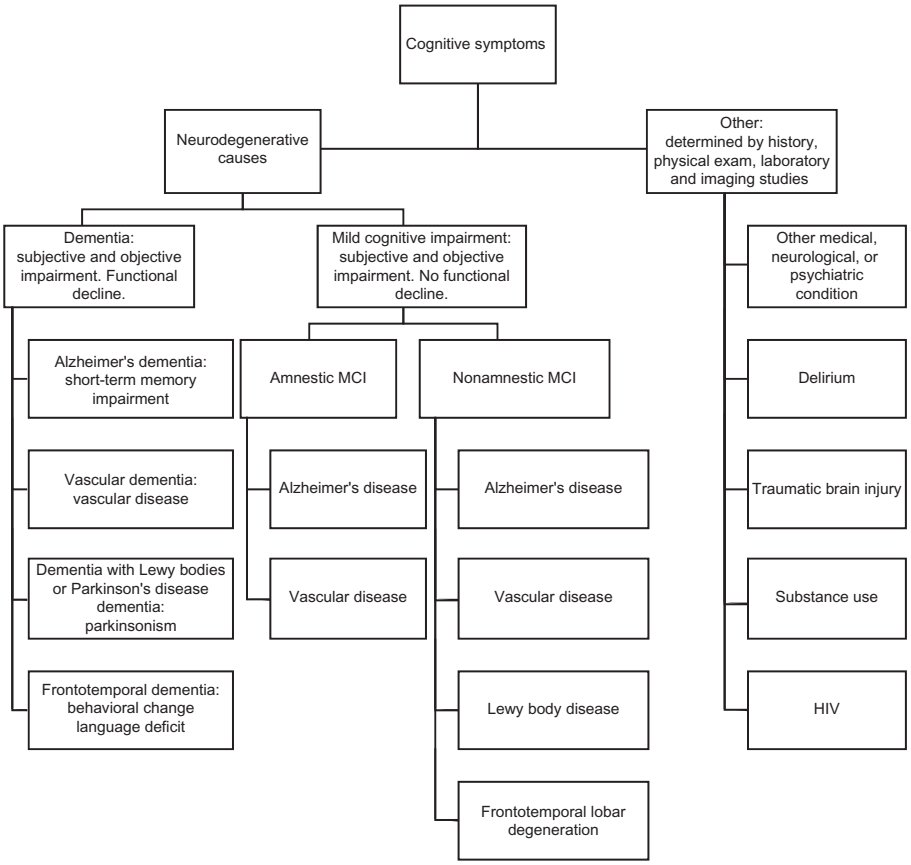


FIGURE 14.1 General diagnostic approach.

Alzheimer's disease

AD is the most common cause of dementia, affecting one in 10 people age 65 or older (Alzheimer's Association, 2018). As the baby boomer generation reaches this age range, the number of people in the United States with Alzheimer's dementia will increase. The Alzheimer's Association provides some sobering statistics about the health and economic impacts of AD (Alzheimer's Association, 2018). The number of deaths due to AD increased 125% from 2000 to 2015, whereas in other diseases such as cancer, heart disease, stroke, and HIV, the number of deaths declined. Direct health care costs of Alzheimer's dementia in 2018 were estimated to be $277 billion in the United States and relied (and continue to rely) heavily on Medicare and Medicaid. In 2017, caregivers in the United States provided an estimated 18.4 billion hours of unpaid care, equivalent to $232.1 billion (National Alliance for Caregiving, 2017).

Public health implications aside, the health and emotional toll on individual patients and their caregivers are substantial, as they face a gradual decline of function and abilities, loss of future hopes and plans, and the likelihood of increased burden on loved ones. Caregiver depression is common and can go unrecognized. Health care professionals and laypeople alike may assume the mindset of: "There is nothing that can be done." On the contrary, it is our observation that where patients and caregivers are coping with a slowly progressive disease, and where they are often becoming more isolated over time, having regular contact with a health care provider knowledgeable in dementia care is invaluable. This starts with a clinician's ability to recognize clinical features of the disorder, provide a timely diagnosis, and implement appropriate treatment, management, and education.

Clinical features

In a classic presentation of Alzheimer's dementia, short-term memory and executive functioning impairment are early symptoms. Clinical examples of short-term memory deficits include repeating questions, forgetting recent conversations, and forgetting to take medications. Executive functioning involves planning and organizing complex tasks. Examples of impairment include financial matters such as tax preparation and bill paying, organization of a complex holiday dinner, and driving. Symptoms gradually progress to all other cognitive functions, leading to significant

impairment in day-to-day functioning. Over time, even simple tasks or chores become more difficult, communication and social skills become impaired, and in severe stages, ability to maintain personal care is lost, including dressing, bathing, and toileting.

Historically, diagnostic criteria relied primarily on clinical features of this typical presentation of Alzheimer's dementia, with a requirement for the presence of short-term memory impairment. However, now recognized are atypical presentations for Alzheimer's dementia, often occurring in patients with early-onset disease. In these cases, other cognitive impairments may be more prominent, such as visuospatial, language, and praxis impairment (Scheltens et al., 2016). Also, early diagnostic criteria did not have the benefit of recent research advances supporting the roles for biomarkers in diagnosis, such as PET demonstration of beta-amyloid deposition or low beta-amyloid and elevated tau in cerebrospinal fluid (CSF).

In light of this recognition of atypical presentations, as well as emerging technologies that may detect AD through biomarkers, newer diagnostic criteria have evolved to include both clinical and biomarker aided diagnoses. NIA-AA criteria provide diagnostic guidance based both on clinical features (gradually progressive disease, multiple cognitive domains affected both noticed by the patient or caregivers and objectively determined on cognitive testing), as well as incorporation of biomarkers to weigh certainty of the diagnosis, or provide support for the diagnosis in atypical presentations (McKhann et al., 2011). DSM-5 criteria predominantly utilize clinical features for diagnosis, although also accepts known causative genetic mutations for a diagnosis (American Psychiatric Association, 2013).

Preclinical disease

Evidence of the AD process can be detected before the clinical symptoms emerge. Biomarkers capitalize on the hallmark pathologic features of AD, which are brain accumulations of abnormally folded proteins, beta-amyloid (also known as amyloid plaques) and tau (also known as neurofibrillary tangles). CSF biomarkers include low concentrations of $A\beta_{42}$ and high concentrations of total tau and phosphorylated tau (p-tau) (McKhann et al., 2011). PET modalities with ligands specific to β amyloid and tau can detect brain depositions of these proteins, also consistent with the presence of early development of disease.

The preclinical disease diagnosis is controversial because of the lack of full correlation between AD pathology and clinical symptoms. Autopsy studies have long recognized the existence of people with substantial neuropathology consistent with AD, but no clinical symptoms (Garrett & Valle, 2016). Likewise, these technologies do not fully account for the common occurrence of mixed pathology with vascular and Lewy body disease, which influence the rate of progression to the dementia syndrome and would have different approaches to treatment. There are also no currently known treatments effective in preclinical disease (or even MCI). Given the uncertainty over prognosis and lack of current treatment, diagnosis of preclinical AD has been primarily limited to research settings; this may change as technologies and treatment developments emerge.

Management

There are four drugs approved for the treatment of Alzheimer's dementia by the FDA: the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine, and the glutamate antagonist memantine. Of note, there are no FDA-approved treatments for MCI. While several ChEIs have received FDA approval for mild-to-moderate stage Alzheimer's dementia only, for all practical purposes these medications are used in every stage except terminal stage, particularly as there is little evidence guiding when these medications are to be discontinued, and therefore they are often prescribed through moderate to severe−stage disease. Memantine, which is FDA-approved for moderate-to-severe Alzheimer's dementia, may be added to a ChEI, as the combination of donepezil and memantine can lead to greater improvement in cognitive functions, behavioral and psychiatric symptoms of dementia, and global functions than donepezil alone (Chen et al., 2017).

The benefit of these agents is considered by many to be modest. Guidelines do generally recommend pharmacotherapy with ChEIs or memantine, including statements from the American Psychiatric Association, American Association for Geriatric Psychiatry, and American Academy of Neurology (Doody et al., 2001; Lyketsos et al., 2006; Rabins et al., 2007). A Cochrane systematic review found moderate-quality evidence that people with mild, moderate, or severe dementia due to Alzheimer's dementia treated for periods of 12 or 24 weeks with donepezil experience small benefits in cognitive function, activities of daily living, and clinician-rated global clinical state. Other findings include some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total health care resource costs (Birks & Harvey, 2018).

Several behavioral interventions to improve memory have been developed, and of these, cognitive stimulation therapy (CST) has the most evidence and support. CST is a 12–14 week group–based therapy for persons with dementia, founded on the principle that stimulating and enjoyable activities may slow cognitive decline (Morley & Cruz-Oliver, 2014; Rai, Yates, & Orrell, 2018). This manualized treatment allows facilitators to adapt group activities such that they are appropriately and maximally tailored for participants' cognitive abilities. Studies have shown short-term improvements in cognitive measures and quality of life measures, but long-term improvement has not been consistently demonstrated. Nor has benefit been seen for an individualized adaptation of this protocol, which may highlight the importance of social stimulation and connectedness. In areas where this treatment is not available, it is appropriate to counsel patients and caregivers that engaging in enjoyable, social, and stimulating activities can have cognitive benefit in the short term, as well as contribute positively to quality of life.

A key treatment modality for Alzheimer's dementia is supportive care from family and other caregivers. Family caregivers need education and training on how to manage the progressive nature of the illness as well as guidance on how to mobilize the resources needed to maintain care for their loved one while preserving their own well-being, including support groups and respite services. The local Alzheimer's Association is an excellent resource for most communities. Patients and their families may also find it helpful to know about the option to participate in a clinical trial. The Alzheimer's Association's TrialMatch and NIH's clinicaltrials.gov are portals patients and families can use to access information about clinical trials (Geldmacher & Kerwin, 2013).

Vascular dementia

Vascular dementia refers to a dementia process for which cerebrovascular disease constitutes the primary etiology. Historically, vascular dementia was thought to clinically present with stepwise decline, caused by multiple large cortical infarcts over time. However, pathological studies have clarified that most cases involve subcortical small vessel disease, and cognitive decline can be gradually progressive. Subtypes of vascular dementia are now recognized, and include multiinfarct dementia (cortical vascular dementia), small vessel dementia (subcortical vascular dementia), strategic infarct dementia, hypoperfusion dementia, hemorrhagic dementia, hereditary vascular dementia (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), and mixed AD with vascular disease (O'Brien & Thomas, 2015). Because of the heterogeneous group of etiologies involved and the differing clinical presentations that can exist, often the term "vascular cognitive impairment" is most appropriate. The term vascular cognitive impairment encompasses not only the dementia syndrome, but also mild and nonprogressive presentations as well.

Vascular dementia is the second most common cause of dementia, after AD. A diagnosis of pure vascular dementia is relatively rare. However, if individuals with mixed vascular and other etiologies are included in estimates, vascular disease is a contributor to 50%–70% of dementias (Schneider, Arvanitakis, Bang, & Bennett, 2007; Toledo et al., 2013).

Clinical features

Consistent with the heterogeneity of vascular pathologies involved, the clinical presentation of vascular dementia is variable (O'Brien & Thomas, 2015). Deficits in attention, processing speed, and executive functioning are commonly seen, associated with subcortical vascular pathology that interrupts frontostriatal circuits. But other cognitive functions such as memory, language, and praxis are less consistently affected. Some patients will present with stepwise declines associated with large or strategically located infarcts, while many have a gradual progressive course associated with subcortical small vessel disease. Psychiatric and behavioral symptoms can occur as well, and noncognitive impairment including parkinsonism, rigidity, and focal neurologic deficits can be present depending on the location or extent of vascular pathology.

A majority of patients with cerebrovascular pathology have mixed neuropathology with other dementia types, most commonly AD. In these cases, the clinical course will essentially be that of a patient with Alzheimer's dementia. There does appear to be an additive effect when vascular disease is combined with AD, where clinically relevant symptoms occur at lower thresholds of AD pathology mixed with cerebrovascular disease than AD pathology alone (Snowdon et al., 1997).

Diagnosis

There are several diagnostic criteria commonly used for vascular dementia. An early set of criteria, known as the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en

Neurosciences (NINDS-AIREN) criteria, has been frequently used in research literature (Román et al., 1993). However, with emerging understanding that memory is often not the predominant cognitive dysfunction in vascular dementia, newer criteria including DSM-5 criteria and the American Heart Association/American Stroke Association (AHA/ASA) criteria have been developed (American Psychiatric Association, 2013; Gorelick et al., 2011). Diagnostic features common to these criteria include the presence of symptomatology consistent with dementia, plus history, physical exam findings, or radiologic evidence supporting an association of symptoms with cerebrovascular disease. DSM criteria also recognize that cognitive domains that are predominantly affected include processing speed and executive functioning.

Neuroimaging is central to the diagnostic workup. MRI is considered a gold standard (Skrobot et al., 2017), and should include T1-weighted, T2-weighted, and fluid-attenuated inversion recovery imaging. CT is inferior to MRI for the detection of small and lacunar infarcts and white matter lesions, but can still detect large infarcts and atrophy and therefore is useful for those patients unable to tolerate an MRI.

Management

Reducing cardiovascular risk factors is a core management approach toward vascular dementia. Monitoring and managing hypertension, diabetes, and hyperlipidemia, as well as incorporating health-promoting behaviors such as a balanced diet and regular exercise, are important. Computer models suggest that the elimination of obesity, hypertension, diabetes, elevated cholesterol, smoking, low education level, and cardiovascular disease can lead to an estimated reduction of one-third of dementia cases (de Bruijn et al., 2015; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014), primarily vascular dementia. For those with impairment due to ischemic stroke, guidelines for the prevention of recurrent stroke are applicable; these may include the use of antithrombotics, antihypertensives, and lipid-lowering agents (van der Flier et al., 2018).

Mixed results of studies examining ChEIs and memantine leave unanswered the degree of benefit expected from these treatments for vascular dementia. Subgroup analyses suggest that ChEIs can provide benefit to those with multiple cortical lesions (Kavirajan & Schneider, 2007), whereas memantine may be more effective in those with subcortical vascular dementia (Möbius & Stöffler, 2003). Because of the high degree of comorbid AD pathology associated with vascular dementia, if a patient is exhibiting a steady decline, it is appropriate to offer these medications that have shown efficacy for Alzheimer's dementia.

Lewy body disease

We use the term Lewy body disease to refer to the pathology that causes PDD and DLB. Both disorders share the neuropathologic feature of alpha-synuclein protein accumulations known as Lewy bodies and clinically feature both motor and cognitive symptoms. In PDD, motor symptoms precede cognitive symptoms, whereas the opposite is the case with DLB, in which cognitive symptoms precede or emerge at the same time as motor symptoms. Consensus guidelines propose a "one year rule," where patients who develop cognitive impairment more than 1 year after motor symptoms develop are diagnosed with PDD and those who develop cognitive impairment within 1 year before motor symptoms develop are diagnosed with DLB (McKeith et al., 2017). In practicality, whether a patient meets this 1-year cutoff can be difficult to determine, so referring to the broader term of Lewy body disease is appropriate.

Parkinson's disease dementia

While Parkinson's disease (PD) is classically considered a movement disorder, the development of dementia is frequent. An estimate of cumulative incidence of dementia is 83% 20 years after PD diagnosis (Hely, Reid, Adena, Halliday, & Morris, 2008). Risk factors include older age, greater motor severity of disease, disease duration, presence of rapid eye movement (REM) sleep behavior disorder, and atypical neurologic features (e.g., early autonomic symptoms, symmetrical disease presentation) (Hanagasi, Tufekcioglu, & Emre, 2017).

Early cognitive symptoms typically involve impairments of executive functioning, attention, visuospatial skills, and episodic memory (Petrova, Raycheva, & Traykov, 2012). Apathy is a common early neuropsychiatric symptom, as well as depression and anxiety. Psychotic symptoms similar to those seen in DLB are also common, typically involving well-formed visual hallucinations of children or animals. Delusions are another distressing symptom to patients and families, with the delusion of infidelity being frequently reported.

Dementia with Lewy bodies

Diagnostic criteria of DLB, in addition to emergence of cognitive symptoms concurrently or prior to motor symptoms, include the presence of other core and supportive clinical features (McKeith et al., 2017). Core features are fluctuating cognition involving attention and alertness, well-formed and detailed visual hallucinations, REM sleep behavior disorder (which may precede cognitive decline), and parkinsonism. A diagnosis of DLB is appropriate if two or more of these core features are present, or one clinical feature plus one or more biomarkers are present. Biomarkers include reduced dopamine transporter uptake in basal ganglia by SPECT or PET, low uptake iodine-metaiodobenzylguanidine myocardial scintigraphy (a marker of reduced postganglionic sympathetic cardiac innervation), and polysomnographic confirmation of REM sleep without atonia. Supportive clinical features are sensitivity to antipsychotic-induced parkinsonism, postural sensitivity, falls, syncope, autonomic dysfunction, hypersomnia, hyposmia, and other neuropsychiatric symptoms (specifically, hallucinations, delusions, apathy, anxiety, and depression).

Imaging

Unique to PD and DLB is the availability of nuclear imaging with a dopamine transporter−specific tracer to aid diagnosis. Dopamine transporter uptake through 123I-FP-CIT SPECT, a modality referred to as a DaTscan, can distinguish conditions where there is nigrostriatal degeneration, such as in PD and DLB, from other conditions that do not have nigrostriatal involvement. Typically used to differentiate PD from essential tremor, a DaTscan can be helpful when the clinical picture is unclear or a need to differentiate from drug-induced parkinsonism is present. A limitation of this modality is in specificity, in that several conditions other than DLB and PDD result in reduced nigrostriatal dopamine transporter uptake, including progressive supranuclear palsy (PSP), corticobasal degeneration, and multiple system atrophy. Differentiating between these disorders is still a clinical determination.

Management

ChEIs have been studied in patients with PDD and DLB. Rivastigmine and donepezil have been found to have benefit over placebo in areas of cognition (particularly in attention), activities of daily living, global function, and behavioral symptoms (Stinton et al., 2015; Wang et al., 2015). These agents may reduce apathy, visual hallucinations, and delusions and therefore are an appropriate option to address these noncognitive symptoms (McKeith et al., 2000). Memantine has also been studied in PDD and DLB patients but with mixed results, so suitability for use is less clear (Aarsland et al., 2009; Emre et al., 2010).

Frontotemporal lobar degeneration

FTLD refers to a group of neurodegenerative diseases predominantly affecting the frontal and anterior temporal lobes of the brain (Mackenzie et al., 2010). The first description of a clinical syndrome caused by FTLD was published by Arnold Pick in 1892, describing a patient with aphasia, dementia, and lobar atrophy, later recognized to have characteristic Pick bodies on neuropathologic evaluation (Alzheimer, 1911; Pick, 1892). Known as Pick's disease, this description was used for many years as synonymous with FTD. Recent developments have identified additional disorders with differing underlying pathologies, such that the terms FTLD (the neuropathological designation) and FTD (the clinical syndrome) have become umbrella terms for a heterogeneous group of neurodegenerative disorders. The commonality amongst these disorders is a selective degeneration of the frontal and temporal cortices, resulting in distinct clinical syndromes early in the course of the disease (Bang, Spina, & Miller, 2015). These syndromes have been divided into two primary types: behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al., 2011) or primary progressive aphasia (PPA), with PPA further subdivided into nonfluent and semantic variants (Gorno-Tempini et al., 2011).

As the third most prevalent form of dementia overall, it is also a leading cause of early-onset dementia with a mean age of onset of approximately 56 years (Vieira et al., 2013). The estimated combined population prevalence of FTD in individuals of 45−64 years of age, according to studies conducted in North America, Asia, and Europe, is 2−31/100,000 (Onyike & Diehl-Schmid, 2013).

Clinical features

FTD is classified into clinical variants (bvFTD, nfvPPA, and svPPA), but as the disease advances, symptoms of the three variants converge, as once focal degeneration spreads to larger regions of the frontal and temporal lobes. With

time, patients develop global cognitive impairment and motor deficits, including parkinsonism and motor neuron disease in some patients (Bang et al., 2015). Disease duration varies widely from 3 to 14 years, with an average of about 8 years (Onyike & Diehl-Schmid, 2013), although a well-recognized minority of patients manifest a very slowly progressive form of FTD (Kipps, Hodges, & Hornberger, 2010).

Behavioral variant frontotemporal dementia

bvFTD is the most common variant of FTD and is associated with early behavioral and executive deficits. Clinically, bvFTD accounts for roughly 60% of FTD cases, with the other 40% being language variants of FTD (Onyike & Diehl-Schmid, 2013). Historically, physicians recognized bvFTD under the narrow rubric of Pick's disease, as initially described by the Czech neurologist for whom it was named (Pick, 1892). The term Pick's disease is now reserved to identify a specific pathological subtype of FTLD.

BvFTD is marked by a wide range of changes in behavior and personality that manifest long before cognitive changes ensue, often leading to initial presentation in mental health settings. A clinical diagnosis of bvFTD requires at least three symptoms from the following six categories: disinhibition, apathy, lack of empathy, compulsions, hyperorality, and executive dysfunction (Rascovsky et al., 2011). Examples of behavioral disinhibition include tactless and socially inappropriate behavior, impulsive or careless actions (e.g., bad fiscal decisions or reckless driving), and new criminal behaviors. Patients often lose the ability to interpret the emotional states of people and animals, lack interpersonal warmth, and have diminished response to social cues. Stereotyped behaviors include simple repetitive movements or verbal utterances (e.g., tapping or throat clearing), compulsive ritualistic behaviors (e.g., counting or organizing), and repetitive use of verbal phrases. Hyperorality and impulsivity result in binge eating, often with increased consumption of sweets or alcohol, and significant weight gain is common.

BvFTD variant is the most likely FTD variant to be misdiagnosed as a psychiatric disorder (Woolley, Khan, Murthy, Miller, & Rankin, 2011). The psychopathological changes of early bvFTD (disinhibition, impulsivity, apathy, compulsive behaviors) can occur in the absence of other neurological signs or symptoms, including impairment in commonly assessed cognitive domains such as memory (Rascovsky et al., 2011). These factors, in addition to the lack of insight typical of early bvFTD (Mendez & Shapira, 2005), often prompt psychiatric referrals from caregivers and primary care physicians. In fact, in one large study, up to 50% of patients diagnosed with bvFTD received a previous psychiatric diagnosis (Woolley et al., 2011). In a review of 751 selected cases of FTD published between 1950 and 2007, 6% presented with schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, or unspecified psychotic states (Velakoulis, Walterfang, Mocellin, Pantelis, & McLean, 2009). Obsessive–compulsive behaviors typical of obsessive–compulsive disorder can occur in early bvFTD (Tonkonogy, Smith, & Barreira, 1994). Similarly, apathy and emotional withdrawal might lead to a misdiagnosis of depression. Clinicians evaluating adult patients with "late-onset" or "atypical" psychiatric disease should consider early bvFTD in their differential diagnosis, while being fully aware that primary psychiatric disorders are far more common than bvFTD.

The behavioral symptoms of bvFTD result from dysfunction in the paralimbic areas including medial frontal, orbital frontal, anterior cingulate, and frontoinsular cortices (Rosen et al., 2002; Seeley et al., 2008).

Primary progressive aphasia

PPA is characterized by a progressive decline in linguistic skills as the main symptom for the first 2 years of the illness. The three main clinical subtypes of PPA are the nonfluent or agrammatic (nfvPPA), semantic (svPPA), and logopenic (lvPPA) variants. (lvPPA is typically caused by AD, so is often not considered under the rubric of FTD.)

nfvPPA is anatomically correlated with Broadman's Area 44, 45 (Broca's area) in the left inferior frontal gyrus and the anterior insula (Gorno-Tempini et al., 2011), areas heavily involved in speech production. Clinical criteria for nfvPPA include apraxia of speech or improper use of grammar (Gorno-Tempini et al., 2011), and as the disease progresses, patients will have decreased verbal output and eventually become nonverbal. SvPPA has been associated with atrophy in the ventral and lateral portions of the anterior temporal lobes, areas implicated in semantic memory. The core features of this disorder are impaired object naming and impaired single-word comprehension, but with spared repetition, grammar, and fluency. Other supportive features include impaired object knowledge and surface dyslexia (where words with unusual spellings are mispronounced).

Motor syndromes

In fewer than 5% of cases, the disease process is focused in cortices involved in motor control and sensorimotor integration, and manifesting in predominantly motor syndromes. Examples include corticobasal syndrome (CBS),

TABLE 14.1 Motor syndromes in FTD.

	Corticobasal syndrome	Progressive supranuclear palsy	Motor neuron disease
Motor features	Parkinsonism	Parkinsonism	Fasciculations
	Asymmetric motor	Vertical supranuclear	Dysphagia
	symptoms	gaze palsy	Spasticity
	Alien limb phenomena	Early postural instability	Hyperreflexia
			Pseudobulbar affect
Commonly associated FTD variants	bvFTD	bvFTD	bvFTD
	PPA	nfvPPA	

PSP syndrome, and motor neuron disease syndromes (Rohrer et al., 2011). Table 14.1 lists distinguishing features of these motor syndromes and the behavioral or cognitive variants frequently associated with them.

Imaging

Structural MRI and CT in FTD show predominant frontal or temporal atrophy, and atrophy in the frontoinsular region is particularly indicative of FTD, including bvFTD (Rosen et al., 2002). Fluorodeoxyglucose PET, functional MRI, and SPECT also show disproportionate hypoperfusion and hypometabolism in these regions (Le Ber et al., 2006). Amyloid PET imaging can rule out AD and may be particularly helpful in patients younger than 65 years with an atypical presentation. The next frontier in molecular PET imaging is tau imaging that can potentially differentiate between AD, non-Alzheimer's tauopathies, and tau-negative dementias (Maruyama et al., 2013).

Brain imaging of patients with nfvPPA reveals predominant left posterior frontoinsular atrophy on MRI and/or hypoperfusion/hypometabolism in this area on SPECT/PET (Gorno-Tempini et al., 2004). In svPPA, predominant anterior temporal lobe atrophy can be seen on MRI along with hypoperfusion/hypometabolism of this area on SPECT/PET imaging (Gorno-Tempini et al., 2011).

Treatment

There are currently no evidence-based treatments for FTD, including any disease-modifying drugs. ChEIs are not beneficial and may actually worsen behavioral symptoms of FTD (Kimura & Takamatsu, 2013; Mendez, Shapira, McMurtray, & Licht, 2007). Memantine did not improve or delay progression of FTD symptoms in one trial (Boxer et al., 2013).

Treatment is largely focused on the management of behavioral symptoms in which pharmacological and behavioral interventions can be helpful. FTD symptoms and behavior including compulsions, agitation, aggressiveness, impulsivity, and aberrant eating behavior can improve with selective serotonin uptake inhibitors (SSRIs) (Herrmann et al., 2012; Mendez, Shapira, & Miller, 2005; Swartz, Miller, Lesser, & Darby, 1997). Atypical antipsychotics should be used with caution in FTD, as these patients may have increased vulnerability to the extrapyramidal side effects (Pijnenburg, Sampson, Harvey, Fox, & Rossor, 2003), but may have some benefit with low doses (Asmal et al., 2013). There is little evidence for benefit from mood stabilizers in FTD (Chow & Mendez, 2002; Cruz, Marinho, Fontenelle, Engelhardt, & Laks, 2008). One small randomized, placebo-controlled double-blinded trial of trazodone in FTD patients showed improvement in neuropsychiatric symptoms but no change in MMSE (Lebert, Stekke, Hasenbroekx, & Pasquier, 2004). Oxytocin has been proposed as a potential therapy targeting the emotional changes in FTD, and a small double-blind placebo-controlled pilot study showed mild improvement in psychiatric symptoms after its use (Finger, 2011; Jesso et al., 2011).

There are also important nonpharmacological therapies to treat FTD symptoms. Caregiver education about behavioral, environmental, and physical techniques can minimize or redirect unwanted behaviors (Merrilees, 2007). Patients with nfvPPA, svPPA, and language deficits may benefit from speech therapy; although patients will not regain lost function, therapy can maximize their remaining communication skills (Kortte & Rogalski, 2013). Clinicians should also

TABLE 14.2 General treatment approach for psychiatric symptoms in dementia.

Identify and describe the behavior, including severity and frequency
Rule out other causes • Environmental factors • Primary psychiatric conditions (e.g., history of bipolar disorder, PTSD, major depressive disorder) • Physical illness (e.g., pain, infection) • Medication side effects
Implement nonpharmacologic treatment approaches • Caregiver education and support • Modification of the environment • Specific modalities pertinent to the symptom (e.g., modified CBT for depression or anxiety)
If the behavior risks harm to the patient or others, causes significant distress, or is not responsive to nonpharmacologic approaches, consider medications
Review treatment goals with patient and caregivers
Monitor treatment response and progress toward goals. If taking a medication, monitor side effects

become aware of resources for their patients and families such as The Association for Frontotemporal Degeneration, and of opportunities for their patients to participate in clinical trials of disease-modifying therapies for FTLD.

Common psychiatric symptoms in dementia and their management

Common to all of the above-described disorders is the high incidence of psychiatric symptoms. Psychiatric symptoms in this context are also often referred to as behavioral and psychological symptoms in dementia or neuropsychiatric symptoms. Dementia results from brain injuring processes that can affect any aspect of brain function, including regulation of emotions, moods, perceptions, and behaviors. Further, in this chapter, we describe several of these in more detail, including apathy, agitation, psychosis, depression, and anxiety. However, there are general principles to treatment and management that can be applied to any of these symptoms.

Table 14.2 summarizes this general treatment approach toward assessing and addressing psychiatric symptoms. Obtaining a good history from caregivers, and from patients to the degree they are able, is of key importance. Because there is a wide range of behaviors that respond differently to different treatment approaches, it is useful to identify the specific behavior involved. Quantifying the frequency and severity of this behavior will also aid in developing treatment goals and later monitoring treatment response. Ruling out other causes of psychiatric symptoms including a clear environmental contributor, primary psychiatric illness, or general medical illness ensures that patients receive appropriate treatment for these causes if present.

After obtaining a history and ruling out other conditions, a treatment plan can be determined. Nonpharmacologic treatments are universally recommended by treatment guidelines, as they have been shown to be effective and have the advantage of not incurring side effects. When nonpharmacologic approaches alone are not sufficient, medications can be considered, keeping in mind the risk−benefit ratios of specific medications as well as patient and family preferences. The more effective treatment plans often involve both nonpharmacologic and pharmacologic interventions, with ongoing monitoring, reassessment, and adjustment over time.

Apathy

Apathy is an under-recognized psychiatric symptom of dementia and is characterized by core features of diminished motivation, diminished initiative and interest, and blunting of emotions (Starkstein, Petracca, Chemerinski, & Kremer, 2001). In dementia, it has been proposed that apathy is an aspect of executive dysfunction syndrome caused by damage to frontal-subcortical brain circuits (Lyketsos, Rosenblatt, & Rabins, 2004). Apathy has been associated with functional disability, self-neglect, and caregiver distress (Landes, Sperry, Strauss, & Geldmacher, 2001; Politis et al., 2004). It has also been associated with more rapid cognitive and functional decline (Starkstein, Jorge, Mizrahi, & Robinson, 2006), increased mortality in AD (Spalletta et al., 2015) and worse outcomes across an array of neurological diagnoses (Jorge, Starkstein, & Robinson, 2010; Wee et al., 2016).

In addition to being one of the most salient behavioral and psychological symptoms of dementia, it is also one of the most common. In subjects with Alzheimer's disease, apathy is the most frequent neuropsychiatric symptom (Mega, Cummings, Fiorello, & Gornbein, 1996). Apathy is also common in numerous other neurodegenerative disorders including FTD, dementia with Lewy bodies, and Parkinson's disease (Cummings, Diaz, Levy, Binetti, & Litvan, 1996).

Nonpharmacologic treatments

Nonpharmacological interventions for apathy were examined in a systematic review (Theleritis, Siarkos, Katirtzoglou, & Politis, 2017). Interventions from included studies were various: activity programming, family support, caregiver education, simulated presence, walking/talking programs, meetings with an activity therapist, reminiscence programs, live interactive music, validation therapy, strengthening and balance exercise, progressive muscle relaxation, CST, art therapy, and Snoezelen. A real effect could not be quantified given limitations in study designs; however, aggregated studies suggest that apathy improves with a variety of nonpharmacological individual or group interventions including programs of cognitive stimulation, physical activity, and socialization. It appears that combined treatments might be of greater benefit than monotherapies, and since these nonpharmacological treatments are quite safe and well accepted, they should be heartily encouraged. Treatments could be individualized to take into account the patient's past preferences and environmental factors. Family and caregivers should be educated to address the common misperception that apathetic patients are lazy or oppositional. This may better enable caregivers to implement interventions that may improve apathy, such as directly prompting them to initiate activities, using visual cues to behaviors and establishing routines for daily activities.

Pharmacologic treatments

Pharmacological strategies have produced varying results. A recent Cochrane systematic review examining the treatment of apathy in AD (Ruthirakuhan, Herrmann, Abraham, Chan, & Lanctôt, 2018) included 21 studies involving a total of 6384 participants in the quantitative analyses. Only four studies, three with methylphenidate and one with modafinil, had apathy as a primary outcome. These suggest that methylphenidate may be beneficial in the treatment of apathy and may slightly improve cognition and instrumental activities of daily living in patients with Alzheimer's dementia. The risk of adverse events between methylphenidate and placebo may be no different. In all other included studies, apathy was a secondary outcome, and thus the evidence on apathy from these studies was indirect and potentially associated with publication bias. There was low or very low quality of evidence for ChEIs, ChEI discontinuation, antipsychotics, antipsychotic discontinuation, antidepressants, mibampator, valproate, and semagacestat.

Agitation

Agitation is a term used to describe a broad range of behaviors, examples of which can include motor activity (e.g., pacing, rocking), verbal aggression (e.g., yelling, using profanity), or physical aggression (e.g., hitting others, throwing objects). In 2015, the International Psychogeriatric Association's Agitation Definition Working Group published a consensus definition, summarized as follows: (1) the patient meets criteria cognitive impairment or dementia, (2) there is emotional distress associated with at least one of three types of behavior (motor activity, verbal aggression, and physical aggression), occurring for at least 2 weeks, (3) the behavior causes disability, and (4) the behavior cannot be solely attributable to another cause (e.g., environment, psychiatric or medical illness, effects of a substance) (Cummings et al., 2015).

The sequelae of agitation are significant. Caregivers identify agitation as one of the more distressing symptoms in patients and a contributor to caregiver depression (Fauth & Gibbons, 2014). Agitation has been identified as a leading precipitant for institutionalization (Okura et al., 2011). The significance of agitation is compounded by how commonly it occurs, with some estimates describing prevalence rates of 40%−60% of patients with Alzheimer's dementia living in long-term care facilities and 30% of community-dwelling patients (Lyketsos et al., 2002; Margallo-Lana et al., 2001).

Nonpharmacologic treatments

Nonpharmacologic treatments vary widely, ranging from specific modalities (e.g., music therapy) to algorithms that provide caregivers a systematic approach to addressing symptoms (Teri et al., 2010). One way to conceptualize these treatments is to consider their underlying theoretical frameworks (Cohen-Mansfield, 2001).

One such framework is the unmet needs model, and as its name implies, states that behaviors can result from a patient's inability to communicate needs, both physical and emotional. Interventions are intended to meet these needs preemptively such that behaviors no longer result. Examples of such interventions that may fit in this model include

those that provide social or sensory stimulation, such as exercise therapy, music therapy, real or simulated contact, pet therapy, and structured activities. Interventions that address a physical need can include scheduled toileting, ensuring consistent use of sensory aids such as eyeglasses and hearing aids, and assessing for adequate pain control.

The reduced (or progressively lowered) stress threshold model refers to the experience that patients with dementia lose their abilities to process stimuli, resulting in their being overwhelmed more easily than those without cognitive impairment. Interventions that focus on reducing stimuli or producing a calmer environment fall within this model and may include relaxation therapies, caregiver education to simplify interactions, changes to the living environment, and appropriately tailoring activities to the patient's cognitive level (Hall & Buckwalter, 1987).

Functional analysis, which is based on learning/behavioral theory, is a model by which providers can conceptualize the function behind repeated behaviors, allowing the development of a tailored intervention for that behavior (Moniz Cook et al., 2012). Also known as the A-B-C's (Antecedents [A], Behavior [B], and Consequences [C]), this approach can be utilized by providers or taught to caregivers. Research studies of this approach typically include functional analysis as one component in a larger systematic approach. One clinical example could be a patient who is resistant to showering (Behavior), resulting in the requirement of multiple staff members to assist (Consequence). History obtained from family may discover that the patient had a history of trauma and therefore need for security and privacy (Antecedent), and that the presence of multiple staff perpetuates the behavior (both a Consequence and Antecedent). This analysis provides the space to creatively develop interventions, such as instituting bed baths instead of showering or working with specific staff the patient has a greater affinity with.

Pharmacologic treatments

Pharmacologic treatments can be a key treatment option when symptoms are severe or when nonpharmacologic approaches are not sufficient. The challenge with choosing a medication lies in the fact that many have limited research supporting use, and the class of medications with the strongest research base, the atypical antipsychotics, have modest efficacy and often are limited by side effects, such as sedation and parkinsonism. And there is a black box warning for increased risk of mortality associated with antipsychotics in this population.

Therefore, the choice of pharmacologic agent is guided by weighing potential benefits, the potential risk or side effects of the medication, and the risk of undertreatment. A summary of this approach is summarized in Table 14.3. For example, in the case of a patient with severe symptoms that risk harm to self or others (e.g., daily physical aggression), an antipsychotic would be appropriate, as the risk of not treating is high and outweighs the side effect profile and risk for mortality associated with these agents. On the other hand, in the case of a patient with milder symptoms (e.g., verbal aggression a few times a week), a medication with fewer side effects than antipsychotics would be appropriate, even if this agent has less demonstrated efficacy in the research literature. It is helpful to discuss with patients and families their goals of care, as palliative approaches are appropriate in this clinical context (Passmore, Ho, & Gallagher, 2012).

TABLE 14.3 Medication choices based on risk–benefit ratio.

Agitation characteristics	Medication choices	Time to response
Infrequent	Cholinesterase inhibitors	Weeks
Mild distress	Memantine	
	SSRIs	
Frequent	Atypical antipsychotics	Days to weeks
Significant distress	SSRIs	
Interferes with necessary care	Prazosin	
	Dextromethorphan-quinidine	
	anticonvulsants	
Physical aggression (hitting, kicking, throwing things)	Atypical antipsychotics	Days
The safety of the patient or others is at risk	Benzodiazepines	

For example, some patients and families are willing to accept sedating side effects or mortality risk if a treatment results in greater patient comfort. Others may wish to avoid side effects, and therefore accept some degree of agitation remaining present.

Antipsychotics

Atypical antipsychotics are the most studied class of medications for the treatment of agitation in dementia. As a whole, published efficacy studies showed benefit over placebo (Katz et al., 1999; Street et al., 2000; Streim et al., 2008; Zhong, Tariot, Mintzer, Minkwitz, & Devine, 2007). However, several challenges were present, limiting interpretability of these studies. One of these was regulatory, in that early studies seeking FDA approval designated psychosis of dementia as the primary outcome measure, with agitation being measured as a secondary outcome. While agitation improved in these studies, the primary outcome measure of psychosis was generally not shown to be meaningfully better than placebo, and FDA approval was in the end not obtained (Raskind & Wang, 2014).

Another challenge lies in the fact that trials typically enroll participants with milder severity symptoms, as understandably families of patients with severe symptoms may not be comfortable enrolling a loved one in a study with a placebo arm. However, those with more severe baseline symptoms are more likely to respond to atypical antipsychotics; for example, a meta-analysis of risperidone trials found a larger effect size for patients with more severe psychosis and aggression symptoms at baseline (Katz et al., 2007). Devenand et al. addressed this difficulty through a discontinuation study design, in which participants with dementia-related agitation or psychosis received open-label risperidone and were then randomly assigned in a double-blind manner to continued risperidone or placebo; in patients who had responded to risperidone therapy, discontinuation of risperidone (i.e., being placed in the placebo arm) was associated with a higher risk of symptom recurrence (Devanand et al., 2012).

Results from the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) study, added question over benefit for these medications in light of their side effects (Schneider et al., 2006). In this trial, risperidone, olanzapine, quetiapine, and placebo were compared head-to-head, with the primary outcome measure being time to discontinuation for any reason, including lack of efficacy or side effects. No difference was found amongst the treatment groups or placebo. Around this time, a meta-analysis of 17 placebo-controlled trials of aripiprazole, olanzapine, quetiapine, and risperidone in patients with dementia-related agitation and psychosis raised the question of an increased all-cause mortality risk associated with use of these medications (Schneider, Dagerman, & Insel, 2005). In this analysis, the risk of mortality was 1.6−1.7 times greater in those taking atypical antipsychotic medications than those taking placebo. There now exists an FDA black box warning describing this risk in elderly patients with dementia-related psychosis and agitation.

These conflicting findings add to the complexity behind decision-making around prescribing atypical antipsychotics. These agents have demonstrated benefits for many, but not all. There are side effects and an increased mortality risk, but this is a clinical scenario where patients and families often value quality of life over length of life. And there do not exist better-studied alternatives to treatment, particularly for severe symptoms. Atypical antipsychotics remain commonly used agents and, if carefully prescribed and monitored, are often beneficial for treatment of severe agitation and aggression.

In 2016, the American Psychiatric Association published new guidelines on the use of antipsychotic medications for treating dementia-related psychosis and agitation (Reus et al., 2016). These guidelines reinforce use where there is significant distress to the patient or behaviors risk harm to themselves or others. To ensure appropriate monitoring, they recommend assessing patients' response to these medications and stopping use if insufficient benefit is seen. Because psychiatric symptoms in dementia can wax and wane, many people tolerate discontinuation of agents after a period of improvement. Guidelines therefore recommend trial dose reductions after 4 months, with monthly monitoring for 4 months afterward to ensure that those in whom symptoms do recur are treated promptly.

Antidepressants

A multisite randomized clinical trial of citalopram (the CitAD trial) demonstrated superiority of citalopram over placebo for reducing agitation (Porsteinsson et al., 2014). Forty percent of patients in the citalopram arm were rated as moderately to markedly improved compared to 26% receiving placebo. However, adverse effects included lengthening of the QT interval and a decline in cognition as measured by the MMSE was greater than in the placebo arm. Another *caveat* is that the target dose in this trial was 30 mg daily, exceeding the current FDA advisory limit of 20 mg in older adults because of a dose-dependent risk for QTc prolongation.

A subsequent secondary analysis identified likely AD responders to citalopram for agitation (Schneider et al., 2016). Those living at home, who had milder cognitive symptoms and had moderate baseline agitation, were more likely to respond. In those participants living in long-term care facilities and who had more severe dementia and more severe agitation, placebo tended to outperform citalopram. Citalopram remains a pharmacologic option for outpatients with mild-to-moderate agitation but does not appear to be useful for treating severe agitation in the long-term care setting.

Anticonvulsants

Carbamazepine and valproic acid have been studied for treating dementia-related agitation. Carbamazepine is supported by several small studies for treating agitation (Tariot et al., 1994; Tariot et al., 1998), which also demonstrated good tolerability in their participants. Drug−drug interactions, need for blood level monitoring, and a black box warning for hematologic toxicity are reasons for caution when considering this agent. Initial studies of valproic acid suggested efficacy for agitation (Porsteinsson et al., 2001; Tariot et al., 2001), but a subsequent larger-scale randomized clinical trial failed to support these early findings (Tariot et al., 2005).

Antiadrenergic medications

CSF and postmortem brain autopsy studies have found alterations in the noradrenergic system in patients with AD, suggesting that although the number of norepinephrine-producing neurons decreases, a compensatory upregulation in this system occurs, including increased norepinephrine production in remaining noradrenergic neurons and increased number of alpha-1 adrenoreceptors (Elrod et al., 1997; Szot et al., 2006, 2007). In a clinical study in which AD and control participants were given yohimbine, which stimulates norepinephrine outflow (and confirmed in this study through CSF norepinephrine measurements), AD patients developed agitation symptoms, whereas the control participants did not (Peskind et al., 1995). Increased alpha-1 receptor number measured postmortem has been associated with agitation in AD patients (Sharp, Ballard, Chen, & Francis, 2007). Taken together, this evidence suggests that compensatory noradrenergic upregulation likely contributes to agitation in AD.

Subsequently, we evaluated prazosin, an alpha-1 receptor antagonist, in a double-blind placebo-controlled pilot study of patients with dementia-related agitation (Wang et al., 2009). Study results showed improvement in overall psychiatric symptomatology as measured by the Neuropsychiatric Inventory, as well as clinical global improvement compared to placebo. A multisite randomized controlled clinical trial in long-term care patients is currently underway. Anecdotally, we have seen a reduction in agitation in patients who have not tolerated or have not responded to other approaches, including atypical antipsychotics. Because prazosin has a benign side effect profile compared to other agents and notably lacks the side effects of sedation and parkinsonism, prazosin is a promising alternative to atypical antipsychotics. It is noteworthy that the antipsychotic drugs effective for agitation in AD also have substantial alpha-1 adrenoreceptor antagonist activity.

Dextromethorphan-quinidine

Dextromethorphan-quinidine, which is a treatment FDA approved for pseudobulbar affect, was found in a 2015 Phase 2 study to reduce agitation in outpatients with AD (Cummings et al., 2015). The medication was generally well tolerated. This proprietary drug combination has not been evaluated in AD patients with severe agitation residing in long-term care, and costs may be prohibitive.

Benzodiazepines

Guidelines appropriately recommend against the use of benzodiazepines except in emergency situations and for short-term use. Adverse effects include cognitive impairment, sedation, and an increase in fall risk, and benzodiazepines can cause a paradoxical increase in agitation in some patients. Use of benzodiazepines in older adults without dementia has been associated with an increased risk for subsequent development of dementia (Billioti de Gage et al., 2014). Shorter-acting benzodiazepines such as lorazepam, oxazepam, and temazepam are preferred over longer-acting benzodiazepines, as they are less likely to accumulate and metabolism is less affected by liver function.

Psychosis

Psychotic symptoms common in dementia include hallucinations and delusions (Jeste & Finkel, 2000). Such symptoms occur frequently with one study estimating a 4-year cumulative incidence of 51% in patients with AD (Paulsen et al., 2000). Hallucinations may be auditory or visual. Visual hallucinations are known to be associated with DLB and PDD,

such that visual hallucinations are considered a core diagnostic feature of DLB. Delusions tend to be paranoid, but non-bizarre, and it can often be difficult to differentiate a delusion from a patient misinterpreting a situation because of cognitive impairment. An example scenario is a patient believing an item has been stolen, when in fact the item was misplaced. Other common delusions include suspicion of infidelity of a spouse, a belief that their home is not truly their home, or misidentifying caregivers.

Nonpharmacologic treatment

Because psychotic symptoms can be misinterpreted by observers, an initial first step is to assess for an alternative explanation (Cohen-Mansfield, 2003). Caregivers or family members may infer that hallucinations have occurred when hearing a patient describe nonreality-based experiences (e.g., patient talking about a conversation with a deceased relative), when another explanation could be the patient describing a memory. If there is vision and hearing impairment, addressing the need for corrective lenses, hearing aids, and appropriate lighting is important. Statements about one's home not being his or her home or misidentifying caregivers may instead be a manifestation of anxiety in combination with memory impairment. Often, symptoms are more distressing to caregivers than to the patients themselves. In such cases, education for caregivers about the nature of dementia, memory loss, and ways to address a patient's underlying needs is therapeutic.

Pharmacologic treatment for patients without Parkinson's disease

A challenge with regards to pharmacologic treatment of psychotic symptoms is that antipsychotic medications have demonstrated limited efficacy for patients with dementia types other than PDD. In clinical trials investigating atypical antipsychotics for the treatment of agitation and psychosis in AD, the effect on psychosis was considered nonsignificant with the exception of risperidone, where the effect was small (Maher et al., 2011). Therefore, it is important to gage whether a patient is experiencing significant distress from psychotic symptoms, with a preference toward not using an antipsychotic if symptoms are not adversely affecting quality of life. If psychotic symptoms are indeed distressing to patients and impair quality of life, an atypical antipsychotic medication is appropriate. The same practice guidelines as described above in the agitation section apply, including careful monitoring of response, and gradual dose reductions after 4 months of response, if tolerated.

Pharmacologic treatment for patients with Parkinsons' disease dementia

Psychotic symptoms are a common occurrence in PDD. While the emphasis on nonpharmacologic approaches remains, different pharmacologic strategies exist for this population. Reexamining their PD medication regimen is an important initial step, as psychotic symptoms in many cases can be side effects of PD medications. Steps include first reducing or stopping adjunct therapy (e.g., anticholinergics, monoamine oxidase inhibitors (MAOIs), amantadine), then reducing or stopping dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors, and then reducing levodopa. It is important to bear in mind that these medications are necessary to treat motor symptoms, so reductions in these medications may not be possible, resulting in persistent psychotic symptoms. With the progression of PDD, psychotic symptoms often worsen in spite of unchanged or lowering doses of PD mediations. Therefore, antipsychotics do play a role in treatment.

Because patients with PDD are sensitive to extrapyramidal symptoms caused by antipsychotic medications, the decision to treat symptoms is not taken lightly. Antipsychotics are best avoided when hallucinations or delusions are mild or nondistressing. If symptoms are distressing to the patient and impairing quality of life, the three antipsychotic medications appropriate for use in PDD patients are pimavanserin, clozapine, and quetiapine. Pimavanserin is FDA-approved specifically for PD-related psychosis (Cummings et al., 2014). Clozapine has been shown to be effective, but significant side effects include agranulocytosis, requiring prescribers to have specific training and monitoring with up to weekly blood tests. Efficacy for quetiapine is less clear, but a perceived lower risk of extrapyramidal symptoms has led to quetiapine's use in this setting.

Depression

Depression is a common symptom in dementia, with prevalence estimates ranging up to 50% (Steinberg et al., 2008). Depression also contributes to caregiver burden and has been associated with other symptoms including anxiety, sleep disturbance, and suicide (Seyfried, Kales, Ignacio, Conwell, & Valenstein, 2011; Van der Mussele et al., 2013).

Depression in dementia often presents differently than in people without cognitive impairment. NIMH provisional diagnostic criteria for depression in AD were formulated in 2002, with key differences from DSM criteria for major depressive disorder intended to accommodate cognitive impairment and include a wider range of presentations. These differences included "decreased positive affect or pleasure" in place of "loss of interest or pleasure in most or all activities," and the removal of "poor concentration" (Olin et al., 2002). Added criteria include irritability and social isolation. The use of these criteria can result in the inclusion of people with a milder symptom presentation, which increases depression prevalence estimates compared to use of DSM major depressive disorder criteria (Sepehry et al., 2017).

As the presentation of depression differs compared to people without dementia, treatment approaches also differ. Consistent with approaches to other psychiatric symptoms in dementia, nonpharmacologic approaches are preferred, driven by the demonstrated efficacy of some nonpharmacologic approaches and limited evidence for antidepressant medications.

Nonpharmacologic treatments

Psychotherapies for depression in patients with mild dementia include problem-solving therapy and modified cognitive behavioral therapy (CBT). Problem-solving therapy is one of the more rigorously studied psychotherapies for patients with cognitive impairment. It provides a structured approach where patients select and examine a problem, develop potential solutions, and implement such solutions. Elements including calendars, notebooks, and checklists provide adaptability. It is thought that this approach addresses the executive functioning deficits seen in mild dementia stages (Alexopoulos, Raue, Kanellopoulos, Mackin, & Arean, 2008). CBT in patients with dementia has been examined, with modifications including more emphasis on behavioral aspects of treatment, more practice time in sessions, provision of written summaries of sessions, and inclusion of a caregiver who can assist in reviewing material and implementing homework between sessions.

Behavioral activation has also been evaluated in patients with dementia of varying stages. This approach emphasizes regularly scheduling pleasurable activities, and benefits can be seen in both patients and their caregivers. Community programs exist that promote engagement of dementia patients in pleasurable activities. Examples include senior center programs, adult day care and day health programs, and memory and Alzheimer's cafes.

Pharmacologic treatments

In early studies, antidepressant medications were demonstrated to have efficacy and tolerability in patients with depression and dementia (Lyketsos et al., 2003; Nelson & Devanand, 2011). Two large randomized controlled clinical trials shed doubt over these conclusions, however. The sertraline or mirtazapine for depression in dementia (HTA-SADD) trial and the Depression in Alzheimer's Disease-2 (DIADS-2) (sertraline) trial both did not find a difference in response between antidepressant medication and placebo (Banerjee et al., 2011; Rosenberg et al., 2010). Adverse effects were more common in the active drug groups, including gastrointestinal and respiratory side effects.

Although research results are mixed, when behavioral and environmental approaches are inadequate, antidepressant medications remain a mainstay in treatment. They are generally well tolerated by patients and there are no other medication classes thought to be effective for depression. Serotonin reuptake inhibitors have more favorable side effect profiles, with sertraline, citalopram, and escitalopram specifically preferred in older adults because of fewer drug−drug interactions than other SSRIs. Mirtazapine and trazodone are also commonly used if sedating side effects can be of assistance with sleep disturbance. Serotonin-norepinephrine reuptake inhibitors are also options, with the caution that with severe renal impairment, venlafaxine requires a dose reduction and duloxetine is contraindicated. Bupropion is reputed to have a more activating effect than SSRIs, but caution is recommended due to seizure risk, which is higher in dementia patients. Tricyclic antidepressants have anticholinergic side effects that can worsen cognition and contribute to constipation and urinary retention. MAOIs require a tyramine-free diet restriction to avoid hypertensive crisis.

Electroconvulsive therapy and transcranial magnetic stimulation

Electroconvulsive therapy (ECT) is a safe and effective treatment for depression, although studies in cases of depression in dementia are limited. ECT should be considered when safety is threatened and rapid improvement is needed. Short-term memory loss is a known side effect of ECT, and worsening of cognitive symptoms with dementia patients can occur. Patients taking ChEIs during ECT may experience less cognitive impairment following ECT than those not taking these agents (Hausner, Damian, Sartorius, & Frolich, 2011).

Repetitive transcranial magnetic stimulation is an FDA-approved treatment for treatment-resistant depression. Case reports suggest improvement in depression and cognitive symptoms in patients with AD and DLB, but this modality is

yet to be studied systematically in the dementia population (Elder & Taylor, 2014). Transient localized pain is a potential side effect, and in rare instances (prevalence less than 1% in normal populations), TMS can induce seizures.

Anxiety

Anxiety is closely related to depression in dementia, and some have suggested that anxiety is best considered a component of depression. Anxiety is a common symptom, with some studies reporting prevalence estimates in dementia patients ranging from 5% to 21% for anxiety disorders and 8% to 71% for anxiety symptoms (Seignourel, Kunik, Snow, Wilson, & Stanley, 2008). How anxiety is defined in the literature is variable, as commonly used rating scales have not been robustly validated in patients with dementia. In clinical practice, DSM criteria for anxiety can be applied.

Nonpharmacologic treatments

Similar to depression treatment, modified CBT is an approach that can be beneficial for anxiety symptoms. Modifications include emphasizing skills (as opposed to cognitive interventions), focusing on one skill at a time, and spending more time in session practicing skills. Caregivers are present and involved in sessions as well, learning skills and principles, and can take on the role of coaches for patients. One protocol, called Peaceful Mind (Stanley et al., 2013), has modules on self-awareness, breathing techniques, calming statements, increasing activity, and sleep skills. Both patients and caregivers report benefit from these approaches, with reductions in anxiety and in caregiver stress.

Music therapy has been studied for many psychiatric symptoms in dementia, but may be particularly beneficial in anxiety. One meta-analysis found that the largest effect of music therapy was seen in anxiety symptoms both in the short and long term (Ueda, Suzukamo, Sato, & Izumi, 2013).

Pharmacologic treatments

Use of medications for the treatment of anxiety symptoms in dementia has not been as robustly studied as other symptoms. Retrospective case studies or case reports describe potential benefits from mirtazapine, buspirone, and quetiapine (Cooper, 2003; Gardner, Malone, Sey, & Babington, 2004; Savaskan et al., 2006). Because of the lack of clear guidance, if a medication is considered necessary, SSRIs are often used. This is in part due to effectiveness of this class for anxiety disorders in general and relatively safe tolerability profile compared to other medication classes. Benzodiazepines are best used for short-term treatment and for severe symptoms, due to potential risks including falls and confusion.

References

Aarsland, D., Ballard, C., Walker, Z., Bostrom, F., Alves, G., Kossakowski, K., ... Londos, E. (2009). Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: A double-blind, placebo-controlled, multicentre trial. *Lancet Neurology*, *8*(7), 613−618. Available from https://doi.org/10.1016/s1474-4422(09)70146-2.

Abraha, I., Rimland, J. M., Trotta, F. M., Dell'Aquila, G., Cruz-Jentoft, A., Petrovic, M., ... Cherubini, A. (2017). Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open*, *7*(3), e012759. Available from https://doi.org/10.1136/bmjopen-2016-012759.

Alexopoulos, G. S., Raue, P. J., Kanellopoulos, D., Mackin, S., & Arean, P. A. (2008). Problem solving therapy for the depression-executive dysfunction syndrome of late life. *International Journal of Geriatric Psychiatry*, *23*(8), 782−788. Available from https://doi.org/10.1002/gps.1988.

Alzheimer, A. (1911). Uber eigenartige Karnkheitsfalle der spateren Alters. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, *4*, 356−385.

Alzheimer's Association. (2018). *Alzheimer's disease facts and figures*. <https://www.alz.org/alzheimers-dementia/facts-figures>.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Asmal, L., Flegar, S. J., Wang, J., Rummel-Kluge, C., Komossa, K., & Leucht, S. (2013). Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* (11), CD006625. Available from https://doi.org/10.1002/14651858.CD006625.pub3.

Banerjee, S., Hellier, J., Dewey, M., Romeo, R., Ballard, C., Baldwin, R., ... Burns, A. (2011). Sertraline or mirtazapine for depression in dementia (HTA-SADD): A randomised, multicentre, double-blind, placebo-controlled trial. *Lancet*, *378*(9789), 403−411. Available from https://doi.org/10.1016/s0140-6736(11)60830-1.

Bang, J., Spina, S., & Miller, B. L. (2015). Frontotemporal dementia. *Lancet*, *386*(10004), 1672−1682. Available from https://doi.org/10.1016/s0140-6736(15)00461-4.

Billioti de Gage, S., Moride, Y., Ducruet, T., Kurth, T., Verdoux, H., Tournier, M., ... Bégaud, B. (2014). Benzodiazepine use and risk of Alzheimer's disease: Case-control study. *British Medical Journal*, *349*, g5205. Available from https://doi.org/10.1136/bmj.g5205.

Birks, J. S., & Harvey, R. J. (2018). Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews*, *6*, CD001190. Available from https://doi.org/10.1002/14651858.CD001190.pub3.

Boxer, A. L., Knopman, D. S., Kaufer, D. I., Grossman, M., Onyike, C., Graf-Radford, N., … Miller, B. L. (2013). Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurology*, *12*(2), 149−156. Available from https://doi.org/10.1016/S1474-4422(12)70320-4.

Chen, R., Chan, P. T., Chu, H., Lin, Y. C., Chang, P. C., Chen, C. Y., & Chou, K. R. (2017). Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: A meta-analysis. *PLoS One*, *12*(8), e0183586. Available from https://doi.org/10.1371/journal.pone.0183586.

Chow, T. W., & Mendez, M. F. (2002). Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration. *American Journal of Alzheimer's Disease and Other Dementias*, *17*(5), 267−272. Available from https://doi.org/10.1177/153331750201700504.

Cohen-Mansfield, J. (2001). Nonpharmacologic interventions for inappropriate behaviors in dementia: A review, summary, and critique. *The American Journal of Geriatric Psychiatry*, *9*(4), 361−381.

Cohen-Mansfield, J. (2003). Nonpharmacologic interventions for psychotic symptoms in dementia. *Journal of Geriatric Psychiatry and Neurology*, *16*(4), 219−224. Available from https://doi.org/10.1177/0891988703258665.

Cooper, J. P. (2003). Buspirone for anxiety and agitation in dementia. *Journal of Psychiatry and Neuroscience*, *28*(6), 469.

Cruz, M., Marinho, V., Fontenelle, L. F., Engelhardt, E., & Laks, J. (2008). Topiramate may modulate alcohol abuse but not other compulsive behaviors in frontotemporal dementia: Case report. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *21*(2), 104−106. Available from https://doi.org/10.1097/WNN.0b013e31816bdf73.

Cummings, J., Mintzer, J., Brodaty, H., Sano, M., Banerjee, S., Devanand, D. P., … Association, I. P. (2015). Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*, *27*(1), 7−17. Available from https://doi.org/10.1017/S1041610214001963.

Cummings, J. L., Diaz, C., Levy, M., Binetti, G., & Litvan, I. (1996). Neuropsychiatric syndromes in neurodegenerative disease: Frequency and signficance. *Seminars in Clinical Neuropsychiatry*, *1*(4), 241−247. Available from https://doi.org/10.1053/scnp00100241.

Cummings, J. L., Isaacson, S., Mills, R., Williams, H., Chi-Burris, K., Corbett, A., … Ballard, C. (2014). Pimavanserin for patients with Parkinson's disease psychosis: A randomised, placebo-controlled phase 3 trial. *Lancet*, *383*(9916), 533−540. Available from https://doi.org/10.1016/s0140-6736(13)62106-6.

Cummings, J. L., Lyketsos, C. G., Peskind, E. R., Porsteinsson, A. P., Mintzer, J. E., Scharre, D. W., … Siffert, J. (2015). Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: A randomized clinical trial. *The Journal of the American Medical Association*, *314*(12), 1242−1254. Available from https://doi.org/10.1001/jama.2015.10214.

de Bruijn, R. F., Bos, M. J., Portegies, M. L., Hofman, A., Franco, O. H., Koudstaal, P. J., & Ikram, M. A. (2015). The potential for prevention of dementia across two decades: The prospective, population-based Rotterdam Study. *BMC Medicine*, *13*, 132. Available from https://doi.org/10.1186/s12916-015-0377-5.

Devanand, D. P., Mintzer, J., Schultz, S. K., Andrews, H. F., Sultzer, D. L., de la Pena, D., … Levin, B. (2012). Relapse risk after discontinuation of risperidone in Alzheimer's disease. *The New England Journal of Medicine*, *367*(16), 1497−1507. Available from https://doi.org/10.1056/NEJMoa1114058.

Doody, R. S., Stevens, J. C., Beck, C., Dubinsky, R. M., Kaye, J. A., Gwyther, L., … Cummings, J. L. (2001). Practice parameter: Management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, *56*(9), 1154−1166.

Elder, G. J., & Taylor, J. P. (2014). Transcranial magnetic stimulation and transcranial direct current stimulation: Treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? *Alzheimer's Research & Therapy*, *6*(9), 74. Available from https://doi.org/10.1186/s13195-014-0074-1.

Elrod, R., Peskind, E. R., DiGiacomo, L., Brodkin, K. I., Veith, R. C., & Raskind, M. A. (1997). Effects of Alzheimer's disease severity on cerebrospinal fluid norepinephrine concentration. *The American Journal of Psychiatry*, *154*(1), 25−30. Available from https://doi.org/10.1176/ajp.154.1.25.

Emre, M., Tsolaki, M., Bonuccelli, U., Destée, A., Tolosa, E., Kutzelnigg, A., … Investigators, S. (2010). Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: A randomised, double-blind, placebo-controlled trial. *Lancet Neurology*, *9*(10), 969−977. Available from https://doi.org/10.1016/s1474-4422(10)70194-0.

Fauth, E. B., & Gibbons, A. (2014). Which behavioral and psychological symptoms of dementia are the most problematic? Variability by prevalence, intensity, distress ratings, and associations with caregiver depressive symptoms. *International Journal of Geriatric Psychiatry*, *29*(3), 263−271. Available from https://doi.org/10.1002/gps.4002.

Finger, E. C. (2011). New potential therapeutic approaches in frontotemporal dementia: Oxytocin, vasopressin, and social cognition. *Journal of Molecular Neuroscience*, *45*(3), 696−701. Available from https://doi.org/10.1007/s12031-011-9550-2.

Gardner, M. E., Malone, D. C., Sey, M., & Babington, M. A. (2004). Mirtazapine is associated with less anxiolytic use among elderly depressed patients in long-term care facilities. *Journal of the American Medical Directors Association*, *5*(2), 101−106. Available from https://doi.org/10.1097/01.JAM.0000110650.51872.91.

Garrett, M. D., & Valle, R. (2016). A methodological critique of the National Institute of Aging and Alzheimer's Association Guidelines for Alzheimer's disease, dementia, and mild cognitive impairments. *Dementia (London)*, *15*(2), 239−254. Available from https://doi.org/10.1177/1471301214525166.

Geldmacher, D. S., & Kerwin, D. R. (2013). Practical diagnosis and management of dementia due to Alzheimer's disease in the primary care setting: An evidence-based approach. *The Primary Care Companion for CNS Disorders*, *15*(4). Available from https://doi.org/10.4088/PCC.12r01474.

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., ... Council on Cardiovascular Surgery and Anesthesia. (2011). Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke*, *42*(9), 2672–2713. Available from https://doi.org/10.1161/STR.0b013e3182299496.

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., ... Miller, B. L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology*, *55*(3), 335–346. Available from https://doi.org/10.1002/ana.10825.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., ... Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006–1014. Available from https://doi.org/10.1212/WNL.0b013e31821103e6.

Hall, G. R., & Buckwalter, K. C. (1987). Progressively lowered stress threshold: A conceptual model for care of adults with Alzheimer's disease. *Archives of Psychiatric Nursing*, *1*(6), 399–406.

Hanagasi, H. A., Tufekcioglu, Z., & Emre, M. (2017). Dementia in Parkinson's disease. *Journal of the Neurological Sciences*, *374*, 26–31. Available from https://doi.org/10.1016/j.jns.2017.01.012.

Hausner, L., Damian, M., Sartorius, A., & Frolich, L. (2011). Efficacy and cognitive side effects of electroconvulsive therapy (ECT) in depressed elderly inpatients with coexisting mild cognitive impairment or dementia. *The Journal of Clinical Psychiatry*, *72*(1), 91–97. Available from https://doi.org/10.4088/JCP.10m05973gry.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778–1783. Available from https://doi.org/10.1212/WNL.0b013e31828726f5.

Hely, M. A., Reid, W. G., Adena, M. A., Halliday, G. M., & Morris, J. G. (2008). The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders*, *23*(6), 837–844. Available from https://doi.org/10.1002/mds.21956.

Herrmann, N., Black, S. E., Chow, T., Cappell, J., Tang-Wai, D. F., & Lanctôt, K. L. (2012). Serotonergic function and treatment of behavioral and psychological symptoms of frontotemporal dementia. *The American Journal of Geriatric Psychiatry*, *20*(9), 789–797. Available from https://doi.org/10.1097/JGP.0b013e31823033f3.

Jesso, S., Morlog, D., Ross, S., Pell, M. D., Pasternak, S. H., Mitchell, D. G., ... Finger, E. C. (2011). The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. *Brain*, *134*(Pt 9), 2493–2501. Available from https://doi.org/10.1093/brain/awr171.

Jeste, D. V., & Finkel, S. I. (2000). Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *The American Journal of Geriatric Psychiatry*, *8*(1), 29–34.

Jorge, R. E., Starkstein, S. E., & Robinson, R. G. (2010). Apathy following stroke. *Canadian Journal of Psychiatry*, *55*(6), 350–354. Available from https://doi.org/10.1177/070674371005500603.

Katz, I. R., de Deyn, P. P., Mintzer, J., Greenspan, A., Zhu, Y., & Brodaty, H. (2007). The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: A meta-analysis of 4 placebo-controlled clinical trials. *International Journal of Geriatric Psychiatry*, *22*(5), 475–484. Available from https://doi.org/10.1002/gps.1792.

Katz, I. R., Jeste, D. V., Mintzer, J. E., Clyde, C., Napolitano, J., & Brecher, M. (1999). Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: A randomized, double-blind trial. Risperidone Study Group. *The Journal of Clinical Psychiatry*, *60*(2), 107–115.

Kavirajan, H., & Schneider, L. S. (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: A meta-analysis of randomised controlled trials. *Lancet Neurology*, *6*(9), 782–792. Available from https://doi.org/10.1016/s1474-4422(07)70195-3.

Kimura, T., & Takamatsu, J. (2013). Pilot study of pharmacological treatment for frontotemporal dementia: Risk of donepezil treatment for behavioral and psychological symptoms. *Geriatrics & Gerontology*, *13*(2), 506–507. Available from https://doi.org/10.1111/j.1447-0594.2012.00956.x.

Kipps, C. M., Hodges, J. R., & Hornberger, M. (2010). Nonprogressive behavioural frontotemporal dementia: Recent developments and clinical implications of the "bvFTD phenocopy syndrome". *Current Opinion in Neurology*, *23*(6), 628–632. Available from https://doi.org/10.1097/WCO.0b013e3283404309.

Knopman, D. S., DeKosky, S. T., Cummings, J. L., Chui, H., Corey-Bloom, J., Relkin, N., ... Stevens, J. C. (2001). Practice parameter: Diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, *56*(9), 1143–1153.

Kortte, K. B., & Rogalski, E. J. (2013). Behavioural interventions for enhancing life participation in behavioural variant frontotemporal dementia and primary progressive aphasia. *International Review of Psychiatry*, *25*(2), 237–245. Available from https://doi.org/10.3109/09540261.2012.751017.

Landes, A. M., Sperry, S. D., Strauss, M. E., & Geldmacher, D. S. (2001). Apathy in Alzheimer's disease. *Journal of the American Geriatrics Society*, *49*(12), 1700–1707.

Le Ber, I., Guedj, E., Gabelle, A., Verpillat, P., Volteau, M., Thomas-Anterion, C., ... French Research Network on FTD/FTD-MND. (2006). Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain*, *129* (Pt 11), 3051–3065. Available from https://doi.org/10.1093/brain/awl288.

Lebert, F., Stekke, W., Hasenbroekx, C., & Pasquier, F. (2004). Frontotemporal dementia: A randomised, controlled trial with trazodone. *Dementia and Geriatric Cognitive Disorders*, *17*(4), 355–359. Available from https://doi.org/10.1159/000077171.

Lyketsos, C. G., Colenda, C. C., Beck, C., Blank, K., Doraiswamy, M. P., Kalunian, D. A., ... Task Force of American Association for Geriatric Psychiatry. (2006). Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *14*(7), 561–572. Available from https://doi.org/10.1097/01.JGP.0000221334.65330.55.

Lyketsos, C. G., DelCampo, L., Steinberg, M., Miles, Q., Steele, C. D., Munro, C., ... Rabins, P. V. (2003). Treating depression in Alzheimer disease: Efficacy and safety of sertraline therapy, and the benefits of depression reduction: The DIADS. *Archives of General Psychiatry*, *60*(7), 737–746. Available from https://doi.org/10.1001/archpsyc.60.7.737.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *The Journal of the American Medical Association*, *288*(12), 1475–1483.

Lyketsos, C. G., Rosenblatt, A., & Rabins, P. (2004). Forgotten frontal lobe syndrome or "Executive Dysfunction Syndrome". *Psychosomatics*, *45*(3), 247–255. Available from https://doi.org/10.1176/appi.psy.45.3.247.

Mackenzie, I. R., Neumann, M., Bigio, E. H., Cairns, N. J., Alafuzoff, I., Kril, J., ... Mann, D. M. (2010). Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. *Acta Neuropathologica*, *119*(1), 1–4. Available from https://doi.org/10.1007/s00401-009-0612-2.

Maher, A. R., Maglione, M., Bagley, S., Suttorp, M., Hu, J. H., Ewing, B., ... Shekelle, P. G. (2011). Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. *The Journal of the American Medical Association*, *306*(12), 1359–1369. Available from https://doi.org/10.1001/jama.2011.1360.

Margallo-Lana, M., Swann, A., O'Brien, J., Fairbairn, A., Reichelt, K., Potkins, D., ... Ballard, C. (2001). Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *International Journal of Geriatric Psychiatry*, *16*(1), 39–44.

Maruyama, M., Shimada, H., Suhara, T., Shinotoh, H., Ji, B., Maeda, J., ... Higuchi, M. (2013). Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron*, *79*(6), 1094–1108. Available from https://doi.org/10.1016/j.neuron.2013.07.037.

McKeith, I., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., ... Spiegel, R. (2000). Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet*, *356*(9247), 2031–2036. Available from https://doi.org/10.1016/s0140-6736(00)03399-7.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., ... Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88–100. Available from https://doi.org/10.1212/wnl.0000000000004058.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., ... Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 263–269. Available from https://doi.org/10.1016/j.jalz.2011.03.005.

Mega, M. S., Cummings, J. L., Fiorello, T., & Gornbein, J. (1996). The spectrum of behavioral changes in Alzheimer's disease. *Neurology*, *46*(1), 130–135.

Mendez, M. F., & Shapira, J. S. (2005). Loss of insight and functional neuroimaging in frontotemporal dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(3), 413–416. Available from https://doi.org/10.1176/jnp.17.3.413.

Mendez, M. F., Shapira, J. S., McMurtray, A., & Licht, E. (2007). Preliminary findings: Behavioral worsening on donepezil in patients with frontotemporal dementia. *The American Journal of Geriatric Psychiatry*, *15*(1), 84–87. Available from https://doi.org/10.1097/01.JGP.0000231744.69631.33.

Mendez, M. F., Shapira, J. S., & Miller, B. L. (2005). Stereotypical movements and frontotemporal dementia. *Movement Disorders*, *20*(6), 742–745. Available from https://doi.org/10.1002/mds.20465.

Merrilees, J. (2007). A model for management of behavioral symptoms in frontotemporal lobar degeneration. *Alzheimer Disease and Associated Disorders*, *21*(4), S64–S69. Available from https://doi.org/10.1097/WAD.0b013e31815bf774.

Möbius, H. J., & Stöffler, A. (2003). Memantine in vascular dementia. *International Psychogeriatrics*, *15*(Suppl. 1), 207–213. Available from https://doi.org/10.1017/s1041610203009219.

Moniz Cook, E. D., Swift, K., James, I., Malouf, R., De Vugt, M., & Verhey, F. (2012). Functional analysis-based interventions for challenging behaviour in dementia. *Cochrane Database of Systematic Reviews* (2), CD006929. Available from https://doi.org/10.1002/14651858.CD006929.pub2.

Morley, J. E., & Cruz-Oliver, D. M. (2014). Cognitive stimulation therapy. *Journal of the American Medical Directors Association*, *15*(10), 689–691. Available from https://doi.org/10.1016/j.jamda.2014.07.015.

National Alliance for Caregiving. (2017). *Dementia caregiving in the U.S.* <https://www.caregiving.org/wp-content/uploads/2014/01/Dementia-Caregiving-in-the-US_February-2017.pdf>.

Nelson, J. C., & Devanand, D. P. (2011). A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *Journal of the American Geriatrics Society*, *59*(4), 577–585. Available from https://doi.org/10.1111/j.1532-5415.2011.03355.x.

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurology*, *13*(8), 788–794. Available from https://doi.org/10.1016/s1474-4422(14)70136-x.

O'Brien, J. T., & Thomas, A. (2015). Vascular dementia. *Lancet*, *386*(10004), 1698–1706. Available from https://doi.org/10.1016/s0140-6736(15)00463-8.

Okura, T., Plassman, B. L., Steffens, D. C., Llewellyn, D. J., Potter, G. G., & Langa, K. M. (2011). Neuropsychiatric symptoms and the risk of institutionalization and death: The aging, demographics, and memory study. *Journal of the American Geriatrics Society*, *59*(3), 473–481. Available from https://doi.org/10.1111/j.1532-5415.2011.03314.x.

Olin, J. T., Schneider, L. S., Katz, I. R., Meyers, B. S., Alexopoulos, G. S., Breitner, J. C., ... Lebowitz, B. D. (2002). Provisional diagnostic criteria for depression of Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *10*(2), 125–128.

Onyike, C. U., & Diehl-Schmid, J. (2013). The epidemiology of frontotemporal dementia. *International Review of Psychiatry*, *25*(2), 130–137. Available from https://doi.org/10.3109/09540261.2013.776523.

Passmore, M. J., Ho, A., & Gallagher, R. (2012). Behavioral and psychological symptoms in moderate to severe Alzheimer's disease: A palliative care approach emphasizing recognition of personhood and preservation of dignity. *Journal of Alzheimer's Disease: JAD*, *29*(1), 1–13. Available from https://doi.org/10.3233/jad-2012-111424.

Paulsen, J. S., Salmon, D. P., Thal, L. J., Romero, R., Weisstein-Jenkins, C., Galasko, D., ... Jeste, D. V. (2000). Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology*, *54*(10), 1965–1971.

Peskind, E. R., Wingerson, D., Murray, S., Pascualy, M., Dobie, D. J., Le Corre, P., ... Raskind, M. A. (1995). Effects of Alzheimer's disease and normal aging on cerebrospinal fluid norepinephrine responses to yohimbine and clonidine. *Archives of General Psychiatry*, *52*(9), 774–782.

Petersen, R. C. (2016). Mild cognitive impairment. *Continuum (Minneap Minn)*, *22*(2Dementia), 404–418. Available from https://doi.org/10.1212/con.0000000000000313.

Petrova, M., Raycheva, M., & Traykov, L. (2012). Cognitive profile of the earliest stage of dementia in Parkinson's disease. *American Journal of Alzheimer's Disease and Other Dementias*, *27*(8), 614–619. Available from https://doi.org/10.1177/1533317512460562.

Pick, A. (1892). Uber die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Med Wochenschr*, *17*, 165–167.

Pijnenburg, Y. A., Sampson, E. L., Harvey, R. J., Fox, N. C., & Rossor, M. N. (2003). Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. *International Journal of Geriatric Psychiatry*, *18*(1), 67–72. Available from https://doi.org/10.1002/gps.774.

Politis, A. M., Vozzella, S., Mayer, L. S., Onyike, C. U., Baker, A. S., & Lyketsos, C. G. (2004). A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. *International Journal of Geriatric Psychiatry*, *19*(11), 1087–1094. Available from https://doi.org/10.1002/gps.1215.

Porsteinsson, A. P., Drye, L. T., Pollock, B. G., Devanand, D. P., Frangakis, C., Ismail, Z., ... CitAD Research Group. (2014). Effect of citalopram on agitation in Alzheimer disease: The CitAD randomized clinical trial. *The Journal of the American Medical Association*, *311*(7), 682–691. Available from https://doi.org/10.1001/jama.2014.93.

Porsteinsson, A. P., Tariot, P. N., Erb, R., Cox, C., Smith, E., Jakimovich, L., ... Irvine, C. (2001). Placebo-controlled study of divalproex sodium for agitation in dementia. *The American Journal of Geriatric Psychiatry*, *9*(1), 58–66.

Rabins, P. V., Blacker, D., Rovner, B. W., Rummans, T., Schneider, L. S., Tariot, P. N., ... Steering Committee on Practice Guidelines. (2007). American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *The American Journal of Psychiatry*, *164*(12 Suppl.), 5–56.

Rai, H., Yates, L., & Orrell, M. (2018). Cognitive stimulation therapy for dementia. *Clinics in Geriatric Medicine*, *34*(4), 653–665. Available from https://doi.org/10.1016/j.cger.2018.06.010.

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., ... Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(Pt 9), 2456–2477. Available from https://doi.org/10.1093/brain/awr179.

Raskind, M. A., & Wang, L. Y. (2014). Antipsychotic drugs for psychosis and agitation in dementia: Efficacy, safety, and a possible noradrenergic mechanism of action. *International Psychogeriatrics*, *26*(6), 879–883. Available from https://doi.org/10.1017/S1041610214000477.

Reus, V. I., Fochtmann, L. J., Eyler, A. E., Hilty, D. M., Horvitz-Lennon, M., Jibson, M. D., ... Yager, J. (2016). The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *The American Journal of Psychiatry*, *173*(5), 543–546. Available from https://doi.org/10.1176/appi.ajp.2015.173501.

Rohrer, J. D., Lashley, T., Schott, J. M., Warren, J. E., Mead, S., Isaacs, A. M., ... Warren, J. D. (2011). Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain*, *134*(Pt 9), 2565–2581. Available from https://doi.org/10.1093/brain/awr198.

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., ... Hofman, A. (1993). Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, *43*(2), 250–260.

Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M., ... Miller, B. L. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*, *58*(2), 198–208.

Rosenberg, P. B., Drye, L. T., Martin, B. K., Frangakis, C., Mintzer, J. E., Weintraub, D., ... DIADS-2 Research Group. (2010). Sertraline for the treatment of depression in Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *18*(2), 136–145. Available from https://doi.org/10.1097/JGP.0b013e3181c796eb.

Ruthirakuhan, M. T., Herrmann, N., Abraham, E. H., Chan, S., & Lanctôt, K. L. (2018). Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database of Systematic Reviews*, *5*, CD012197. Available from https://doi.org/10.1002/14651858.CD012197.pub2.

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: The DSM-5 approach. *Nature Reviews Neurology*, *10*(11), 634–642. Available from https://doi.org/10.1038/nrneurol.2014.181.

Savaskan, E., Schnitzler, C., Schroder, C., Cajochen, C., Muller-Spahn, F., & Wirz-Justice, A. (2006). Treatment of behavioural, cognitive and circadian rest-activity cycle disturbances in Alzheimer's disease: Haloperidol vs. quetiapine. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *9*(5), 507–516. Available from https://doi.org/10.1017/S1461145705006036.

Scheltens, P., Blennow, K., Breteler, M. M., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *Lancet*, *388*(10043), 505–517. Available from https://doi.org/10.1016/s0140-6736(15)01124-1.

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*(24), 2197−2204. Available from https://doi.org/10.1212/01.wnl.0000271090.28148.24.

Schneider, L. S., Dagerman, K. S., & Insel, P. (2005). Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. *The Journal of the American Medical Association*, *294*(15), 1934−1943. Available from https://doi.org/10.1001/jama.294.15.1934.

Schneider, L. S., Frangakis, C., Drye, L. T., Devanand, D. P., Marano, C. M., Mintzer, J., ... CitAD Research Group. (2016). Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: The CitAD randomized clinical trial. *The American Journal of Psychiatry*, *173*(5), 465−472. Available from https://doi.org/10.1176/appi.ajp.2015.15050648.

Schneider, L. S., Tariot, P. N., Dagerman, K. S., Davis, S. M., Hsiao, J. K., Ismail, M. S., ... CATIE-AD Study Group. (2006). Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *The New England Journal of Medicine*, *355*(15), 1525−1538. Available from https://doi.org/10.1056/NEJMoa061240.

Seeley, W. W., Crawford, R., Rascovsky, K., Kramer, J. H., Weiner, M., Miller, B. L., & Gorno-Tempini, M. L. (2008). Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Archives of Neurology*, *65*(2), 249−255. Available from https://doi.org/10.1001/archneurol.2007.38.

Seignourel, P. J., Kunik, M. E., Snow, L., Wilson, N., & Stanley, M. (2008). Anxiety in dementia: A critical review. *Clinical Psychology Review*, *28*(7), 1071−1082. Available from https://doi.org/10.1016/j.cpr.2008.02.008.

Sepehry, A. A., Lee, P. E., Hsiung, G. R., Beattie, B. L., Feldman, H. H., & Jacova, C. (2017). The 2002 NIMH Provisional Diagnostic Criteria for depression of Alzheimer's Disease (PDC-dAD): Gauging their validity over a decade later. *Journal of Alzheimer's Disease: JAD*, *58*(2), 449−462. Available from https://doi.org/10.3233/jad-161061.

Seyfried, L. S., Kales, H. C., Ignacio, R. V., Conwell, Y., & Valenstein, M. (2011). Predictors of suicide in patients with dementia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(6), 567−573. Available from https://doi.org/10.1016/j.jalz.2011.01.006.

Sharp, S. I., Ballard, C. G., Chen, C. P., & Francis, P. T. (2007). Aggressive behavior and neuroleptic medication are associated with increased number of alpha1-adrenoceptors in patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *15*(5), 435−437. Available from https://doi.org/10.1097/01.JGP.0000237065.78966.1b.

Skrobot, O. A., O'Brien, J., Black, S., Chen, C., DeCarli, C., Erkinjuntti, T., ... VICCCS Group. (2017). The vascular impairment of cognition classification consensus study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(6), 624−633. Available from https://doi.org/10.1016/j.jalz.2016.10.007.

Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *The Journal of the American Medical Association*, *277*(10), 813−817.

Spalletta, G., Long, J. D., Robinson, R. G., Trequattrini, A., Pizzoli, S., Caltagirone, C., & Orfei, M. D. (2015). Longitudinal neuropsychiatric predictors of death in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD*, *48*(3), 627−636. Available from https://doi.org/10.3233/jad-150391.

Stanley, M. A., Calleo, J., Bush, A. L., Wilson, N., Snow, A. L., Kraus-Schuman, C., ... Kunik, M. E. (2013). The peaceful mind program: A pilot test of a cognitive-behavioral therapy-based intervention for anxious patients with dementia. *The American Journal of Geriatric Psychiatry*, *21*(7), 696−708. Available from https://doi.org/10.1016/j.jagp.2013.01.007.

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A prospective longitudinal study of apathy in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(1), 8−11. Available from https://doi.org/10.1136/jnnp.2005.069575.

Starkstein, S. E., Petracca, G., Chemerinski, E., & Kremer, J. (2001). Syndromic validity of apathy in Alzheimer's disease. *The American Journal of Psychiatry*, *158*(6), 872−877. Available from https://doi.org/10.1176/appi.ajp.158.6.872.

Steinberg, M., Shao, H., Zandi, P., Lyketsos, C. G., Welsh-Bohmer, K. A., Norton, M. C., ... Investigators, C. C. (2008). Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County Study. *International Journal of Geriatric Psychiatry*, *23*(2), 170−177. Available from https://doi.org/10.1002/gps.1858.

Stinton, C., McKeith, I., Taylor, J. P., Lafortune, L., Mioshi, E., Mak, E., ... O'Brien, J. T. (2015). Pharmacological management of Lewy body dementia: A systematic review and meta-analysis. *The American Journal of Psychiatry*, *172*(8), 731−742. Available from https://doi.org/10.1176/appi.ajp.2015.14121582.

Street, J. S., Clark, W. S., Gannon, K. S., Cummings, J. L., Bymaster, F. P., Tamura, R. N., ... Breier, A. (2000). Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: A double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Archives of General Psychiatry*, *57*(10), 968−976.

Streim, J. E., Porsteinsson, A. P., Breder, C. D., Swanink, R., Marcus, R., McQuade, R., & Carson, W. H. (2008). A randomized, double-blind, placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *16*(7), 537−550. Available from https://doi.org/10.1097/JGP.0b013e318165db77.

Swartz, J. R., Miller, B. L., Lesser, I. M., & Darby, A. L. (1997). Frontotemporal dementia: Treatment response to serotonin selective reuptake inhibitors. *The Journal of Clinical Psychiatry*, *58*(5), 212−216.

Szot, P., White, S. S., Greenup, J. L., Leverenz, J. B., Peskind, E. R., & Raskind, M. A. (2006). Compensatory changes in the noradrenergic nervous system in the locus ceruleus and hippocampus of postmortem subjects with Alzheimer's disease and dementia with Lewy bodies. *The Journal of Neuroscience*, *26*(2), 467−478. Available from https://doi.org/10.1523/JNEUROSCI.4265-05.2006.

Szot, P., White, S. S., Greenup, J. L., Leverenz, J. B., Peskind, E. R., & Raskind, M. A. (2007). Changes in adrenoreceptors in the prefrontal cortex of subjects with dementia: Evidence of compensatory changes. *Neuroscience*, *146*(1), 471−480. Available from https://doi.org/10.1016/j.neuroscience.2007.01.031.

Tariot, P. N., Erb, R., Leibovici, A., Podgorski, C. A., Cox, C., Asnis, J., ... Irvine, C. (1994). Carbamazepine treatment of agitation in nursing home patients with dementia: A preliminary study. *Journal of the American Geriatrics Society*, *42*(11), 1160–1166.

Tariot, P. N., Erb, R., Podgorski, C. A., Cox, C., Patel, S., Jakimovich, L., & Irvine, C. (1998). Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *The American Journal of Psychiatry*, *155*(1), 54–61. Available from https://doi.org/10.1176/ajp.155.1.54.

Tariot, P. N., Raman, R., Jakimovich, L., Schneider, L., Porsteinsson, A., Thomas, R., ... Valproate Nursing Home Study Group. (2005). Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: A randomized, controlled trial. *The American Journal of Geriatric Psychiatry*, *13*(11), 942–949. Available from https://doi.org/10.1176/appi.ajgp.13.11.942.

Tariot, P. N., Schneider, L. S., Mintzer, J. E., Cutler, A. J., Cunningham, M. R., Thomas, J. W., & Sommerville, K. W. (2001). Safety and tolerability of divalproex sodium in the treatment of signs and symptoms of mania in elderly patients with dementia: Results of a double-blind, placebo-controlled trial. *Current Therapeutic Research*, *62*(1), 51–67. Available from https://doi.org/10.1016/S0011-393X(01)80042-4.

Teri, L., McKenzie, G. L., Pike, K. C., Farran, C. J., Beck, C., Paun, O., & LaFazia, D. (2010). Staff training in assisted living: Evaluating treatment fidelity. *The American Journal of Geriatric Psychiatry*, *18*(6), 502–509. Available from https://doi.org/10.1097/JGP.0b013e3181c37b0e.

Theleritis, C., Siarkos, K., Katirtzoglou, E., & Politis, A. (2017). Pharmacological and nonpharmacological treatment for apathy in Alzheimer disease: A systematic review across modalities. *Journal of Geriatric Psychiatry and Neurology*, *30*(1), 26–49. Available from https://doi.org/10.1177/0891988716678684.

Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., ... Trojanowski, J. Q. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*, *136*(Pt 9), 2697–2706. Available from https://doi.org/10.1093/brain/awt188.

Tonkonogy, J. M., Smith, T. W., & Barreira, P. J. (1994). Obsessive-compulsive disorders in Pick's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *6*(2), 176–180. Available from https://doi.org/10.1176/jnp.6.2.176.

Ueda, T., Suzukamo, Y., Sato, M., & Izumi, S. (2013). Effects of music therapy on behavioral and psychological symptoms of dementia: A systematic review and meta-analysis. *Ageing Research Reviews*, *12*(2), 628–641. Available from https://doi.org/10.1016/j.arr.2013.02.003.

van der Flier, W. M., Skoog, I., Schneider, J. A., Pantoni, L., Mok, V., Chen, C. L. H., & Scheltens, P. (2018). Vascular cognitive impairment. *Nature Reviews Disease Primers*, *4*, 18003. Available from https://doi.org/10.1038/nrdp.2018.3.

Van der Mussele, S., Bekelaar, K., Le Bastard, N., Vermeiren, Y., Saerens, J., Somers, N., ... Engelborghs, S. (2013). Prevalence and associated behavioral symptoms of depression in mild cognitive impairment and dementia due to Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *28*(9), 947–958. Available from https://doi.org/10.1002/gps.3909.

Velakoulis, D., Walterfang, M., Mocellin, R., Pantelis, C., & McLean, C. (2009). Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. *The British Journal of Psychiatry*, *194*(4), 298–305. Available from https://doi.org/10.1192/bjp.bp.108.057034.

Vieira, R. T., Caixeta, L., Machado, S., Silva, A. C., Nardi, A. E., Arias-Carrión, O., & Carta, M. G. (2013). Epidemiology of early-onset dementia: A review of the literature. *Clinical Practice and Epidemiology in Mental Health: CP & EMH*, *9*, 88–95. Available from https://doi.org/10.2174/1745017901309010088.

Wang, H. F., Yu, J. T., Tang, S. W., Jiang, T., Tan, C. C., Meng, X. F., ... Tan, L. (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: Systematic review with meta-analysis and trial sequential analysis. *Journal of Neurology, Neurosurgery, and Psychiatry*, *86*(2), 135–143. Available from https://doi.org/10.1136/jnnp-2014-307659.

Wang, L. Y., Shofer, J. B., Rohde, K., Hart, K. L., Hoff, D. J., McFall, Y. H., ... Peskind, E. R. (2009). Prazosin for the treatment of behavioral symptoms in patients with Alzheimer disease with agitation and aggression. *The American Journal of Geriatric Psychiatry*, *17*(9), 744–751. Available from https://doi.org/10.1097/JGP.0b013e3181ab8c61.

Wee, N., Kandiah, N., Acharyya, S., Chander, R. J., Ng, A., Au, W. L., & Tan, L. C. (2016). Baseline predictors of worsening apathy in Parkinson's disease: A prospective longitudinal study. *Parkinsonism & Related Disorders*, *23*, 95–98. Available from https://doi.org/10.1016/j.parkreldis.2015.12.004.

Woolley, J. D., Khan, B. K., Murthy, N. K., Miller, B. L., & Rankin, K. P. (2011). The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *The Journal of Clinical Psychiatry*, *72*(2), 126–133. Available from https://doi.org/10.4088/JCP.10m06382oli.

Zhong, K. X., Tariot, P. N., Mintzer, J., Minkwitz, M. C., & Devine, N. A. (2007). Quetiapine to treat agitation in dementia: A randomized, double-blind, placebo-controlled study. *Current Alzheimer Research*, *4*(1), 81–93.

This page intentionally left blank

Chapter 15

Substance use disorders in the elderly

Tylor J. Jilk[1,2] and Martin S. Mumenthaler[3]

[1]Department of Public Health, Baylor University, Waco, TX, United States, [2]Space Exploration Technologies, Hawthorne, CA, United States, [3]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Introduction

Scientific research, the media, and society have made substantial progress over the last 20 years in recognizing and understanding the significant substance use disorder (SUD) problem in older adults. While evidence has long indicated that there are specific age-related issues with regards to substance abuse (Atkinson, 1984, 1990; Atkinson & Kofoed, 1982; Atkinson & Schuckit, 1984; Schuckit, 1977), the last 20 years have provided a vast amount of new knowledge about the elderly and SUDs. In this chapter, we present an updated review of geriatric SUDs: epidemiology, assessment and management, and disorder-specific information.

Older adults are placed at increased risk of SUDs due to environmental and social influences associated with aging. Moreover, age-related biological and psychological changes in elderly individuals leave them vulnerable to the effects of these influences, thereby lowering the barrier for SUDs to develop and go unnoticed, undetected, and untreated. We begin our discussion with alcohol use disorders (AUD), of which geriatric rates have been steadily increasing in recent years. AUDs are also the most prevalent of SUDs in the elderly. Next, prescription psychoactive drugs are explored, The recent opioid use disorder (OUD) epidemic, which resulted in widespread unintentional overdose and overdose death, addiction, and diversion (Le Roux, Tang, & Drexler, 2016), highlighted the importance of age-related differences in SUDs and the susceptibility of older adults to the effects of certain drugs. We go on to discuss other substances, including illegal drugs, over-the-counter drugs, and tobacco and nicotine. The late outbreak of e-cigarettes among the youth has led researchers to express concern of their potential effects on an older population (Conway et al., 2017). In addition, legalization of marijuana in various countries and US states, which might have promoted increasing rates of cannabis use disorder, including a 250% increase of past-year cannabis use between 2006 and 2013 in adults aged 65 + (Han, Sherman, et al., 2017), may have significant effects on the elderly. This review concludes with "looking ahead," a section about future research directions, case volume, and prevention of SUDs in older adults.

Even though much of the literature is based upon definitions from the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV, which distinguished abuse and dependence), the latest edition of the DSM (DSM-5) has abandoned these categorical definitions in favor of a continuous approach, defining 11 SUD criteria, with diagnoses ranging from mild (patients endorsing two or three criteria) to severe (more than 6) SUD. Here, we utilize, as much as possible, terminology from the DSM-5 to delve into SUDs in the elderly.

Epidemiology

Risk factors for substance use disorders

Cohort and period effects

It is important to consider cohort and period effects apart from aging effects in order to understand risks for alcohol and SUDs in the elderly. While cohort effects are changes that characterize populations born at a specific point in time, independent of the process of aging, period effects are changes that occur at a particular time that affect all age groups and cohorts equally.

The baby boomer generation (generally defined as Americans born between the years of 1946 and 1964) is an important large cohort that came of age during the 1960s and 1970s, a period of changing attitudes toward and rates of

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00015-6

drug and alcohol use. Baby boomers have had more exposure to alcohol, tobacco, and illegal drugs in their youth and tended to be more lenient about substance use than previous generations (Blow & Barry, 2012). Additionally, psychoactive medications became available as a widespread method to deal with anxiety, pain, and stress in response to life's pressures (Wang & Andrade, 2013). The prevalence of SUD has remained high among this group as they age, and SUDs among people older than 50 years are projected to increase from about 2.8 million in 2006 to 5.7 million in 2020 (Kuerbis, Sacco, Blazer, & Moore, 2014). To add, young and middle-aged cohorts have a relatively heavy use of substances earlier in life that is expected to continue to late life, resulting in higher use in younger cohorts as they age compared to older cohorts (Blazer & Wu, 2009).

Turning to period effects, we see a wet period of drinking and decreased social sanctions on women's drinking in the 1970s that had a lasting impact on women's drinking patterns, resulting in a "closing of the gender gap" in the subsequent decades. There are notable policy changes that occurred in the 1980s that were seen as effective in reducing drinking in general. These included raising the minimum drinking age, lowering the blood alcohol concentration limit for drunk driving to 0.08, and increasing enforcement and associated penalties. In recent years, however, the US real price of alcohol has continued to decline, making alcoholic beverages more available to younger adults and other low-income demographics in comparison to earlier eras (Kerr, Greenfield, Bond, Ye, & Rehm, 2009).

Biological risk factors

The elderly show increased sensitivity to the effects of most psychoactive drugs. Drug sensitivity is determined by both pharmacokinetic and pharmacodynamic processes. The first pharmacokinetic processes are mechanisms of drug deactivation and elimination, or what the body does to the drug. Next, pharmacodynamic processes are mechanisms of drug action upon the central nervous system and other organs, or what drugs do to the body. Age-related pharmacokinetic changes include a reduction in renal and hepatic clearance and an increase in volume of distribution of lipid-soluble drugs, resulting in longer elimination half-life, whereas pharmacodynamic changes involve altered (usually increased) sensitivity to several classes of drugs, including psychoactive drugs. More generally, modified drug sensitivity is determined by progressive accumulation of more or less random changes in several biological systems, contributions from each of which vary with the drug in question (Mangoni & Jackson, 2004).

Psychoactive drugs can also increase the symptoms of certain medical disorders that are more common in the elderly, especially cognitive dysfunction and cardiovascular and pulmonary disorders. Furthermore, there can be clinical complications from the adverse interactions of psychoactive substances and other prescribed medications, known as drug−drug interactions. Alterations in biological sensitivity to drugs in the elderly can influence the potential for SUDs in several ways, causing an increased vulnerability to drug effects and drug interactions (Kuerbis et al., 2014).

Psychosocial and psychiatric risk factors

Risk factors for substance use in the elderly vary by drug and patient clinical presentation, but may include role/identity loss, friends' approval, depression, interpersonal conflicts, solitude, and major life stressor events (Caputo et al., 2012; Emiliussen, Nielsen, & Andersen, 2017). Although gerontologists have often attributed late substance use problems to major loss and other life stress, this relationship is complex; life stressors are ubiquitous among the elderly, while only a minority develop SUDs. Major losses and other dramatic life events, long-term strains, and the ordinary tribulations of daily life constitute distinctive forms of life stressors. Through a review of 175 studies published from 1980 to 2007, Kotov et al. leveraged the five-factor model of personality traits, which organizes trait descriptors in the natural language into a continuum of the "Big Five" (openness, extraversion, conscientiousness, agreeableness, and neuroticism), to find substantially increased SUDs with two factors: disinhibition and disagreeableness (Kotov, Gamez, Schmidt, & Watson, 2010).

Subjective symptoms of chronic illness, such as pain, insomnia, anxiety, and depression, may increase the likelihood of some elderly persons to abuse various substances, especially alcohol, in self-medication efforts (Aira, Hartikainen, & Sulkava, 2008). Relatives may supply substances to an elderly person, family members may become drinking partners, or family may support ill-advised prescribing by the physician. Caregivers may also become overcontrolling, using "as needed" sedatives excessively to suppress "inappropriate" behavior.

Underrecognition of substance use disorders in later life

Special clinical features, social factors, and professional biases contribute to underrecognition of these problems in the elderly. The nature of the presentation of SUD is likely to be disguised, as older adults and their families might fear

stigma and deflect substance-related questions and providers might be uncomfortable asking older individuals about substance abuse. SUDs can mimic symptoms of other geriatric illnesses such as cognitive decline, incontinence, falls, and depression (Le Roux et al., 2016). Furthermore, older adults are less likely to endorse some key diagnostic criteria, including problems related to work, social interaction, and tolerance (Wang & Andrade, 2013).

Younger individuals with SUDs are often first identified by others: employer, spouse, arresting officer, or judge. Older adults who are retired and living in isolation may not have sufficient contact with others, so that opportunities for detection are missed. Family members may also cover up the abuse because of embarrassment of a misguided wish to preserve the dignity or indulge the "final pleasures" of their elder relative. Caregivers may gradually assume functional roles of the impaired elderly abuser, further masking the substance abuse to outside view.

Stereotypes and age-related biases also contribute to the underrecognition and underdetection of SUDs in the elderly. For example, one study explored whether there were age-related biases among the criteria for AUD and found that older adults (defined as 50 years or older) were half as likely as middle-aged adults (26–49 years old) to endorse the criteria related to tolerance, activities to obtain alcohol, social or interpersonal problems, legal problems, and physically hazardous situations (Kuerbis, Hagman, & Sacco, 2013). Additionally, the criterion related to continued use despite persistent or recurrent problems may not apply to many older adults who do not recognize that their problems, such as depression, are related to drinking (Kuerbis et al., 2014).

Comparative prevalence of substance use disorders

Even with differing methods and study populations, reports comparing the prevalence of SUD in older adults generally agree that alcohol and prescription drug problems are far more common than those with illegal drugs (Wang & Andrade, 2013). An examination of data from the 2005 and 2006 National Surveys on Drug Use and Health (NSDUH) found that the prevalence of SUD in the 50 + age group was 0.33% for any substance use abuse, 0.12% for cannabis, and 0.18% for cocaine (Blazer & Wu, 2009). Notable in recent years is the increasing trend in cannabis use. Han et al. conducted a secondary analysis of NSDUH from 2006 to 2013 of older adults and found that individuals aged 65 + had a relative increase in past-year cannabis use of 250% in contrast to a 57.8% increase for adults aged 50–64 (Han, Sherman, et al., 2017).

Principles of assessment and management

Assessment of substance use disorders

While general awareness of SUDs and their potential for detrimental health consequences when untreated seems to have increased over the last 20 years, possibly due to increasing reports in mass and social media, negative attitudes of health professionals toward patients with SUDs continue to be common, contributing to suboptimal health care for these patients (Van Boekel, Brouwers, Van Weeghel, & Garretsen, 2013). Patients do not often disclose or admit having a substance use problem (Substance Abuse and Mental Health Administration, 2011), partly because denial of substance abuse at all ages is common in affected individuals due to reasons such as substance-induced amnesia for many intoxication episodes, shame about reliance on alcohol or drugs, pessimism about recovery, and the desire to continue use. Older adults, however, are more likely to hide their substance use problems and are less likely to ask for help than younger adults (Han, Gfroerer, Colliver, & Penne, 2009). Moreover, older adults are less likely than younger adults to be assessed for SUDs due to the limited time clinicians have to screen for several potential problems or illnesses, the potential stigma related to assessing for addiction, the similarities of the symptoms of alcohol and other drug use with other illnesses common in later life, and the common perception among older adults that symptoms experienced by the use of alcohol or drugs are seen as a part of normal aging rather than resulting from the substance use itself (Kuerbis et al., 2014). For all these reasons, screening for and assessment of SUDs are particularly important in elderly patients. Careful rapport building through repeated contacts, inquiry with relatives, caregivers, and others in the social network, reviews of medical and pharmacy records, and home visitation are especially useful case-assessment methods. By asking detailed questions about quantity and frequency of drinking with the assumption that this information is important, medical professionals can reduce stigma by normalizing the behavior without endorsing it. The most important step a medical professional can take is to ask in the first place.

Screening instruments often overlook the possibility of SUDs in the elderly, largely due to the fact that they do not take into account aging effects. For example, one study suggests that rather than using the full-length Alcohol Use Disorders Identification Test (AUDIT), using the AUDIT-C (questions 1–3) is more appropriate in older adults

(Le Roux et al., 2016). Still, the substance use abuse worksheet from the DSM-5 as well as criteria from the International Classification of Diseases and Health Problems (ICD-10) are gold-standard tools to use at the onset. To add, toxicological examinations of urine, blood, and breath samples, in addition to neuropsychological and neurological evaluation, may help complete or corroborate the story of substance use. As SUD among older adults is often underdiagnosed, misdiagnosed, undertreated, or untreated, primary care physicians can play significant roles in screening for substance use problems in older adults, with approaches such as Screening, Brief Intervention and Referral to Treatment. Recent reports have proven the effectiveness of integrating primary care with substance abuse treatment programs. They suggest that providing substance abuse services in primary care settings would be particularly helpful for older adults, as they tend to have multiple comorbid conditions and visit their physicians regularly. SUDs, like other chronic illnesses, require early intervention and continued care (Han et al., 2009).

Management and treatment

While managing and treating SUDs in the elderly certainly comes with unique challenges, the overarching goals of treatment are similar to those of younger patients. How these goals are achieved, however, will change with the needs of older adults. The goals of SUD treatment in the elderly are threefold: stabilization and reduction of substance consumption or ultimately achievement of abstinence, treatment of coexisting problems, and arrangement of appropriate social interventions. The first, stabilization and reduction of substance consumption, may be as simple as providing education and advice in mild dependence cases. However, in cases of long-standing, high-dose SUDs, it may be very complicated and hazardous with the potential of medical and neurological complications. Admission to a dedicated out- or inpatient course including careful medication-assisted detoxification may be necessary. Next, treatment of coexisting problems can be a crucial step, especially when chronic pain, chronic insomnia, or a mood disorder has been a major factor sustaining the disorder, or when serious complications of SUD are present. Finally, social interventions range from informal plans, such as arranging for increased visitation by loved ones or enrollment in a senior activity center, to major formal interventions (e.g., admission to a senior substance abuse program, or to a nursing home). Persuading the elderly patient and family to accept treatment often requires carefully arranged counseling.

In general, a multidimensional approach, including pharmacological, psychological, and socio-behavioral treatment, is crucial in treating AUDs (Caputo et al., 2012) as well as SUDs in the older population. Research suggests a heterogeneous response to SUD treatment in older adults, which affords the potential for more efficient treatment matching (Kuerbis & Sacco, 2013). Thus critically evaluating elderly patients is essential in order to tailor their treatment plan with the goals of consumption reduction or abstinence, treatment of coexisting problems, and with appropriate social interventions in mind.

Alcohol use disorders

Epidemiology

Use, heavy use, and problem use in the elderly

In a recent US study, over 80% of people surveyed reported drinking alcohol at some point in their lifetimes (Le Roux et al., 2016). Recent data from the NSDUH show an increase in alcohol use among older men and women. From 2005 to 2014 in adults ≥ 50 years of age, there was a relative increase of 23.3% in AUD cases, including increasing trends among females (Han, Moore, Sherman, Keyes, & Palamar, 2017). One study showed that for adults ≥ 60 years of age, drinking increased among men on an average of 0.7% per year, while it increased among women on an average of 1.6% per year (Breslow, Castle, Chen, & Graubard, 2017). Male gender and higher socioeconomic status (SES) were associated with greater drinking in studies in the United States and in the WHO European Region (Le Roux et al., 2016; Nuevo et al., 2015). Additionally, alcohol consumption varies across countries, with Hungary and Slovakia having markedly high percentages of heavy drinkers at 58.1% and 54.2%, respectively, compared to an average of 10.2% heavy drinking across many European countries; with heavy drinking defined as drinking 15 or more standard drinks for men and 12 or more for women during the week and 5 or more for men or 4 or more for women on at least 1 day (Nuevo et al., 2015).

Age versus cohort effects on prevalence

The prevalence of AUDs is impacted by both age and cohort effects. While age effects are changes in variable values that occur among all cohorts independent of time period, cohort effects characterize populations born at a particular

point in time, independent of the process of aging. Measuring either effect is limited by cross-sectional design, but with large, nationally representative samples, trends can be identified.

Firstly, increasing age is broadly associated with decreasing rates of AUD, and older adults also have fewer alcohol-related role-function problems such as problems at work or school (Delker, Brown, & Hasin, 2016). Data from the NSDUH place adults aged 26–34 at a higher risk for such role-function problems than adults aged 65 and older, followed by young adults aged 18–25 and finally adults aged 35–49 (Alameida, Harrington, Laplante, & Kang, 2010; Lee et al., 2018; Sacco, Unick, Kuerbis, Koru, & Moore, 2015). Women are susceptible to menopausal and postmenopausal age effects (stress and depression related to menopause), as a sharp onset of AUD occurs in postmenopausal women (Milic et al., 2018).

Continuing, the recent introduction of severity-graded AUD diagnoses in DSM-5 (American Psychiatric Association (APA), 2013), providing a standard approach for differentiating degrees of clinical significance, allowed recent new lifespan-developmental investigations on how AUD desistance rates may vary as a function of AUD severity. In such a study, for both sexes, severe AUD desistance, going from 6+ symptoms to 0–1 symptom, was more common in young adulthood than in later ages. This means that older people were less likely than younger adults to move from severe AUD to no AUD. For adults aged 30–34, desistance from severe AUD had a likelihood of 0.50, while for adults between 48 and 55 it dropped to 0.22 (Lee et al., 2018). While a higher risk of AUD for younger cohorts compared to people in older age groups was found in both the NSDUH and the National Epidemiologic Survey on Alcohol and Related Conditions, the authors pointed out two important limiting factors in studies of age effects: underrepresentation among older individuals due to differential mortality and poor recall of remote events (Delker et al., 2016).

Next, cohort effects can also impact the prevalence of AUDs among older adults. For example, one study used cross-sectional data from the Nationwide Inpatient Sample between 1993 and 2010. They found that individuals born in later cohorts, such as the baby boomers, had higher rates of alcohol-related hospitalizations, while individuals born during World War II or before (1945 or earlier) had lower rates (Sacco, Unick, et al., 2015). Thus cohort effects could account for a large proportion of the decline seen in AUD with increasing age, and as younger cohorts begin to grow older, higher rates of AUD in the elderly can be expected.

Patterns of alcohol use and abuse

Motives for nonpathological drinking

Motives for drinking fall into two categories: nonpathological and pathological. It is important to distinguish between the two. Here, we consider the former. There is research to suggest that elderly drinkers with a higher mean positive affect are more likely to drink less than those with a lower mean positive affect. Thus negative/positive affect could be conceptualized as time-varying factors that impact the likelihood that one will consume alcohol (Sacco, Burruss, et al., 2015). Positive reasons associated with drinking include (1) to have control or choice over one's actions, (2) to socialize and relax, (3) to take things easy and prevent from "losing touch," and (4) to maintain community, working, or family life (Wilson et al., 2013). An especially prominent reason among nonproblem drinkers in contrast to problem drinkers is the motive of relaxation. However, for every unit increase in drinking to feel more relaxed, the odds of problem drinking increase by a factor of 2.2 (Gilson, Bryant, & Judd, 2017).

Therapeutic use and health maintenance value of alcohol

According to a number of recent studies, alcohol use at lower doses may have some therapeutic value in older adults. For example, a study of attitudes and beliefs about drinking of older adults who were regular drinkers showed that alcohol use offers some positive benefits such as a sense of continuity from before retirement as well as preservation of their identity and autonomy, and these older adults referred to alcohol as a component of socialization and relaxation routines (Burruss, Sacco, & Smith, 2015). One group of researchers conducted a systematic review of 14 qualitative studies of older populations and found that in the majority, alcohol use was linked with social life and social engagement (Kelly, Olanrewaju, Cowan, Brayne, & Lafortune, 2018). In another study, social interaction was found to be a mediating variable for moderate alcohol use's effects on depressive symptomatology and functional ability (Scott, Wiener, & Paulson, 2018). However, the pervasiveness of alcohol in social settings produces skepticism about the health risks of alcohol, even though one of the major reasons for decreasing alcohol consumption later in life is health precautions (Britton & Bell, 2015). While alcohol use for medicinal reasons is common among individuals over age 75 (Aira et al., 2008; Burruss et al., 2015), for example, as a means of relaxation or as a bedtime routine to help falling asleep, such use may be particularly problematic in the elderly for various reasons: alcohol may negatively impact sleep

quality among older adults (Roepke & Ancoli-Israel, 2010) and as older adults often take several medications, the risk of harmful drug−alcohol interactions increases (Moore, Whiteman, & Ward, 2007).

The purported cardio-protective hypothesis, in which moderate alcohol use leads to protection from cardiovascular disease, has been hotly debated. A 2017 meta-analysis of 45 unique studies, collectively containing nearly three million subjects, investigated the extent to which the hypothesis could be confirmed or refuted. The study concluded that a fair amount of skepticism remains about the validity of the cardio-protective hypothesis, as the protective association was not observed in studies of those age 55 years or younger at baseline, in higher quality studies, or in studies that controlled for heart health (Zhao, Stockwell, Roemer, Naimi, & Chikritzhs, 2017). A similar debate exists that low to moderate alcohol use may offer a protective effect against dementia. Again, results from these studies must be interpreted very cautiously, as many selection biases are present (Ormstad, Rosness, Bergem, Bjertness, & Strand, 2016).

When considering the potential guarding effects of alcohol consumption, it is important to take into account both the positive and negative aspects. While an association between cardiovascular disease protection and moderate alcohol use may exist, alcohol consumption also results in mitochondrial dysfunction, changes in circulation, inflammatory response, oxidative stress, programmed cell death, and even anatomical damage to the cardiovascular system itself, all side effects that must be taken into account (Piano, 2017).

Binge drinking and heavy drinking

There is relatively little data on the two important pathologic drinking patterns, binge drinking and heavy drinking, in the elderly. Binge drinking is defined by the US Substance Abuse and Mental Health Services Administration as five or more alcoholic drinks for males or four or more alcoholic drinks for females on the same occasion on at least one day in the past month, while heavy drinking is defined as binge drinking on five or more days in the past month. One group of researchers was studying trends of binge alcohol use and AUDs among older adults. By electing to aggregate data into 2-year intervals, the researchers increased their ability to detect trends, their data showing a significant increase in prevalence of past-month binge drinking and past-year AUDs in the United States among older adults aged 65 + (Han, Moore, et al., 2017). Rates of binge drinking fall between 12% and 14% in older men and 3% and 4% in older women, and some studies have found heavy/binge drinking to be associated with depressive symptoms in either men, women, or both (Parikh, Junquera, Canaan, & Oms, 2015). There is a high relapse rate to heavy drinking, which can be detrimental to behavioral therapy treatment for posttraumatic stress disorder (O'Brien, 2015).

Reactive drinking

While coping mechanisms to alcohol use may be regarded as reactive processes, a questionnaire study of 288 community-dwelling older adults found that the most common "coping reason" was simply to relax. The coping reason more closely associated with reactive drinking, to forget worries, was reported by only 1/4 of problem drinkers (Gilson et al., 2017). In another study, which used daily diaries to track 11 elderly adults, the participants did not report reactive drinking (Burruss et al., 2015). One theory is that older adults have reduced mood variability, which leads to less common reactive drinking (Sacco, Burruss, et al., 2015). Thus it is proposed that as people age, alcohol use changes from a reactive process to a planned process, but more research in this area is necessary (Davies, Paltoglou, & Foxcroft, 2017).

Early versus late-onset alcohol problems

Approximately two-thirds of AUDs have an early adult onset, while the other third is late adult onset. Late adult onset drinkers begin having drinking problems at 40−50 years of age and are generally more educated and have a more stressful life (Rakesh & Pattanayak, 2017). Some researchers hypothesized that those with late-onset alcohol problems are more likely to have better outcomes than those with early-onset problems. In one study, older adults (55 +) were more likely to complete a 6-month day-treatment program if they had begun drinking after the age of 50 (Barry & Blow, 2016). Family pressure and health concerns are two factors that may lead adults with late-onset alcohol problems to treatment (Emiliussen, Andersen, & Nielsen, 2017). One review on late-onset drinkers found that the area was extremely understudied. Overall, they identified chronic stress, role and identity loss, and friends' approval of drinking as increasing the risk of late-onset alcohol problems, while retirement and death of a spouse or close relative did not show an increased risk (Emiliussen, Nielsen, et al., 2017).

Family patterns

Familial and nonfamilial forms of AUD are seen in the elderly. In younger age groups (<40 years), there is a pattern for strong familial confounding, AUD appearing to result largely from shared familial factors including personality traits, rather than the direct effects of AUD itself. However, in older adults (65−70 years), the mortality hazard ratios are constant across the population, suggesting that excess mortality is largely a result of having AUD. Adding years since onset of AUD to the model showed that both increasing age and increasing years of duration of AUD contributed to the reduction of familial confounding in the association between AUD and elevated mortality (Kendler, Ohlsson, Sundquist, & Sundquist, 2016). Research shows that genetic factors play a large role in vulnerability to AUD. One study examined the aggregate effect of common single nucleotide polymorphisms (SNPs) on the variance of vulnerability to substance dependence. They concluded that common SNPs explained 25%−36% of the variance across measures (Palmer et al., 2015). Overall, identifying the genes involved and their relative contribution is difficult because of the considerable variations observed in the design of studies, population phenotypes, the type of data analysis, and potential confounders (Stickel, Moreno, Hampe, & Morgan, 2017).

Clinical features of alcohol use disorders

Essential and associated features

Applying commonly used measures of characterizing alcoholism in younger adults to alcoholism in older adults can have limitations, with measures normally including consumption level, alcohol-related social and legal problems, alcohol-related health problems, symptoms of drunkenness or dependence, and self-recognition of an alcohol problem. These measures do not necessarily map directly to the geriatric population. Yet, some methods have been shown to accurately predict AUD in the elderly. AUD screening tools that have been validated in older adults include CAGE, the Michigan Alcohol Screening Test-Geriatric Version (MAST-G), the Short MAST-G, the AUDIT, the AUDIT-C, and the Comorbidity-Alcohol Risk Evaluation Tool (Kuerbis, Moore, Sacco, & Zanjani, 2016). A 2015 Australian study evaluated the performance of various screening instruments to determine the rates of alcohol and substance use in geriatric hospital and community health settings. They found the AUDIT-C to be the most effective screening measure for detecting risky alcohol use, using modified at-risk levels lowered to a total score of ≥ 5 for men and ≥ 3 for women, as opposed to a blanket score of ≥ 8 (Draper et al., 2015). This points to a difference in essential and associated features of AUD in the elderly, compared to younger individuals, and a corresponding need for modified screening tools in the older population.

Alcoholism often times appears with mood disorders, which may exhibit many of the same symptoms of AUD. One of the most common comorbidities involving AUD is the one with depression. A J-shaped relationship between alcohol consumption and depression has been observed in both Western and non-Western elderly communities (Kim, Kim, Morris, & Park, 2015). Social interaction has been suggested as essential to the dip in depressive symptomology with moderate alcohol use (Scott et al., 2018).

Complications

While moderate alcohol use may exhibit seemingly protective functions for older adults, there are many negative risks as well. Related to heavier alcohol consumption include harmful drug interactions, injury, depression, memory problems, liver disease, cognitive changes, sleep problems, cancer, and even diabetes. To add, heavier drinking can also affect mood disorders, sleep, pain, and general health functioning (Barry & Blow, 2016). With respect to harmful drug interactions, Barry and Blow found that up to 19% of older Americans combine alcohol and medications in a way that can be considered misuse.

Alcohol withdrawal disorders include the tremulous syndrome, hallucinosis, seizures, and delirium tremens. The incidence of medical and neurological complications during alcohol withdrawal syndrome in elderly alcohol users is higher than in younger alcoholics (Caputo et al., 2012), making alcohol withdrawal disorders more difficult to treat. Next, the prevalence of dementia in elderly alcoholics is almost five times higher than in nonalcoholic elderly individuals (Caputo et al., 2012), although some suggest a J-shaped relationship between alcohol use and risk of dementia or Alzheimer's disease (Ormstad et al., 2016). It is estimated that almost 20% of individuals aged 65 and over with a diagnosis of depression have a co-occurring AUD (Caputo et al., 2012). AUD is also associated with an increased probability of suicide in the elderly, especially if combined with psychiatric disorders (Nuevo et al., 2015).

Older adults experience altered volume of distribution for alcohol, as well as changed pharmacokinetics and pharmacodynamics, which can lead to an increase in the effect of alcohol with age (Crome, Li, Rao, & Wu, 2012).

Alcohol use and cognition

Whether or not alcohol use is associated with cognition later in life is an unresolved issue. For one, some studies show that moderate or infrequent drinkers (mean age 73) had better cognitive outcomes when compared to abstainers or heavy and daily drinkers (Reas, Laughlin, Kritz-Silverstein, Barrett-Connor, & Mcevoy, 2016). On the other hand, some studies show that alcohol is associated with negative brain outcomes. An observational cohort study measured weekly alcohol intake and cognitive performance over a 30-year period (550 men and women with a mean age of 43.0 at baseline). The researchers found that alcohol had a negative cognitive impact, even at moderate levels (14–21 units per week in men) (Topiwala et al., 2017). Another researcher found a dose-dependent relationship between alcohol intake and lower cognitive performance, even at levels as low as one unit of alcohol per week (Hassing, 2018). It has been proposed that a history of alcohol dependence can have lasting negative consequences for neurocognitive function (Woods et al., 2016). Yet another group has found regular or episodic drinking not to be associated with cognitive function later in life for 14,575 participants, aged 47–78 years at cognitive assessment (Horvat et al., 2015).

One factor for these discrepancies is the abstainer group. Less healthy ex-drinkers are an important group whose lasting negative effects from previous alcohol usage are often neglected. Another factor is an underrecognized mediating variable, hippocampal volume, which may be a cause of the differences observed in different types of memory in older adults as a function of alcohol consumption (Downer, Jiang, Zanjani, & Fardo, 2015).

Course

As adults age, they exhibit lower rates of severe AUD desistance (Lee et al., 2018). However, for some older adults, rates of alcohol consumption increase instead. Platt, Sloan, and Costanzo took data from the Health and Retirement Study, which included 6,787 individuals starting at an age between 51 and 61 years old. The researchers employed linear regression to determine drinking trajectories from 1992 to 2006. The data suggest that adults whose consumption increased with age are more likely to be affluent, highly educated, male, White, unmarried, less religious, and in excellent to good health. Additionally, a history of problem drinking before baseline was associated with increases in alcohol use (Platt, Sloan, & Costanzo, 2010).

Recent cohorts have declined more slowly with increasing age in comparison to earlier cohorts, suggesting that negative health effects of alcohol could increase in the future (Moore et al., 2005). Next, women who have AUDs have a slightly shorter time between onset of problems and seeking help than men do and are less likely to be violent or arrested (Schuckit, 2009). It is important to note that, in addition to the quantity of alcohol consumed, drinking status can offer a unique view into the course of an AUD. In a 2018 paper, Birditt et al. examined the effects of drinking on older couples. In the study, wives who reported drinking alcohol reported decreased negative marital quality over time when husbands also reported drinking and increased negative marital quality over time when husbands reported not drinking. These findings will be particularly useful when considering the group of individuals (baby boomers) moving into the 65 + years category, and how marital quality may impact possible AUDs (Birditt, Cranford, Manalel, & Antonucci, 2018). Finally, prevention of drinking relapse in older alcoholics is better than in younger patients in some cases. More than 20% of treated elderly alcohol-dependent patients remain abstinent after 4 years (Caputo et al., 2012).

Management and treatment

Little formal research has been done to compare the relative efficacy of various treatment and management options for AUD in older adults. Traditional substance use treatment programs provide services to few older adults, and so therefore sample size issues have been a barrier to studying treatment outcomes for older adults with AUD (Barry & Blow, 2016). Completed studies show promising results, with elderly patients having similar or significantly better outcomes than younger patients, responding well to both psychosocial and pharmacological treatment options (Kuerbis et al., 2016). For example, Emiliussen, Andersen, and Nielsen conducted a qualitative study concerned with the motivations that lead older adults to enter treatment for alcohol problems. After an analysis of the interview data, it was evident that family can function as a pressure structure in terms of fostering motivation for AUD treatment in older adults with late-onset AUD (Emiliussen, Andersen, et al., 2017).

It is generally accepted to start with the least invasive option and then increase intensity as needed. A typical treatment plan may consist of a detoxification step, which closely monitors and compensates for alcohol withdrawal syndrome, followed by rehabilitations, where the goal is to help keep motivation high, to change attitudes toward recovery, and to reduce the risk of relapse (Caputo et al., 2012). Unfortunately, most of the few treatment options available are not designed specifically for older adults. The Elderly Study, consisting of adults aged 60 + at outpatient treatment

facilities in Denmark, Germany, and the United States, was a study that specifically targeted the treatment of the elderly (Andersen et al., 2015). They expect to gain knowledge about brief treatment of AUD for older subjects, which will be essential in the targeting of treatment programs to specific needs.

Medications currently approved in the United States by the Food and Drug Administration (FDA) to treat AUD are disulfiram, acamprosate, and two forms of naltrexone [oral and extended-release (ER) injectable], but there are limited data about their efficacy and safety specific to the elderly population. Pharmacological interventions for older adults are more limited than those in the general population. Disulfiram places extra strain on the cardiovascular system within older adults and may therefore be contraindicated (Kuerbis et al., 2014). No trials have been conducted to specifically examine the efficacy of acamprosate for individuals aged 65 years and older. Naltrexone, however, is the most commonly studied pharmacological agent for AUD treatment in older adults. Its major limitation, especially in an older population, is that it blocks the effects of opiate-based pain medications. It is administered orally once daily or by gluteal injection once monthly. The ER injectable form of naltrexone can help address patients' nonadherence (often an issue in the elderly) by reducing the frequency of medication administration from daily to monthly (Le Roux et al., 2016).

Prescription psychoactive drug use disorders

Epidemiology of sedative-hypnotic drug use and problems

Introduction

The elderly receive far more prescribed drugs than do younger people (Kuerbis et al., 2014) that leads to increased risk for potential drug−drug interactions, accumulated harm from each drug, misuse, and abuse. Data from the National Ambulatory Medical Care Survey show that from 2003 to 2012, use of the most common psychotropic medications [antidepressants, benzodiazepines (BZDs), or other anxiolytic/sedative-hypnotics] among older adults aged 65 + seen in primary care increased (Maust, Blow, Wiechers, Kales, & Marcus, 2017). This is demonstrated by a rise in visit rate from 16.4% to 21.8% by older adults to primary care providers where these psychotropic medications were prescribed. Notably, prescriptions were concentrated among patients with no mental health or pain diagnosis (Maust et al., 2017). For sedative/hypnotics in general, common reported reasons for family practitioners prescribing potentially inappropriate medications (PIM) include limited knowledge regarding PIM, limited applicability of PIM lists in daily practice, lack of time, having no alternatives in medication, stronger patient-related factors than age that influence prescription, and bad experiences regarding changes of medication or refusal of following prescriptions (Voigt et al., 2016). Among the sedative-hypnotics, benzodiazepines (BZDs) have by far the highest abuse potential and are therefore the most concerning (Singh & Sarkar, 2016); particularly in the elderly, considering that BZDs remain one of the main risk factors for falls, fractures, and other accidents, and can also affect cognition and can cause paradoxical disinhibition in older persons (Cloos, 2010).

Benzodiazepine use by the community elderly

BZDs are widely used in the treatment of anxiety and sleep problems, purportedly due to their efficacy in controlling a range of anxiety symptoms and reducing the onset of sleep latency. They are used by nearly 9% of US adults aged 65 + (Maust et al., 2019). In the American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, however, it is *highly recommended* to avoid BZDs for older adults, both short- and intermediate-acting, as well as receptor agonist hypnotics, due to their associated harms and minimal efficacy in treating insomnia (Fick et al., 2019). Yet, they continue to be prescribed. In the United States, BZD usage is substantially higher among women than men and increases with age (Olfson, King, & Schoenbaum, 2015). Olfson, King, and Schoenbaum found that nearly one-third of US adults aged 65−80 treated with BZD use BZDs on a long-term basis, and that approximately 9 of 10 of the long-term user adults have their prescriptions written exclusively by primary care physicians or other nonpsychiatrists (Olfson et al., 2015). Most people use BZDs as prescribed, while about 2% misuse them, most commonly underuse (Hashmi et al., 2018).

The reported prevalence of BZD usage in older adults is largely impacted by the age definition of "older adults." Between the ages of 60 and 70 years, for example, the exposure to environmental risk factors for addictive behaviors changes significantly, for example, from work stressors to retirement consequences on health behaviors and the prevalence of sleep disorders and cognitive impairment increases, both of which are frequently involved in inappropriate BZD or BZD-related hypnotic prescription (Airagnes, Pelissolo, Lavallée, Flament, & Limosin, 2016). Thus BZD usage statistics among the elderly may be partially controlled by other mediating variables, such as prevalence of sleep disorders.

Institutional benzodiazepine use

There is a wide concern that in nursing homes and residential care facilities, older patients may be particularly likely to be dosed with excessive sedatives to control behavior. In a 2010 article published in the *American Journal of Geriatric Psychiatry*, researchers analyzed data from the 2004 National Nursing Home Survey, focusing on antipsychotic and BZD use in 12,090 residents aged 60 years or older. They found that of the 13% of residents who took BZDs, 42% did not have an appropriate indication. Also, the odds of taking BZDs without an appropriate indication were highest for nursing home residents who were female, white, and had behavioral symptoms (Stevenson et al., 2010).

As BZDs are inappropriately prescribed for the treatment of insomnia, it is relevant to consider the risk factors for developing insomnia in the older adult. Excessive noise, hot or cold temperatures, light during the sleep period, moving to a new home or downsizing to a smaller space or a retirement community or related facility, and institutionalization have all been highlighted as environmental risk factors for elderly insomnia (Burhenn, 2013). These risk factors are present in the nursing home and residential care facility environment, and therefore the environment itself may indirectly increase the risk of BZD prescription.

Long-term benzodiazepine use and the development of dependence

It is now well established that long-term BZD use can result in development of dependence and tolerance (Ashton, 2005). BZDs are unique as physical and mental dependence can develop in the absence of tolerance, a feature known as low-dose dependence (Soyka, 2019). Particularly susceptible are individuals aged 85 years or over and those with cognitive impairment, poor health, mental disorders, previous use of BZDs, concomitant antidepressant use, multiple drug use, and multiple chronic and psychiatric diseases (Vaapio et al., 2015). Tolerance of BZDs can be easily underestimated in older adults, and therefore statistics may severely underestimate elderly BZD dependence. It has been suggested that BZDs are frequently introduced during hospitalization without plans for subsequent withdrawal (Airagnes et al., 2016).

A 2015 study entitled "Symptoms Associated with Long-term Benzodiazepine Use in Elderly Individuals Aged 65 Years and Older: A Longitudinal Descriptive Study" investigated the effects of withdrawal or reduction of BZD use on symptom changes. Through a 12-month randomized, controlled fall-prevention trial, including 248 adults aged 65 + , researchers found that withdrawal or reduction of BZD produced positive effects on physical, psychological, or cognitive symptoms among all participants (Vaapio et al., 2015). The recommendation is that withdrawal interventions be initiated for community-dwelling users aged 65 + , especially among long-term BZD users (Vaapio et al., 2015).

Other risk factors for benzodiazepine dependence

Besides duration of treatment, there are a variety of other variables to consider with BZD dependence. Dosage of the drug, duration of action, and potency can influence risk of dependence. Taking these factors into consideration, recommendations for prescribing BZDs in elderly are to "start low and go slow" and to prefer drugs with a shorter half-life and those that do not undergo oxidative metabolism (e.g., lorazepam, temazepam) (Singh & Sarkar, 2016). Previous BZD users are at a higher risk of long-term use. Psychiatric history, including anxiety, tension, schizophrenia, bipolar disorder, depression, and Alzheimer's disease, is a patient factor that increases the risk of BZD continuation, while concurrent use of antipsychotics and mood stabilizers is associated with BZD discontinuation (Hata et al., 2018). Chronic psychotropic drug use has also been positively associated with fear of uncertainty, which is related to harm avoidance (Airagnes et al., 2016). Insomnia is another strong risk factor for BZD dependence (Pergolizzi, Taylor, LeQuang, Gould, & Raffa, 2019).

Bourcier et al. conducted a retrospective observational study in France including 1194 inpatients aged 65 + without sedative-hypnotic medications prior to hospitalization. They wanted to determine the cumulative incidence of sedative-hypnotic medications initiated during a hospital stay. They found that hospitalization is a period of particular risk for sedative-hypnotic initiation in older patients, and that renewals on discharge prescriptions affected more than half of the patients discharged to rehabilitation facilities and a third of patients discharged home (Bourcier et al., 2018). As BZDs were one of the drugs included in their study, hospitalization may be a risk factor for BZD dependence, as it increases the chance of a prescription with renewal.

Limitations of the epidemiologic data

First of all, older adults are often underrepresented in drug trials, which can lead to a dearth of data regarding the elderly (Fick et al., 2019). Next, BZD used to treat insomnia is often distinguished in studies by the time of day the drug is reportedly taken. This may be misleading, as one of the behavioral correlates of BZD dependence is taking hypnotic agents during the day (Soyka, 2019). Additionally, what is defined as "older adult" varies from study to study, anywhere from 50 to 85 years old. As many important physiological and environmental changes occur during these decades, comparing datasets with different age cutoffs may be limiting.

In many studies, drug use was self-reported, which is associated with lower recall accuracy than alternative methods and is particularly worse among older adults and those prescribed more medications (Maust et al., 2019). Thus actual drug usage may be higher than reported, particularly in the elderly. Lastly, researchers have identified a need for greater understanding of the clinical reasons for BZD use in community practice, especially long-term use by older patients, which would help to focus quality improvement initiatives (Olfson et al., 2015).

Clinical features and complications of benzodiazepine dependence

Low-dose dependence

Dependence to low-dose BZD can occur with few signs or symptoms, perhaps unnoticeable until abrupt cessation leads to withdrawal symptoms (Cloos, 2010). Therapeutic doses for as little as 3−6 weeks are associated with the development of physical dependence (Hood, Norman, Hince, Melichar, & Hulse, 2014). Some behavioral correlates of low-dose BZD dependence include taking BZDs at therapeutic doses for months or years, gradually coming to need BZDs to carry out normal, day-to-day activities, and continuing to take BZDs even though the original indication for the prescription has disappeared (Soyka, 2019).

Due to declining metabolic function with age, older adults are particularly susceptible to low-dose dependence, as BZD and associated metabolites may remain in the body for much longer than expected. This can leave an elderly patient with residual daytime sleepiness and cognitive impairment (Markota, Rummans, Bostwick, & Lapid, 2016).

High-dose dependence

Although they only comprise a minority of BZD users, some older patients increase their dosage excessively. This is achieved by persuading doctors to increase prescriptions, attending several doctors or hospital departments simultaneously (supposedly taking low doses at each), or even resorting to "street" BZDs (Ashton, 2005). Other clinical features include taking hypnotic agents during the day, contacting their doctor regularly to obtain repeat prescriptions, or having anxiety between doses or a craving for the next dose (Soyka, 2019).

Generally, high-dose dependence occurs from short-acting agents, which are more dangerous for falls and fractures (Markota et al., 2016). Treatment plans to reduce high-dose BZD dependence should include strict, progressively tapering and alternative therapies in order to reduce the severity of withdrawal symptoms (Cloos, 2010).

Acute side effects and toxicity

As adults age, there is an increased sensitivity, in the form of greater confusion and disorientation, to the effects of BZDs, directly related to the accumulation of BZDs and related active metabolites (Griffin, Kaye, Bueno, & Kaye, 2013). Thus elderly patients suffer from increased intensity of BZD-mediated responses and duration of BZD-mediated effects.

High doses or poorly tolerated BZDs can lead to numerous significant consequences. The first is anterograde amnesia, with impairments in explicit memory surfacing sooner and lasting longer than impairments in implicit memory. Another effect is disinhibition, which can lead a patient to behave out of character, including scenarios such as high-risk sexual behavior and reckless driving. It is suggested that BZD usage nearly doubles the risk of motor vehicle accidents. Thirdly, BZD usage increases the risk of delirium, which is marked by impaired attention and cognition, especially for older patients in the intensive care unit setting (Airagnes et al., 2016; Griffin et al., 2013).

Chronic toxicity

Because older adults have a slower metabolism of BZDs, toxic metabolites, as well as BZDs themselves, can build up over time to dangerous levels, even at low-dose administration. Chronic usage has been associated with lower cognitive performance, as demonstrated by improved cognitive performance multiple weeks after BZD cessation (Airagnes et al., 2016).

Some studies suggest lasting and possibly irreversible cognitive deficits for long-term BZD users, with medium effect sizes in most cognitive domains, but with large effect sizes for the domain of verbal memory (Markota et al., 2016). BZD usage has been associated with Alzheimer's disease and dementia, although evidence for both is still widely debated, being criticized for study biases (Airagnes et al., 2016). More research and analysis is needed in this area.

Complications associated with other disorders

BZDs increase the effects of the neurotransmitter GABA in the brain and therefore can exacerbate certain preexisting disorders also associated with this signaling pathway. Some examples include other cardiovascular complications and metabolic disturbances, which, when combined with BZDs, may increase the risk of developing life-threatening delirium (Singh & Sarkar, 2016).

Discontinuation symptoms

Many medical practitioners are reluctant to plan BZD withdrawal as they consider the negative withdrawal symptoms to outweigh the benefits of drug continuance. It is true that the occurrence of withdrawal syndrome is more frequent with high dosage and long-term treatment, but neither dosage nor duration of treatment is closely related to symptom severity (Airagnes et al., 2016). Upon discontinuation, there is underactivation of GABA, which results in a surge in excitatory nervous activity (Ashton, 2005). Symptoms of withdrawal include insomnia, anxiety, agitation, confusion, and panic and even more severe somatic symptoms such as seizures and death in extreme cases (Kripke, 2018). It is important to note that symptoms can be diverse, chronic, variable, and patient-specific, and so symptoms may present themselves in a variety of ways (Pergolizzi et al., 2019).

Symptoms develop earlier for short-acting dependence (2−3 days) and later for long-acting dependence (5−10 days) (Ashton, 2005). Most symptoms subside within 5−28 days, with a peak occurring 2 weeks after discontinuation and the possibility of protracted withdrawal months after stopping BZDs. There are some findings that point to a lower intensity of symptoms in the elderly compared to younger adults, which could be due to a slower decrease in BZD plasmatic concentration (Airagnes et al., 2016). For elderly patients, it is recommended to educate about the harms associated with continued BZD use and to encourage gradual discontinuation of prescription BZD refills as well as avoidance of new BZD prescriptions (Singh & Sarkar, 2016).

Assessment and management of benzodiazepine use disorders

Assessment of dependence and withdrawal

Research on assessment and management of BZD use disorders in the elderly is limited. Management begins with an assessment of the patient for signs of abuse or dependence through clinical history taking and a thorough physical and mental state examination. The Alcohol, Smoking and Substance Involvement Screening Test is a useful screening tool to look for drug misuse by the elderly (Singh & Sarkar, 2016). "Red flags" to look for include strong family or personal history of substance use, a chaotic life environment, frequent emergency department (ED) visits, "losing" medications, frequent mental illness relapses, psychiatric treatment resistance, signs of withdrawal, and family concern (Hashmi et al., 2018).

It has been suggested that withdrawal interventions should be proposed to all patients aged 65 and older who have been using BZD or BZD-related hypnotics for more than a month (Airagnes et al., 2016).

Drug discontinuation and rehabilitation of the dependent patient

The path to drug discontinuation and rehabilitation depends strongly on the severity of BZD dependence/abuse as well as patient factors (living conditions, history, concomitant drug use, etc.). For acute BZD overdoses or severe withdrawal symptoms, inpatient detoxification followed by prolonged outpatient rehabilitation may be required. For mild withdrawal, both pharmacological and psychotherapeutic treatment strategies, in addition to strict monitoring for compliance, are required on an outpatient basis (Hashmi et al., 2018).

Effective strategies for stopping sedative-hypnotic drug use include simple recommendations to stop, tapering protocols, cognitive behavioral therapy, and melatonin. They may be used alone or in combination, and there is evidence for specifically combining tapering protocols with cognitive behavioral therapy (McMillan, Aitken, & Holroyd-Leduc, 2013). It has been shown that minimal interventions are needed to initiate tapering, and that educating patients about

the potential risks of long-term BZD use is the most effective first step (Markota et al., 2016). Few studies have investigated the optimal rate of tapering among elderly BZD-dependent users, but some recommendations have been to switch all BZDs before tapering to diazepam (relatively long half-life), or to oxazepam (better choice in case of liver insufficiency). The proposed protocol of withdrawal symptoms management based on a 3-day administration of phenobarbital, however, is contraindicated in older patients due to the frequent presence of liver disease (Airagnes et al., 2016).

There is promising research regarding the use of low-dose flumazenil to manage BZD withdrawal symptoms and potentially to control the initial development of BZD tolerance. Due to the low oral bioavailability and very short half-life of flumazenil, i.v.-administered flumazenil continuous infusion has been pursued and shown to alleviate both long-term and acute BZD withdrawal symptoms (Hood et al., 2014). Either concurrently with a tapering protocol or following BZD cessation, i.v. flumazenil may be an interesting way to manage persistent withdrawal symptoms (Airagnes et al., 2016).

Preventing benzodiazepine use disorder

Common advice to prevent BZD misuse, abuse, dependence, or use disorder [as defined in the latest edition of the DSM (DSM-5) that replaced the categorical distinction between abuse and dependence with SUD based on 11 criteria] is to avoid BZD treatments lasting 2−3 months or more and to refrain from marked dose increases. For some patients, particularly those with sleep disorders, intervals of treatment rather than continuous treatment are preferred. Crucial for older patients is avoiding long-term BZD prescriptions in the absence of a clear target symptom (Soyka, 2019).

Another way to prevent BZD use disorder and dependence is to reduce prescribing sedative-hypnotics in the hospital setting. To illustrate, in one study, 1 month after discharge, patients were more likely to stop previous BZD use if they did not receive them during the hospital stay, and were more likely to start taking BZDs if they were prescribed them during the hospital stay (McMillan et al., 2013).

It has been shown that direct-to-consumer education evokes shared decision making around the overuse of medications that increase the risk of harm in older adults. A cluster-randomized clinical trial was conducted in Quebec, Canada, between 2010 and 2012, with a 6-month follow-up. The study included 261 participants aged 65 + who were receiving long-term BZD therapy. While the "control arm" received usual care (no intervention), the "active arm" received a patient empowerment intervention, an eight-page booklet based on social constructivist learning and self-efficacy theory, which described the risks of BZD use and included a stepwise tapering protocol. The investigators found that the intervention yielded a 27% rate of BZD discontinuation, compared to 5% in the control group (Tannenbaum, Martin, Tamblyn, Benedetti, & Ahmed, 2014). Thus a first step in reducing inappropriate BZD use may be as simple as the delivery of an informational booklet.

Opioid use disorder

OUD is the best-studied illicit SUD. Opioids have been disproportionately overused in the United States, which has led to unintentional overdose and overdose death, addiction, and diversion (Le Roux et al., 2016), and resulted in what is now known as the "Opioid Crisis." Of the 44,000 drug-overdose deaths reported in 2013, 37% were attributable to pharmaceutical opioids. In 2014, 3%−4% of the adult population were prescribed long-term (>3 weeks) opioid therapy, which was mirrored by a parallel increase in opioid addiction, affecting 2.5 million adults that same year (Volkow & McLellan, 2016).

Significant risk factors for lifetime opioid dependence include younger age, pain impairment, higher drug dependence severity, a greater number of opioid orders in the electronic health record, and history of antisocial personality. Current opioid dependence risk factors include history of drug abuse, younger age, pain impairment, history of higher dependence severity, history of depression, and current psychotropic medication use (Boscarino et al., 2010). When using the DSM-5 to diagnose OUD, it is important to note that older adults might not trigger certain criteria, meaning a broader understanding of addiction is required to diagnose the condition.

Reasons for increased opioid use include increased advocacy for opioid treatment of chronic noncancer pain, availability of long-acting pain medication formulations, lessened perceived risk or greater social acceptability of substances that can be obtained by legitimate prescription, drug diversion, aggressive marketing by pharmaceutical companies, disregard for the lack of long-term effectiveness, and lack of understanding of opioids' addiction potential. Interestingly, the reported motivation for first opioid use for women is pain, while for men it is euphoria. In recent years, the gender gap (where men were more likely to develop a use disorder) has been narrowing (Saha et al., 2016).

Medication-assisted treatment (MAT) is strongly recommended as a first-line treatment for most patients with moderate to severe OUD. The FDA-approved medications in the United States are methadone, buprenorphine (daily sublingual, monthly injectable, and 6-month implant), and ER injectable naltrexone (Le Roux et al., 2016). As long-acting formulations of these medications require a lower frequency of administration, their usage could be a way to combat adherence issues that often occur in the elderly.

Prescription analgesic drug use and abuse

Aging is associated with more degeneration-related physical pain and therefore more opportunities for exposure to analgesics (Le Roux et al., 2016). In the last few decades, opioid analgesics in particular have become epidemic. Their usage was escalated first with the introduction of Oxycontin near the turn of the century, and later when the Joint Commission on Accreditation of Healthcare Organizations named pain as the fifth vital sign and recommended that opioids be used much more (Cicero, Surratt, Kurtz, Ellis, & Inciardi, 2012).

When elderly patients abuse analgesics, they often misuse their own prescription medications for pain management. Younger adults are more likely to use dealers rather than doctors to acquire their analgesics, while older adults are more likely to use their own doctor (Cicero et al., 2012; Levi-Minzi, Surratt, Kurtz, & Buttram, 2013). Thus it has been suggested by many that it is easier for aging patients with pain to get a doctor's prescription for analgesics than it is for younger patients with pain. The problem extends to the ED setting. ED pain score documentation is associated with a higher likelihood of analgesic prescription. However, in a cross-sectional analysis of documented ED visits by elderly patients from the National Hospital Ambulatory Medical Care Survey, patients aged 65−70 were 1.55 times more likely than patients aged 80 + to have pain score documentation. This leads to pain undertreatment for many older adults, which may in turn promote the misuse and abuse of their current analgesic prescription medications (Iyer, 2011).

Other predictors of analgesic use and abuse include ambulatory surgery and internal / external factors. Prescription of analgesics immediately after ambulatory surgery occurs frequently in older adults and is associated with long-term use (Alam, 2012). Internal factors influencing analgesic use include pain severity, perceived efficacy of analgesics, occurrence of adverse effects and concerns about addiction or dependence. External factors include views of family members, access to specialized care and the individual's interaction with medical providers (Kennedy, Cousins, & Henman, 2017). In sum, analgesic use in the elderly has unique features that need to be taken into consideration by medical practitioners when assessing or managing pain and analgesic prescriptions.

Other substances

Illegal drugs

Varieties of drugs and disorders

Among older adult illicit substance abusers, some of the most common drugs include cocaine, heroin, and cannabis (here listed as illicit drug, despite legalization in numerous states in the United States and in other countries) (Taylor & Grossberg, 2012), although different types of data collection and locations from which samples are obtained make it difficult to conclusively rank the prevalence of different substances used (Diniz et al., 2017). However, cannabis usage by older adults is considerably higher than other drugs. Among adults aged 50 years and older in 2012, 4.6 million reported past-year cannabis use, while less than one million reported past-year cocaine, inhalants, hallucinogens, methamphetamine, and/or heroin use (Kuerbis et al., 2014). It has also been shown that the "young" elderly, aged 50−64, show preference for cocaine and heroin, while the "old" elderly, aged 65 and above, show preference for cocaine and cannabis (Taylor & Grossberg, 2012). Clinical disorders caused by illegal drugs vary by drug class and include intoxication, withdrawal, delirium, dementia, and delusional, mood, and amnesic disorders. There is research to suggest that, although elderly illicit drug users place a high demand on available services, they respond well to treatment in comparison to younger patients (Chhatre, Cook, Mallik, & Jayadevappa, 2017; Shah & Fountain, 2008), especially women (Wu & Blazer, 2011).

Prevalence of disorders

The prevalence of illicit and problematic drug use in the elderly was traditionally thought to be very low. That said, the use of illegal drugs in the elderly has increased in recent years and is now considered a serious problem for public health (Shah & Fountain, 2008). For example, repeated, cross-sectional data of adults aged 65 or older from the NSDUH between 2002 and 2014 showed a significant increase in the prevalence of past-year marijuana use,

from 0.15% in 2003 to a high of 2.04% in 2014. These upward trends remained significant even when accounting for sociodemographic, substance use, behavioral, and health-related factors (Salas-wright et al., 2017). Furthermore, between 2000 and 2012, the proportion of substance abuse admissions attributable to older adults aged 55 + increased by more than a factor of two. It has also been observed that cocaine- and heroin-related admissions are on the rise in this older population (Chhatre et al., 2017). Rates of opioid use have increased dramatically in past decades, with prescription opioid abuse disorder largely dwarfing heroin and other designer opioids (Taylor & Grossberg, 2012). OUD is not covered here, but is instead detailed in section V part D.

Although rates of illicit SUDs are increasing, they are still relatively low. Reasons for the minimal prevalence of illicit drug use disorders in the elderly include cohort and cultural lack of involvement with illicit drugs and the limited acceptability of illicit drugs among the elderly, increased early mortality among illicit drug users, "maturing" out of using these drugs, and underidentification of elderly illicit drug users (Shah & Fountain, 2008). Consumption of illegal drugs is associated with being male, a low level of education (although levels of education have been increasing), lack of employment, being unmarried, and living in isolation (Diniz et al., 2017). Gender and racial/ethnic differences in specific drug use disorders remain unclear, as there is a lack of distinction between illicit and prescription drug use disorders (Wu & Blazer, 2011). As the Baby Boomer generation ages, their seemingly small percentage among all illicit drug users will correspond to a much larger total number of older individuals in need of treatment (Barry & Blow, 2016).

Cannabis use disorder

From 2006/07 to 2012/13, there was a 57.8% relative increase in past-year cannabis use for adults aged 50−64 and a 250% relative increase for those aged greater than 65. However, older adults had a significantly lower prevalence of cannabis use compared to adults aged 50−64, at 1.4% compared to 7.1% in 2012/13 (Han, Sherman, et al., 2017). Age cohort effects result in older users delaying initiation of cannabis use longer than middle-aged and younger users, largely due to the increasing availability and access to cannabis in recent years (Haug et al., 2017). There is evidence to suggest that elderly individuals may be sensitive to the cognitive effects of cannabis, and there is a growing concern that cannabis use may be associated with dementia (Bonomo, Souza, Jackson, Crippa, & Solowij, 2018). To add, it has been shown that cannabis use increases the likelihood of ED visits through increased injury risk (Choi, Marti, DiNitto, & Choi, 2018). Compared to younger age groups, older cannabis users prefer oral ingestion and primarily use it for medical reasons later in life, notably cancer, glaucoma, and HIV/AIDS (Haug et al., 2017). As cannabis becomes increasingly more accessible, as well as prominent for a larger duration of adults' lives, we can expect a continued increasing trend in cannabis use, and subsequently cannabis use disorder, in older adults.

Other drugs

Little information is available regarding the use of other illegal drugs by the elderly. Older cocaine abusers are predisposed to several of the most dangerous consequences of cocaine abuse, including myocardial infarction, cerebrovascular accident, delirium, and heat stroke (Taylor & Grossberg, 2012). There is research suggesting that cocaine use increases the risk of these events specifically for elders, in comparison to younger substance abusers or nonabusing elders (Taylor & Grossberg, 2012). Amphetamines have been linked to an increased risk of developing Parkinson's Disease later in life (Todd et al., 2016). Overall, the effects of illicit drug use accumulate over time, resulting in a higher rate of mortality and morbidity for older illicit drug users than abstainers.

Over-the-counter drugs

Prevalence of use

There are over 100,000 over-the-counter (OTC) drugs on the market, of which adults over 65 years old are the largest users, accounting for up to 40% of all nonprescription medication use in the United States (Glaser & Rolita, 2009). In general, the use of OTC medications increases with age, although use of psychoactive OTC drugs in the elderly is uncommon. In recent years, overall OTC drug use has declined among older adults. Various studies have reported prevalence between 38% and 63% among the elderly population (Paul, Marconi, Gohain, & Bhatt, 2016). One US study, a descriptive analysis of a longitudinal, nationally representative sample of community-dwelling older adults 62−85 years old, conducted in-home interviews with direct medication inspection in 2005−06 and again in 2010−11. The researchers found a reduction in OTC drug use from 44.4% to 37.9% ($P < .001$) (Qato, Wilder, Schumm, Gillet, & Alexander, 2016).

Despite these declining numbers, adults over 65 years old still use twice as many OTC medications as prescription medications, and there is a trend of prescriptions being switched to OTCs (Chang et al., 2016). Furthermore, the chances of a serious drug reaction in older adults are increased due to altered pharmacokinetics, pharmacodynamics, impaired renal function, reduced hepatic blood flow and liver size, increased body fat, decreased lean body mass, changes in receptor sensitivity, and increased number of medical conditions (Glaser & Rolita, 2009). Pain (often as joint pain) is the most common symptom treated with OTCs, but they are also used for the treatment of acute symptoms like fever, common cold, and headache. OTCs are not commonly used for chronic conditions like diabetes and hypertension (Glaser & Rolita, 2009; Goh, Vitry, Semple, Esterman, & Luszcz, 2009; Paul et al., 2016). OTC sleep aids are often used for insomnia, as more than a third of older adults use medications or aids to help with their sleep, most commonly in the form of OTC aids (Maust et al., 2019).

Factors affecting use and misuse of OTC drugs

Many reports have indicated that older adults tend not to disclose the use of OTC drugs with their physician, and that better communication between patients and health professionals predicts better self-management of medications (Glaser & Rolita, 2009; Masumoto, Sato, Maeno, Ichinohe, & Maeno, 2018). It has been estimated that the largest misuse of OTC drugs is drug−drug interactions of pain medications and that many older adults have a "go to" pain medication that they usually use based on past experience (Stone et al., 2017). Factors that affect use and misuse of OTCs in older adults include the distance to the nearest health center, waiting time in the hospital, high consultation fee, quick relief of symptoms, lack of family support, physical inability to leave home, and misinformation about OTC use recommendations (Paul et al., 2016). Female sex, higher educational qualifications, and good economic status have been identified as predictors for the use of nonprescription medications in the elderly (Masumoto et al., 2018).

Over-the-counter hypnotics

In a nationally representative, cross-sectional survey of older adults (65−80 years old) in the United States, more than 20% of respondents reported using OTC sleep aids, but less than half of those reporting at least occasional use of product had discussed sleep with their health care provider (Maust et al., 2019). Even though the 2015 Beer's Criteria for Potentially Inappropriate Medication Use in Older Adults recommends that individuals 65 years or older avoid use of diphenhydramine and doxylamine, many OTC sleep products contain these active ingredients. In the elderly, OTC drugs consisting of diphenhydramine and doxylamine increase the risk of hepatic and renal insufficiency, drug interactions, adverse events, and unintended anticholinergic effects, which can result in cognitive impairments, hangover effects, dizziness, and falls (Abraham, Schleiden, & Albert, 2017). Diphenhydramine tolerance develops after 1−2 weeks of uninterrupted use, rendering it an ineffective long-term therapy, and its short-term efficacy is marginal, placing hospitalized older adults at increased risk of delirium and altered consciousness (Schroeck et al., 2016). Moreover, anticholinergic exposure is associated with cognitive decline and increased risk of dementia, even in cases where exposure occurred 15−20 years before the dementia diagnosis (Maust et al., 2019).

Over-the-counter stimulants

There is minimal literature describing OTC stimulant use in the elderly. Caffeine is the only active ingredient in OTC drugs marketed as stimulants. Caffeine improves alertness and decreases fatigue, but in higher doses can cause insomnia, tremor, headache, and rarely, a mild form of delirium. Withdrawal symptoms include headache and fatigue. Elderly people are more sensitive to the physical effects of caffeine, and some studies suggest that caffeine ingestion may reverse the effects of cognitive aging by making greater energy reserves available (Duncan, Clarke, Tallis, Guimarães-Ferreira, & Leddington Wright, 2014). Possible helpful effects of caffeine on the elderly include acute enhanced working memory-related brain activation (Haller et al., 2013) and protection from Parkinson's Disease incidence in both men and women (Palacios et al., 2012). Other OTC preparations with prominent stimulant effects include phenylpropanolamine, ephedrine, and pseudoephedrine, but phenylpropanolamine has been associated with increased risk of hemorrhage stroke in women (Kernan et al., 2000).

Other drugs

Although not marketed primarily for their psychoactive properties, some OTC drugs have significant psychoactive effects when overused or combined with other medications. A retrospective chart review of patterns of OTC products used by older adults (65 +) admitted to the cardiology service in a US tertiary care medical center over a 3-month

period found that the most commonly used products were vitamins (37.3%), followed by laxatives (17%), minerals (13.6%), stomach acid reducers (9%), and analgesics (3.6%) (Sheikh-taha & Dimassi, 2018).

Older adults have been the target of misinformation and fraud regarding the benefits of mega-doses of vitamins, minerals, and other supplements. Supplements promoted as antiaging and sex rejuvenating include Vitamin E, selenium, zinc, bee pollen, and RNA pills. Laxatives, despite their lack of psychoactive effects, are frequently misused, especially by elderly women. Overuse of laxatives may be promoted by age-related increases in constipation but also by the mistaken belief that a daily bowel movement is necessary for good health. Compulsive laxative use can assume addictive behavior.

Four of the ten most frequently used OTC drugs are ibuprofen, aspirin, acetaminophen, and diphenhydramine. The use of nonsteroidal antiinflammatory drugs, including ibuprofen and aspirin, results in 80,000 adverse drug events in older adults annually. Additionally, unintentional overdoses of acetaminophen result in 14,000 ED visits and up to 50% of all acute liver failures per year. Lastly, diphenhydramine has anticholinergic properties that can increase risk of falling (Stone et al., 2017).

Tobacco use disorder

Prevalence of use

Tobacco use disorder is the most common of all SUDs. Its use in patients is entirely obvious, thus taking no special effort to establish the diagnosis, and arguably accounts for far more medical disability and mortality in the elderly than abuse of all other substances combined. Because of its low behavioral toxicity, however, tobacco use disorder has held little interest for mental health professionals. Nicotine is the psychoactive agent in tobacco, and regular, daily tobacco use produces a nicotine-dependence disorder. The pharmacologic and behavioral processes that determine nicotine dependence are similar to processes that determine addictions to drugs such as heroin and cocaine.

In the United States, the prevalence of smoking is lower for older adults, with over age 65 with a prevalence of 8.9%, between 45 and 64 of 19.5%, and between 25 and 44 of 21.6% (Chen & Wu, 2015). One possible explanation is mortality among smokers and smoking cessation (Martin, Schoeni, & Andreski, 2010). Data from the 2012 National Health Interview Survey estimated that about 18.1% (42.1 million) of US adults were current cigarette smokers, who reported smoking at least 100 cigarettes in their lifetime, and reported smoking every day or some days at the time of the interview (Chen & Wu, 2015). Being divorced or separated, as well as Hispanic/Latino, was correlated with more likely to have lifetime and past 12-month tobacco use disorders, while rating current health as very good or excellent was correlated with less likely to have lifetime and past 12-month tobacco use disorders (Lin et al., 2011).

Adverse health consequences of tobacco use

Tobacco use, a leading cause of premature morbidity and mortality in the United States, impacts almost all organs in the human body and is linked to a multitude of cancers and other diseases (Chen & Wu, 2015). There are data that indicate greater vulnerability to substance use for female noncigarette tobacco users compared to men, and tobacco users more broadly are at an increased risk of strong associations for substance use abuse (Conway et al., 2017). A systematic database search was performed that looked for prospective observational studies investigating tobacco smoking status as a mediator of frailty in older adults aged 50 or older, with frailty described as "a multidimensional geriatric syndrome characterized by decreased physiological reserves and increased vulnerability to adverse health outcomes (such as dependency, falls, hospitalization, institutionalization, and death) due to age-related accumulation of multisystem deficits and impaired capacity to maintain homeostasis" (Kojima, Iliffe, & Walters, 2015). The researchers reported most studies demonstrated that baseline smoking significantly predicted worsening of frailty status at follow-up. The authors give multiple interpretations of this result. For one, smoking is associated with cardiovascular diseases, respiratory diseases, and cancers, all of which could cause morbidities and disabilities that potentially contribute to increased risks of frailty status. Second, inflammation is proposed as an explanation for the results. It is well established that chronic inflammation causes muscle wasting and leads to weight loss, exhaustion, weakness or slow gait speed, all indicators of frailty status. The authors theorize that cigarette smoke contains various toxic chemicals that lead to an overall increase in inflammation (Kojima et al., 2015).

Mons et al. (2015) conducted an individual participant meta-analysis using data from 25 cohorts in Europe and United States, including 503,905 participants aged 60 and older. The researchers were interested in the impact of smoking and smoking cessation on cardiovascular mortality, acute coronary events, and stroke events in older adults. They found that smoking strongly contributes to acute coronary events, stroke, and cardiovascular deaths, as demonstrated by

a twofold hazard of cardiovascular mortality compared with never smokers, advancing the risk of dying from cardiovascular disease by 5.5 years. Among smokers, the excess risk increased with higher levels of cigarette consumption (Mons et al., 2015).

Another systematic review of 84 studies found that length of telomeres (ribonucleoprotein structures at the end of linear chromosomes essential for maintaining genome stability) was shorter among ever smokers compared to never smokers in a pack-years dose-dependent manner, indicating mechanisms linking tobacco smoke exposure to aging-related disease (Astuti, Wardhana, Watkins, & Wulaningsih, 2017).

Smoking cessation and its effects on health in the elderly

Smoking cessation at any age has health benefits. Findings from a British study indicate that smoking cessation at age 60, 50, 40, and 30 would increase life expectancy by 3, 6, 9, and 10 years, respectively (Chen & Wu, 2015). Mons et al. (2015) found that the increased excess risk among former smokers aged 60 and above declined with time after smoking cessation in a dose-response manner. The reduction of cardiovascular risk was carried out even into the oldest age groups. After 5 years of abstinence, the hazard ratio was decreased from 2 to 0.84 compared to continuing smokers. After 20 years of nonsmoking, the excess risk compared to never smokers was reduced to a ratio of 1.15 (Mons et al., 2015). This means that, contrary to popular belief that it is "too late to stop," smoking cessation, even later in life, can have substantial positive impacts on risk of cardiovascular disease and stroke.

Smoking cessation methods and outcomes

It has been shown that older cigarette smokers are less likely than younger adults to be interested in quitting smoking, making quit attempts, and achieving smoking cessation (Chen & Wu, 2015). However, when interventions have included or deliberately targeted older adults, older smokers tend to have as much success with cessation as younger smokers (Chen & Wu, 2015). Chen and Wu conducted a weighted least squares meta-regression of cessation rates on trial and sample characteristics of 29 randomized clinical trials, looking specifically at smoking cessation interventions for adults aged 50 or older. They confirmed the previously held belief that multimodal interventions usually produce the highest abstinence rates. In addition, face-to-face interventions saw cessation rates that were higher than interventions by phone. Chen and Wu's research also suggests that interventions using biochemical verification showed higher cessation rates than interventions not using biochemical verification. Overall, increased age may be associated with higher cessation rates among middle- and older-aged smokers, and a lower proportion of male smokers than female smokers quit smoking (Chen & Wu, 2015).

One study used longitudinal data from the Survey of Health, Ageing and Retirement in Europe (aged 50 + years) from four waves from 2004 to 2013 to determine whether the implementation of tobacco control policies was associated with changes in smoking status. The researchers found that increases in tobacco taxes and smoke-free policies were significantly related to a reduction in smoking among European older adults, particularly among the lowest educated (Serrano-Alarcón, Kunst, Bosdriesz, & Perelman, 2019).

E-cigarettes

The first commercialized electronic cigarette (e-cigarette) product was invented in 2003 and officially entered the US marketplace in 2007 (Orellana-Barrios, Payne, Mulkey, & Nugent, 2015). Since then, prevalence and use of the "smoking cessation tool" by many age groups in the United States have been on the rise, in contrast to the decline in adult cigarette use (Conway et al., 2017). For experienced users, e-cigarettes can deliver nicotine levels similar to that of regular cigarettes. In a nationally representative household interview survey among adults who had never smoked cigarettes, young adults aged 18−24 were more likely than older adults to have tried e-cigarettes. Additionally, adults aged 65 + were least likely to have tried or to currently use e-cigarettes (Schoenborn & Gindi, 2015). The small number of trials investigating the effects of e-cigarettes is limiting, but there are data that suggest participants using an e-cigarette are more likely to abstain from smoking for at least 6 months compared with participants using a placebo e-cigarette. In contrast, one study that compared e-cigarettes to nicotine patches found no significant difference in 6-month abstinence rates. No studies reported serious adverse events considered related to e-cigarette use (Hartmann-Boyce et al., 2016).

Polysubstance use disorders

Polysubstance use disorder, also known as polypharmacy, occurs when individuals use five or more medications concurrently. This constitutes between 20% and 40% of older adults (Amanacharla & Ponnaluri, 2015). One study found that, between 2005 and 2011 in the United States, prevalence of polypharmacy among older adults 62–85 years old increased from 30.6% to 35.8% (Qato et al., 2016). With easy access to many potentially drug–drug interacting OTC drugs, the elderly are particularly prone to adverse effects due to polypharmacy, given the changes in renal and hepatic function associated with older age (Sheikh-taha & Dimassi, 2018).

Among older adults, common reasons for polysubstance use include many comorbidities requiring medication and being prescribed more medications for symptoms that are actually side effects of other medications or the effects of drug–drug interactions. Hospital admissions, functional and cognitive impairment, geriatric syndromes (delirium, falls, and frailty), and mortality are all associated with polypharmacy in the elderly. Increased risk of falls is also a common medication-related adverse event, particularly for cardiovascular and psychoactive medications. Every medication has potential adverse side effects that seem to increase with the addition of new drugs (Amanacharla & Ponnaluri, 2015). Polysubstance use can also occur with various illicit substances. Most common among older adults is the combination of these substances with alcohol and tobacco. However, the use of nicotine is not usually documented by the studies (Diniz et al., 2017).

Looking ahead

Predicting future case volume

In the United States, the number of adults aged 50 or older with SUD is projected to double from 2.8 million in 2002 to 5.7 million in 2020, mainly due to the large population size and high substance use rate of the baby boom cohort (Han et al., 2009). Legalization of cannabis and popularity of e-cigarettes may disproportionately increase cannabis use disorder and nicotine problems, respectively. In addition, the advent of synthetic designer drugs (fentanyl analogs, cannabinoids, cathinones, etc.) has created a dangerous landscape of possible drug interactions and adverse health effects, especially for the elderly, who have age-related altered pharmacodynamic and pharmacokinetic drug effects (Cottencin, Rolland, & Karila, 2014; Karila, Megarbane, Cottencin, & Lejoyeux, 2014; Pérez-Mañá et al., 2018; Sharma, Hales, Rao, NicDaeid, & McKenzie, 2019).

In order to accurately predict future case volume, constant monitoring of trends in older adults is necessary. To add, developing SUD screening methods with diagnostic criteria and thresholds specifically geared toward the elderly will ensure these estimates have external validity. As a result of more knowledge of the state of the problem, not only will science need to keep up with the incidence of elderly SUDs and the faster pace of new drugs reaching the market, but also policy-making will need to keep up with the challenging pace set by science.

Research directions

There is a dearth of SUD literature devoted specifically to the elderly. More randomized studies and randomized clinical trials, including longitudinal studies, with high internal validity and fidelity, are needed to determine the efficacy of various assessment and treatment methods for older adults. For example, the proliferation of e-cigarettes warrants research to determine how effective they are in decreasing tobacco use and tobacco product-induced illnesses, as well as to better understand the e-cigarette trade-off; their presence means more adolescents will become addicted who may otherwise have never been exposed to nicotine, while their absence means older adults who are already addicted to nicotine through tobacco products could not use them to evade dangerous tobacco exposure. Another example is geriatric treatment for AUD.

Furthermore, evidence suggests that interventions do work for older adults with SUDs, but there is inconclusive evidence of which work best or why (Kuerbis & Sacco, 2013). Thus in addition to laboratory studies of existing evidence-supported treatments (motivational interviewing, cognitive behavioral therapy, pharmacologic treatments, etc.), identification of the mechanisms of action of treatments and change for older adults is desperately needed. Also, it is essential to investigate factors of SUD in the elderly, such as the differences between early-onset and late-onset SUDs. In general, researchers may choose almost any area of SUDs to specifically study in the elderly and contribute important knowledge to the field.

Planning services

Over the last 20 years, addiction medicine has become more widely recognized. Recently, the American Board of Medical Specialties even recognizing addiction medicine as a subspecialty in the United States, which now allows many more physicians to become certified in addiction medicine. This gives general and primary care physicians, who are often times the first line of treatment, the tools they need to effectively identify SUDs, and related problems in the geriatric population. Moreover, between 2000 and 2017, the percentage of substance abuse treatment facilities offering programs for older adults increased from 17.7% to 19.6% (Substance Abuse and Mental Health Services Administration, 2002, 2018), which provides more widespread access to the specialized treatment required of the elderly.

Yet, more work is needed. Large-scale training of the general physicians, geriatricians, and health care workers needs to be provided for more accessible services, as studies have shown the improved treatment efficacy of a skilled medical team with specific knowledge of SUDs in the elderly (Cimarolli et al., 2018). As the baby boom generation ages, the demand for SUD treatment will likewise increase, placing current resources at an all-time strain.

Prevention

Recent efforts to reduce and prevent SUDs in the elderly have shown promise by focusing on prevention-targeted initiatives, emphasis on education, and increased prevalence of preventative medicine. Continued action in these areas could help reduce and prevent SUDs in the elderly in the future. Firstly, with prevention-targeted initiatives, a majority of the substance abuse policies focus on younger populations (Chhatre et al., 2017). While these policies are beneficial for younger individuals, initiatives are needed to target prevention in the elderly, which will bring more attention to the group. One example is the National Institute of Health's Helping to End Addiction Long-Term Initiative, which includes research to integrate behavioral interventions with MAT for OUD. Second, education is a powerful method to reduce and prevent geriatric SUDs. With research demonstrating that an intervention as brief as simple, straightforward comments about concerns regarding the patient's pattern of alcohol use in conjunction with recommendations that the patient reduce or stop drinking can be effective at reducing substance use (Barry & Blow, 2016; McMillan et al., 2013), education is an area where a little goes a long ways. Finally, health insurances have been making increasing efforts with preventative medicine, as demonstrated by preventative medicine's listing in The Professional Society for Health Economics and Outcomes Research's (ISPOR) 2018 top 10 health economics and outcomes research (HEOR) trends (ISPOR, 2018).

In sum, prevention of SUDs in older adults is a promising area, as there are many possible approaches that have proven beneficial results. The challenges of the future include continuing existing momentum as well as ensuring policy decisions allow research, treatment, and prevention access and options to grow in parallel with the expanding older age group.

References

Abraham, O., Schleiden, L., & Albert, S. M. (2017). Over-the-counter medications containing diphenhydramine and doxylamine used by older adults to improve sleep. *International Journal of Clinical Pharmacy*, *39*(4), 808−817. Available from https://doi.org/10.1007/s11096-017-0467-x.

Aira, M., Hartikainen, S., & Sulkava, R. (2008). Drinking alcohol for medicinal purposes by people aged over 75: A community-based interview study. *Family Practice*, *25*(6), 445−449. Available from https://doi.org/10.1093/fampra/cmn065.

Airagnes, G., Pelissolo, A., Lavallée, M., Flament, M., & Limosin, F. (2016). Benzodiazepine misuse in the elderly: Risk factors, consequences, and management. *Current Psychiatry Reports*, *18*(10). Available from https://doi.org/10.1007/s11920-016-0727-9.

Alam, A. (2012). Long-term analgesic use after low-risk surgery. *Archives of Internal Medicine*, *172*(5), 425. Available from https://doi.org/10.1001/archinternmed.2011.1827.

Alameida, M. D., Harrington, C., Laplante, M., & Kang, T. (2010). Factors associated with alcohol use and its consequences. *Journal of Addictions Nursing*, *21*(4), 194−206. Available from https://doi.org/10.3109/10884602.2010.515692.

Amanacharla, M., & Ponnaluri, R. R. (2015). Polypharmacy in elderly patients: A review. *Journal of Drug Delivery & Therapeutics*, *5*(2), 17−19. Available from https://doi.org/10.22270/jddt.v5i2.1082.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013.

Andersen, K., Bogenschutz, M. P., Bühringer, G., Behrendt, S., Bilberg, R., Braun, B., ... Nielsen, A. S. (2015). Outpatient treatment of alcohol use disorders among subjects 60 + years: Design of a randomized clinical trial conducted in three countries (Elderly Study). *BMC Psychiatry*, *15*(1), 1−11. Available from https://doi.org/10.1186/s12888-015-0672-x.

Ashton, H. (2005). The diagnosis and management of benzodiazepine dependence. *Current Opinion in Psychiatry*, *18*(3), 249–255. Available from https://doi.org/10.1097/01.yco.0000165594.60434.84.

Astuti, Y., Wardhana, A., Watkins, J., & Wulaningsih, W. (2017). Cigarette smoking and telomere length: A systematic review of 84 studies and meta-analysis. *Environmental Research*, *158*, 480–489. Available from https://doi.org/10.1016/j.envres.2017.06.038.

Atkinson, R. M. (1984). Substance use and abuse in late life. *Alcohol and Drug Abuse in Old Age*, 1–21.

Atkinson, R. M. (1990). Aging and alcohol use disorders: Diagnostic issues in the elderly. *International Psychogeriatrics*, *2*(1), 55–72. Available from https://doi.org/10.1017/S1041610290000308.

Atkinson, R. M., & Kofoed, L. L. (1982). Aging and alcohol use disorders: Diagnosing issues in the elderly. *Substance and Alcohol Actions/Misuse*, *3*, 353–368.

Atkinson., & Schuckit, M. A. (1984). Geriatric alcohol and drug misuse and abuse. *Advances in Substance Abuse*, *3*, 195–237.

Barry, K. L., & Blow, F. C. (2016). Drinking over the lifespan: Focus on older adults. *Alcohol Research: Current Reviews*, *38*(1), 115–120. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T = JS&PAGE = reference&D = emed17&NEWS = N&AN = 616137330.

Birditt, K. S., Cranford, J. A., Manalel, J. A., & Antonucci, T. C. (2018). Drinking patterns among older couples: Longitudinal associations with negative marital quality. *The Journals of Gerontology—Series B, Psychological Sciences and Social Sciences*, *73*(4), 655–665. Available from https://doi.org/10.1093/geronb/gbw073.

Blazer, D. G., & Wu, L.-T. (2009). The epidemiology of substance use and disorders among middle aged and elderly community adults: National Survey on Drug Use and Health. *The American Journal of Geriatric Psychiatry*, *17*(3), 237–245. Available from https://doi.org/10.1097/JGP.0b013e318190b8ef.

Blow, F. C., & Barry, K. L. (2012). Alcohol and substance misuse in older adults. *Current Psychiatry Reports*, *14*(4), 310–319. Available from https://doi.org/10.1007/s11920-012-0292-9.

Bonomo, Y., Souza, J., Jackson, A., Crippa, J., & Solowij, N. (2018). Clinical issues in cannabis use. *British Journal of Clinical Pharmacology*, 2495–2498. Available from https://doi.org/10.1111/bcp.13703.

Boscarino, J. A., Rukstalis, M., Hoffman, S. N., Han, J. J., Erlich, P. M., Gerhard, G. S., & Stewart, W. F. (2010). Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*, *105*(10), 1776–1782. Available from https://doi.org/10.1111/j.1360-0443.2010.03052.x.

Bourcier, E., Baptiste, A., Borowik, A., Zerbib, L., Bonnet-Zamponi, D., Tubach, F., ... Hindlet, P. (2018). Sedative-hypnotic initiation and renewal at discharge in hospitalized older patients: An observational study. *BMC Geriatrics*, *18*(1), 4–11. Available from https://doi.org/10.1186/s12877-018-0972-3.

Breslow, R. A., Castle, I. J. P., Chen, C. M., & Graubard, B. I. (2017). Trends in alcohol consumption among older Americans: National Health Interview Surveys, 1997 to 2014. *Alcoholism: Clinical and Experimental Research*, *41*(5), 976–986. Available from https://doi.org/10.1111/acer.13365.

Britton, A., & Bell, S. (2015). Reasons why people change their alcohol consumption in later life: Findings from the Whitehall II Cohort Study. *PLoS One*, *10*(3), 1–8. Available from https://doi.org/10.1371/journal.pone.0119421.

Burhenn, P. (2013). Insomnia in the older adult with cancer. *Journal of Geriatric Oncology*, *4*(1), S14. Available from https://doi.org/10.1016/j.jgo.2013.09.228.

Burruss, K., Sacco, P., & Smith, C. A. (2015). Understanding older adults' attitudes and beliefs about drinking: Perspectives of residents in congregate living. *Ageing and Society*, *35*(9), 1889–1904. Available from https://doi.org/10.1017/S0144686X14000671.

Caputo, F., Vignoli, T., Leggio, L., Addolorato, G., Zoli, G., & Bernardi, M. (2012). Alcohol use disorders in the elderly: A brief overview from epidemiology to treatment options. *Experimental Gerontology*, *47*(6), 411–416. Available from https://doi.org/10.1016/j.exger.2012.03.019.

Chang, J., Lizer, A., Patel, I., Bhatia, D., Tan, X., & Balkrishnan, R. (2016). Prescription to over-the-counter switches in the United States. *Journal of Research in Pharmacy Practice*, *5*(3), 149–154. Available from https://doi.org/10.4103/2279-042X.185706.

Chen, D., & Wu, L.-T. (2015). Smoking cessation interventions for adults aged 50 or older: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, 14–24. Available from https://doi.org/10.1016/j.drugalcdep.2015.06.004.

Chhatre, S., Cook, R., Mallik, E., & Jayadevappa, R. (2017). Trends in substance use admissions among older adults. *BMC Health Services Research*, *17*(1), 1–8. Available from https://doi.org/10.1186/s12913-017-2538-z.

Choi, N. G., Marti, C. N., DiNitto, D. M., & Choi, B. Y. (2018). Older adults' marijuana use, injuries, and emergency department visits. *American Journal of Drug and Alcohol Abuse*, *44*(2), 215–223. Available from https://doi.org/10.1080/00952990.2017.1318891.

Cicero, T. J., Surratt, H. L., Kurtz, S., Ellis, M. S., & Inciardi, J. A. (2012). Patterns of prescription opioid abuse and co-morbidity in an aging treatment population. *Journal of Substance Abuse Treatment*, *42*(1), 87–94. Available from https://doi.org/10.1016/j.jsat.2011.07.003.

Cimarolli, V. R., Burack, O., Poole-Dayan, G., Liu, I., Samaroo, S. P., & Bondy, M. (2018). An evaluation of a Geriatric Substance Abuse Recovery Program in post-acute care of a skilled nursing facility. *Educational Gerontology*, *44*(1), 28–39. Available from https://doi.org/10.1080/03601277.2017.1388961.

Cloos, J.-M. (2010). Benzodiazepines and addiction: Myths and realities (Part 1). *Psychiatric Times*, *27*(7), 26–29.

Conway, K. P., Green, V. R., Kasza, K. A., Silveira, M. L., Borek, N., Kimmel, H. L., ... Compton, W. M. (2017). Co-occurrence of tobacco product use, substance use, and mental health problems among adults: Findings from Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health (PATH) Study. *Drug and Alcohol Dependence*, *177*, 104–111. Available from https://doi.org/10.1016/j.drugalcdep.2017.03.032.

Cottencin, O., Rolland, B., & Karila, L. (2014). New designer drugs (synthetic cannabinoids and synthetic cathinones): Review of literature. *Current Pharmaceutical Design*, *20*(25), 4106–4111. Available from https://doi.org/10.2174/13816128113199990622.

Crome, I., Li, T. K., Rao, R., & Wu, L. T. (2012). Alcohol limits in older people. *Addiction*, *107*(9), 1541−1543. Available from https://doi.org/10.1111/j.1360-0443.2012.03854.x.

Davies, E. L., Paltoglou, A. E., & Foxcroft, D. R. (2017). Implicit alcohol attitudes predict drinking behaviour over and above intentions and willingness in young adults but willingness is more important in adolescents: Implications for the prototype willingness model. *British Journal of Health Psychology*, *22*(2), 238−253. Available from https://doi.org/10.1111/bjhp.12225.

Delker, E., Brown, Q., & Hasin, D. S. (2016). Alcohol consumption in demographic subpopulations. *Alcohol Research: Current Reviews*, *38*, 7−15.

Diniz, A., Pillon, S. C., Monteiro, S., Pereira, A., Goncalves, J., & dos Santos, M. A. (2017). Elderly substance abuse: An integrative review. *Psicologia: Teoria E Prática*, *19*(2), 42−59. Available from https://doi.org/10.5935/1980-6906/psicologia.v19n2p42-59.

Downer, B., Jiang, Y., Zanjani, F., & Fardo, D. (2015). Effects of alcohol consumption on cognition and regional brain volumes among older adults. *American Journal of Alzheimer's Disease and Other Dementias*, *30*(4), 364−374. Available from https://doi.org/10.1177/1533317514549411.

Draper, B., Ridley, N., Johnco, C., Withall, A., Sim, W., Freeman, M., ... Lintzeris, N. (2015). Screening for alcohol and substance use for older people in geriatric hospital and community health settings. *International Psychogeriatrics*, *27*(1), 157−166. Available from https://doi.org/10.1017/S1041610214002014.

Duncan, M. J., Clarke, N. D., Tallis, J., Guimarães-Ferreira, L., & Leddington Wright, S. (2014). The effect of caffeine ingestion on functional performance in older adults. *Journal of Nutrition, Health and Aging*, *18*(10), 883−887. Available from https://doi.org/10.1007/s12603-014-0474-8.

Emiliussen, J., Andersen, K., & Nielsen, A. S. (2017). How do family pressure, health and ambivalence factor into entering alcohol treatment? Experiences of people aged 60 and older with alcohol use disorder. *NAD Nordic Studies on Alcohol and Drugs*, *34*(1), 28−42. Available from https://doi.org/10.1177/1455072516682639.

Emiliussen, J., Nielsen, A. S., & Andersen, K. (2017). Identifying risk factors for late-onset (50 +) alcohol use disorder and heavy drinking: A systematic review. *Substance Use and Misuse*, *52*(12), 1575−1588. Available from https://doi.org/10.1080/10826084.2017.1293102.

Fick, D. M., Semla, T. P., Steinman, M., Beizer, J., Brandt, N., Dombrowski, R., ... Sandhu, S. (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*, *67*(4), 674−694. Available from https://doi.org/10.1111/jgs.15767.

Gilson, K. M., Bryant, C., & Judd, F. (2017). Understanding older problem drinkers: The role of drinking to cope. *Addictive Behaviors*, *64*, 101−106. Available from https://doi.org/10.1016/j.addbeh.2016.08.032.

Glaser, J., & Rolita, L. (2009). Educating the older adult in over-the-counter medication use. *Geriatrics & Aging*, *12*(2), 103−109.

Goh, L. Y., Vitry, A. I., Semple, S. J., Esterman, A., & Luszcz, M. A. (2009). Self-medication with over-the-counter drugs and complementary medications in South Australia's elderly population. *BMC Complementary and Alternative Medicine*, *9*, 42. Available from https://doi.org/10.1186/1472-6882-9-42.

Griffin, C. E., Kaye, A. M., Bueno, F. R., & Kaye, A. D. (2013). Benzodiazepine pharmacology and central nervous system-mediated effects. *The Ochsner Journal*, *13*(2), 214−223. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23789008%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = PMC3684331.

Haller, S., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., ... Lovblad, K. O. (2013). Acute caffeine administration impact on working memory-related brain activation and functional connectivity in the elderly: A BOLD and perfusion MRI study. *Neuroscience*, *250*, 364−371. Available from https://doi.org/10.1016/j.neuroscience.2013.07.021.

Han, B., Gfroerer, J. C., Colliver, J. D., & Penne, M. A. (2009). Substance use disorder among older adults in the United States in 2020. *Addiction*, *104*(1), 88−96. Available from https://doi.org/10.1111/j.1360-0443.2008.02411.x.

Han, B. H., Moore, A. A., Sherman, S., Keyes, K. M., & Palamar, J. J. (2017). Demographic trends of binge alcohol use and alcohol use disorders among older adults in the United States, 2005−2014. *Drug and Alcohol Dependence*, *170*, 198−207. Available from https://doi.org/10.1016/j.drugalcdep.2016.11.003.

Han, B. H., Sherman, S., Mauro, P. M., Martins, S. S., Rotenberg, J., & Palamar, J. J. (2017). Demographic trends among older cannabis users in the United States, 2006−13. *Addiction*, *112*(3), 516−525. Available from https://doi.org/10.1111/add.13670.

Hartmann-Boyce, J., McRobbie, H., Bullen, C., Begh, R., Stead, L. F., & Hajek, P. (2016). Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* (9)). Available from https://doi.org/10.1002/14651858.CD010216.pub3.

Hashmi, A. M., Han, J. Y., French-Rosas, L., Jabbar, Q., Khan, B. A., & Shah, A. A. (2018). Benzodiazepine use and abuse. *Psychiatric Annals*, *48*(8), 360−365. Available from https://doi.org/10.3928/00485713-20180718-02.

Hassing, L. B. (2018). Light alcohol consumption does not protect cognitive function: A longitudinal prospective study. *Frontiers in Aging Neuroscience*, *10*, 1−8. Available from https://doi.org/10.3389/fnagi.2018.00081.

Hata, T., Kanazawa, T., Hamada, T., Nishihara, M., Bush, A. I., Yoneda, H., ... Katsumata, T. (2018). What can predict and prevent the long-term use of benzodiazepines? *Journal of Psychiatric Research*, *97*, 94−100. Available from https://doi.org/10.1016/j.jpsychires.2017.11.012.

Haug, N. A., Padula, C. B., Sottile, J. E., Vandrey, R., Heinz, A. J., & Bonn-Miller, M. O. (2017). Cannabis use patterns and motives: A comparison of younger, middle-aged, and older medical cannabis dispensary patients. *Addictive Behaviors*, *72*, 14−20. Available from https://doi.org/10.1016/j.addbeh.2017.03.006.

Hood, S. D., Norman, A., Hince, D. A., Melichar, J. K., & Hulse, G. K. (2014). Benzodiazepine dependence and its treatment with low dose flumazenil. *British Journal of Clinical Pharmacology*, *77*(2), 285−294. Available from https://doi.org/10.1111/bcp.12023.

Horvat, P., Richards, M., Kubinova, R., Pajak, A., Malyutina, S., Shishkin, S., ... Bobak, M. (2015). Alcohol consumption, drinking patterns, and cognitive function in older Eastern European adults. *Neurology*, *84*(3), 287−295. Available from https://doi.org/10.1212/WNL.0000000000001164.

ISPOR. (2018). *Top 10 HEOR trends*.

Iyer, R. G. (2011). Pain documentation and predictors of analgesic prescribing for elderly patients during emergency department visits. *Journal of Pain and Symptom Management*, *41*(2), 367–373. Available from https://doi.org/10.1016/j.jpainsymman.2010.04.023.

Karila, L., Megarbane, B., Cottencin, O., & Lejoyeux, M. (2014). Synthetic cathinones: A new public health problem. *Current Neuropharmacology*, *13*(1), 12–20. Available from https://doi.org/10.2174/1570159x13666141210224137.

Kelly, S., Olanrewaju, O., Cowan, A., Brayne, C., & Lafortune, L. (2018). Alcohol and older people: A systematic review of barriers, facilitators and context of drinking in older people and implications for intervention design. *PLoS One*, *13*(1), 1–14. Available from https://doi.org/10.1081/JLC-100100416.

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2016). Alcohol use disorder and mortality across the lifespan a longitudinal cohort and co-relative analysis. *JAMA Psychiatry*, *73*(6), 575–581. Available from https://doi.org/10.1001/jamapsychiatry.2016.0360.

Kennedy, M. C., Cousins, G., & Henman, M. C. (2017). Analgesic use by ageing and elderly patients with chronic non-malignant pain: A qualitative study. *International Journal of Clinical Pharmacy*, *39*(4), 798–807. Available from https://doi.org/10.1007/s11096-017-0466-y.

Kernan, W. N., Viscoli, C. M., Brass, L. M., Broderick, J. P., Brott, T., Feldmann, E., ... Horwitz, R. I. (2000). Phenylpropanolamine and the risk of hemorrhagic stroke. *New England Journal of Medicine*, *343*(25), 1826–1832. Available from https://doi.org/10.3999/jscpt.40.17.

Kerr, W. C., Greenfield, T. K., Bond, J., Ye, Y., & Rehm, J. (2009). Age-period-cohort modelling of alcohol volume and heavy drinking days in the US National Alcohol Surveys: Divergence in younger and older adult trends. *Addiction*, *104*(1), 27–37. Available from https://doi.org/10.1111/j.1360-0443.2008.02391.x.

Kim, S.-A., Kim, E., Morris, R. G., & Park, W.-S. (2015). Exploring the non-linear relationship between alcohol consumption and depression in an elderly population in gangneung: The gangneung health study. *Yonsei Medical Journal*, *56*(2), 418–425. Available from https://doi.org/10.3349/ymj.2015.56.2.418.

Kojima, G., Iliffe, S., & Walters, K. (2015). Smoking as a predictor of frailty: A systematic review. *BMC Geriatrics*, *15*, 1–7. Available from https://doi.org/10.1186/s12877-015-0134-9.

Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "Big" personality traits to anxiety, depressive, and substance use disorders: A meta-analysis. *Psychological Bulletin*, *136*(5), 768–821. Available from https://doi.org/10.1037/a0020327.

Kripke, D. F. (2018). Hypnotic drug risks of mortality, infection, depression, and cancer: But lack of benefit. *F1000Research*, *5*, 918. Available from https://doi.org/10.12688/f1000research.8729.3.

Kuerbis, A., Hagman, B. T., & Sacco, P. (2013). Functioning of alcohol use disorders criteria among middle-aged and older adults: Implications for DSM-5. *Substance Use & Misuse*, *48*(4), 309–322. Available from https://doi.org/10.3109/10826084.2012.762527.

Kuerbis, A., Moore, A. A., Sacco, P., & Zanjani, F. (2016). *Alcohol and aging: Clinical and public health perspectives*. Cham, Switzerland: Springer International Publishing AG. Available from http://doi.org/10.1007/978-3-319-47233-1.

Kuerbis, A., & Sacco, P. (2013). A review of existing treatments for substance abuse among the elderly and recommendations for future directions. *Substance Abuse: Research and Treatment*, *7*, 13–37. Available from https://doi.org/10.4137/SART.S7865.

Kuerbis., Sacco, P., Blazer, D. G., & Moore, A. A. (2014). Substance abuse among older adults. *Clinics in Geriatric Medicine*, *30*(3), 629–654. Available from https://doi.org/10.1016/j.cger.2014.04.008.

Lee, M. R., Boness, C. L., McDowell, Y. E., Vergés, A., Steinley, D. L., & Sher, K. J. (2018). Desistance and severity of alcohol use disorder: A lifespan-developmental investigation. *Clinical Psychological Science*, *6*(1), 90–105. Available from https://doi.org/10.1177/2167702617736852.

Le Roux, C., Tang, Y., & Drexler, K. (2016). Alcohol and opioid use disorder in older adults: Neglected and treatable illnesses. *Current Psychiatry Reports*, *18*(9), 87. Available from https://doi.org/10.1007/s11920-016-0718-x.

Levi-Minzi, M. A., Surratt, H. L., Kurtz, S. P., & Buttram, M. E. (2013). Under treatment of pain: A prescription for opioid misuse among the elderly? *Pain Medicine*, *14*(11), 1719–1729. Available from https://doi.org/10.1111/pme.12189.

Lin, J. C., Karno, M. P., Grella, C. E., Warda, U., Liao, D. H., Hu, P., & Moore, A. A. (2011). Alcohol, tobacco, and non-medical drug use disorders in U.S. adults aged 65 and older: Data from the 2001-2002 National Epidemiologic Survey of Alcohol and Related Conditions. *The American Journal of Geriatric Psychiatry*, *19*(3), 292–299. Available from https://doi.org/10.1097/JGP.0b013e3181e898b4.

Mangoni, A. A., & Jackson, S. H. D. (2004). Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *British Journal of Clinical Pharmacology*, *57*(1), 6–14. Available from https://doi.org/10.1046/j.1365-2125.2003.02007.x.

Markota, M., Rummans, T. A., Bostwick, J. M., & Lapid, M. I. (2016). Benzodiazepine use in older adults: Dangers, management, and alternative therapies. *Mayo Clinic Proceedings*, *91*(11), 1632–1639. Available from https://doi.org/10.1016/j.mayocp.2016.07.024.

Martin, L. G., Schoeni, R. F., & Andreski, P. M. (2010). Trends in health of older adults in the United States: Past, present, future. *Demography*, *47*(S), S17–S40. Available from https://doi.org/10.1353/dem.2010.0003.

Masumoto, S., Sato, M., Maeno, T., Ichinohe, Y., & Maeno, T. (2018). Factors associated with the use of dietary supplements and over-the-counter medications in Japanese elderly patients. *BMC Family Practice*, *19*(1), 1–7. Available from https://doi.org/10.1186/s12875-017-0699-9.

Maust, D. T., Blow, F. C., Wiechers, I. R., Kales, H. C., & Marcus, S. C. (2017). National trends in antidepressant, benzodiazepine, and other sedative-hypnotic treatment of older adults in psychiatric and primary care. *Journal of Clinical Psychiatry*, *78*(5), 363–371. Available from https://doi.org/10.1002/jmri.25711.PET/MRI.

Maust, D. T., Solway, E., Clark, S. J., Kirch, M., Singer, D. C., & Malani, P. (2019). Prescription and nonprescription sleep product use among older adults in the United States. *American Journal of Geriatric Psychiatry*, *27*(1), 32–41. Available from https://doi.org/10.1016/j.jagp.2018.09.004.

McMillan, J. M., Aitken, E., & Holroyd-Leduc, J. M. (2013). A 68-year-old woman with sleep-onset insomnia. *CMAJ*, *185*(17), 1499–1505. Available from https://doi.org/10.1503/cmaj.130260.

Milic, J., Glisic, M., Voortman, T., Borba, L. P., Asllanaj, E., Rojas, L. Z., ... Franco, O. H. (2018). Menopause, ageing, and alcohol use disorders in women. *Maturitas*, *111*, 100−109. Available from https://doi.org/10.1016/j.maturitas.2018.03.006.

Mons, U., Müezzinler, A., Gellert, C., Schöttker, B., Abnet, C. C., Bobak, M., ... Brenner, H. (2015). Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: Meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*, *350*, 1−12. Available from https://doi.org/10.1136/bmj.h1551.

Moore, A. A., Gould, R., Reuben, D. B., Greendale, G. A., Carter, M. K., Zhou, K., & Karlamangla, A. (2005). Longitudinal patterns and predictors of alcohol consumption in the United States. *American Journal of Public Health*, *95*(3), 458−464. Available from https://doi.org/10.2105/AJPH.2003.019471.

Moore, A. A., Whiteman, E. J., & Ward, K. T. (2007). Risks of combined alcohol/medication use in older adults. *American Journal Geriatric Pharmacotherapy*, *5*(1), 64−74. Available from https://doi.org/10.1016/j.amjopharm.2007.03.006.

Nuevo, R., Chatterji, S., Verdes, E., Naidoo, N., Ayuso-Mateos, J. L., & Miret, M. (2015). Prevalence of alcohol consumption and pattern of use among the elderly in the WHO European region. *European Addiction Research*, *21*(2), 88−96. Available from https://doi.org/10.1159/000360002.

O'Brien, C. (2015). In treating alcohol use disorders, why not use evidence-based treatment? *American Journal of Psychiatry*, *172*(4), 305−306. Available from https://doi.org/10.1176/appi.ajp.2014.14111413.

Olfson, M., King, M., & Schoenbaum, M. (2015). Benzodiazepine use in the United States. *JAMA Psychiatry*, *72*(2), 136−142. Available from https://doi.org/10.1001/jamapsychiatry.2014.1763.

Orellana-Barrios, M. A., Payne, D., Mulkey, Z., & Nugent, K. (2015). Electronic cigarettes—A narrative review for clinicians. *The American Journal of Medicine*, *128*(7), 674−681. Available from https://doi.org/10.1016/j.amjmed.2015.01.033.

Ormstad, H., Rosness, T. A., Bergem, A. L. M., Bjertness, E., & Strand, B. H. (2016). Alcohol consumption in the elderly and risk of dementia related death—A Norwegian prospective study with a 17-year follow-up. *International Journal of Neuroscience*, *126*(2), 135−144. Available from https://doi.org/10.3109/00207454.2014.997876.

Palacios, N., Gao, X., McCullough, M. L., Schwarzschild, M. A., Shah, R., Gapstur, S., & Ascherio, A. (2012). Caffeine and risk of Parkinson's disease in a large cohort of men and women. *Movement Disorders*, *27*(10), 1276−1282. Available from https://doi.org/10.1002/mds.25076.

Palmer, R., Nugent, N., Bidwell, L., McGeary, J., Knopik, V., & Keller, M. (2015). Examining the role of common genetic variants on alcohol, tobacco, cannabis, and illicit drug dependence. *Addiction*, *110*(3), 530−537. Available from https://doi.org/10.1111/add.12815.

Parikh, R. B., Junquera, P., Canaan, Y., & Oms, J. D. (2015). Predictors of binge drinking in elderly Americans. *American Journal on Addictions*, *24*(7), 621−627. Available from https://doi.org/10.1111/ajad.12275.

Paul, S., Marconi, S., Gohain, M., & Bhatt, A. (2016). Senior citizens and over the counter drugs: Challenges in rural India. *International Journal of Research in Medical Sciences*, *4*, 1446−1449. Available from https://doi.org/10.18203/2320-6012.ijrms20161207.

Pérez-Mañá, C., Papaseit, E., Fonseca, F., Farré, A., Torrens, M., & Farré, M. (2018). Drug interactions with new synthetic opioids. *Frontiers in Pharmacology*, *9*, 1−17. Available from https://doi.org/10.3389/fphar.2018.01145.

Pergolizzi, J. V., Taylor, R., LeQuang, J. A., Gould, E., & Raffa, R. B. (2019). Treating insomnia in older adult patients: Limiting benzodiazepine use. *Pharmacology & Pharmacy*, *10*(03), 116−129. Available from https://doi.org/10.4236/pp.2019.103010.

Piano, M. R. (2017). Alcohol's effects on the cardiovascular system. *Alcohol Research: Current Reviews*, *38*(2), 219−241. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28988575%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = PMC5513687.

Platt, A., Sloan, F. A., & Costanzo, P. (2010). Alcohol-consumption trajectories and associated characteristics among adults older than age 50*. *Journal of Studies on Alcohol and Drugs*, *71*(2), 169−179. Available from https://doi.org/10.15288/jsad.2010.71.169.

Qato, D. M., Wilder, J., Schumm, L. P., Gillet, V., & Alexander, G. C. (2016). Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Internal Medicine*, *176*(4), 473−482. Available from https://doi.org/10.1001/jamainternmed.2015.8581.

Rakesh, L., & Pattanayak, R. D. (2017). Alcohol use among the elderly: Issues and considerations. *Journal of Geriatric Mental Health*, *4*, 42−47. Available from https://doi.org/10.4103/jgmh.jgmh.

Reas, E. T., Laughlin, G. A., Kritz-Silverstein, D., Barrett-Connor, E., & Mcevoy, L. K. (2016). Moderate, regular alcohol consumption is associated with higher cognitive function in older community-dwelling adults. *The Journal of Prevention of Alzheimer's Diseases*, *3*(2), 105−113. Available from https://doi.org/10.14283/jpad.2016.89.

Roepke, S. K., & Ancoli-Israel, S. (2010). Sleep disorders in the elderly. *Indian Journal of Medical Research*, *131*, 302−310. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10863733.

Sacco, P., Burruss, K., Smith, C. A., Kuerbis, A., Harrington, D., Moore, A. A., & Resnick, B. (2015). Drinking behavior among older adults at a continuing care retirement community: Affective and motivational influences. *Aging and Mental Health*, *19*(3), 279−289. Available from https://doi.org/10.1080/13607863.2014.933307.

Sacco, P., Unick, G. J., Kuerbis, A., Koru, A. G., & Moore, A. A. (2015). Alcohol-related diagnoses in hospital admissions for all causes among middle-aged and older adults. *Journal of Aging and Health*, *27*(8), 1358−1374. Available from https://doi.org/10.1177/0898264315583052.

Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., Jung, J., ... Grant, B. F. (2016). Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *The Journal of Clinical Psychiatry*, *77*(6), 772−780. Available from https://doi.org/10.4088/JCP.15m10386.

Salas-wright, C. P., Vaughn, M. G., Cummings-vaughn, L. A., Holzer, K. J., Nelson, E. J., Abinader, M., & Oh, S. (2017). Trends and correlates of marijuana use among late middle-aged and older adults in the United States, 2002−2014. *Drug and Alcohol Dependence*, *171*, 97−106. Available from https://doi.org/10.1016/j.drugalcdep.2016.11.031.Trends.

Schoenborn, C. A., & Gindi, R. M. (2015). Electronic cigarette use among working adults: United States, 2014. *NCHS Data Brief*, *217*, 1–8.

Schroeck, J. L., Ford, J., Conway, E. L., Kurtzhalts, K. E., Gee, M. E., Vollmer, K. A., & Mergenhagen, K. A. (2016). Review of safety and efficacy of sleep medicines in older adults. *Clinical Therapeutics*, *38*(11), 2340–2372. Available from https://doi.org/10.1016/j.clinthera.2016.09.010.

Schuckit, M. A. (1977). Geriatric alcoholism and drug abuse. *The Gerontologist*, *17*, 168–174.

Schuckit, M. A. (2009). Alcohol use disorders. *The Lancet*, *373*, 492–501. Available from https://doi.org/10.1016/S0140-6736(09)60009-X.

Scott, R. G., Wiener, C. H., & Paulson, D. (2018). The benefit of moderate alcohol use on mood and functional ability in later life: Due to beers or frequent cheers? *The Gerontologist*, 1–9. Available from https://doi.org/10.1093/geront/gny129.

Serrano-Alarcón, M., Kunst, A. E., Bosdriesz, J. R., & Perelman, J. (2019). Tobacco control policies and smoking among older adults: A longitudinal analysis of 10 European countries. *Addiction*, *114*, 1076–1085. Available from https://doi.org/10.1111/add.14577.

Shah, A., & Fountain, J. (2008). Illicit drug use and problematic use in the elderly: Is there a case for concern. *International Psychogeriatrics*, *20*(6), 1081–1089. Available from https://doi.org/10.1017/S1041610208006789.

Sharma, K. K., Hales, T. G., Rao, V. J., NicDaeid, N., & McKenzie, C. (2019). The search for the "next" euphoric non-fentanil novel synthetic opioids on the illicit drugs market: Current status and horizon scanning. *Forensic Toxicology*, *37*(1), 1–16. Available from https://doi.org/10.1007/s11419-018-0454-5.

Sheikh-taha, M., & Dimassi, H. (2018). Use of over the counter products in older cardiovascular patients admitted to a tertiary care center in USA. *BMC Geriatrics*, *18*(1), 1–6. Available from https://doi.org/10.1186/s12877-018-0989-7.

Singh, S., & Sarkar, S. (2016). Benzodiazepine abuse among the elderly. *Journal of Geriatric Mental Health*, *3*(2), 123. Available from https://doi.org/10.4103/2348-9995.195605.

Soyka, M. (2019). Treatment of benzodiazepine dependence. *Fortschritte Der Neurologie Psychiatrie*, *87*(4), 259–270. Available from https://doi.org/10.1055/a-0836-7514.

Stevenson, D. G., Decker, S. L., Dwyer, L. L., Huskamp, H. A., Grabowski, D. C., Metzger, E. D., & Mitchell, S. L. (2010). Antipsychotic and benzodiazepine use among nursing home residents: Findings from the 2004 National Nursing Home Survey. *The American Journal of Geriatric Psychiatry*, *18*(12), 1078–1092. Available from https://doi.org/10.1097/JGP.0b013e3181d6c0c6.

Stickel, F., Moreno, C., Hampe, J., & Morgan, M. Y. (2017). The genetics of alcohol dependence and alcohol-related liver disease. *Journal of Hepatology*, *66*(1), 195–211. Available from https://doi.org/10.1016/j.jhep.2016.08.011.

Stone, J. A., Lester, C. A., Aboneh, E. A., Phelan, C. H., Welch, L. L., & Chui, M. A. (2017). A preliminary examination of over the counter medication misuse rates in older adults. *Research in Social and Administrative Pharmacy*, *13*(1), 187–192. Available from https://doi.org/10.1016/j.sapharm.2016.01.004.

Substance Abuse and Mental Health Administration. (2011). *Results from the 2010 National Survey on Drug Use and Health: Summary of national findings*. Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2002). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2000. Data on substance abuse treatment facilities, DASIS series: S-16, DHHS publication no. (SMA) 02-3668*. Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2018). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2017. Data on substance abuse treatment facilities*. Rockville, MD.

Tannenbaum, C., Martin, P., Tamblyn, R., Benedetti, A., & Ahmed, S. (2014). Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: The EMPOWER cluster randomized trial. *JAMA Internal Medicine*, *174*(6), 890–898. Available from https://doi.org/10.1001/jamainternmed.2014.949.

Taylor, M. H., & Grossberg, G. T. (2012). The growing problem of illicit substance abuse in the elderly: A review. *Primary Care Companion for CNS Disorders*, *14*(4), 1–11. Available from https://doi.org/10.4088/PCC.11r01320.

Todd, G., Pearson-dennett, V., Wilcox, R. A., Chau, M. T., Thoirs, K., Thewlis, D., ... White, J. M. (2016). Parkinsonism and related disorders adults with a history of illicit amphetamine use exhibit abnormal substantia nigra morphology and parkinsonism. *Parkinsonism and Related Disorders*, *25*, 27–32. Available from https://doi.org/10.1016/j.parkreldis.2016.02.019.

Topiwala, A., Allan, C. L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C., ... Ebmeier, K. P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ (Online)*, *357*, 1–20. Available from https://doi.org/10.1136/bmj.j2353.

Vaapio, S., Puustinen, J., Salminen, M. J., Vahlberg, T., Salonoja, M., Lyles, A., & Kivelä, S. L. (2015). Symptoms associated with long-term benzodiazepine use in elderly individuals aged 65 years and older: A longitudinal descriptive study. *International Journal of Gerontology*, *9*(1), 34–39. Available from https://doi.org/10.1016/j.ijge.2014.03.009.

Van Boekel, L. C., Brouwers, E. P. M., Van Weeghel, J., & Garretsen, H. F. L. (2013). Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: Systematic review. *Drug and Alcohol Dependence*, *131*(1–3), 23–35. Available from https://doi.org/10.1016/j.drugalcdep.2013.02.018.

Voigt, K., Gottschall, M., Köberlein-Neu, J., Schübel, J., Quint, N., & Bergmann, A. (2016). Why do family doctors prescribe potentially inappropriate medication to elderly patients? *BMC Family Practice*, *17*(1), 1–11. Available from https://doi.org/10.1186/s12875-016-0482-3.

Volkow, N. D., & McLellan, A. T. (2016). Opioid abuse in chronic pain—Misconceptions and mitigation strategies. *New England Journal of Medicine*, *374*(13), 1253–1263. Available from https://doi.org/10.1056/nejmra1507771.

Wang, Y. P., & Andrade, L. H. (2013). Epidemiology of alcohol and drug use in the elderly. *Current Opinion in Psychiatry*, *26*(4), 343–348. Available from https://doi.org/10.1097/YCO.0b013e328360eafd.

Wilson, G. B., Kaner, E. F. S., Crosland, A., Ling, J., McCabe, K., & Haighton, C. A. (2013). A qualitative study of alcohol, health and identities among UK adults in later life. *PLoS One*, *8*(8). Available from https://doi.org/10.1371/journal.pone.0071792.

Woods, A. J., Porges, E. C., Bryant, V. E., Seider, T., Gongvatana, A., Kahler, C. W., … Cohen, R. A. (2016). Current heavy alcohol consumption is associated with greater cognitive impairment in older adults. *Alcoholism: Clinical and Experimental Research*, *40*(11), 2435−2444. Available from https://doi.org/10.1111/acer.13211.

Wu, L.-T., & Blazer, D. G. (2011). Illicit and nonmedical drug use among older adults: A review. *Journal of Aging and Health*, *23*(3), 481−504. Available from https://doi.org/10.1177/0898264310386224.

Zhao, J., Stockwell, T., Roemer, A., Naimi, T., & Chikritzhs, T. (2017). Alcohol consumption and mortality from coronary heart disease: An updated meta-analysis of cohort studies. *Journal of Studies on Alcohol and Drugs*, *78*(3), 375−386. Available from https://doi.org/10.15288/jsad.2017.78.375.

Chapter 16

Sleep disorders and aging

Logan Schneider[1], Rosy Karna[2], Makoto Kawai[1,2,3] and Kai Parker-Fong[2]

[1]Stanford/VA Alzheimer's Research Center, Palo Alto VA Health Care System, Palo Alto, CA, United States, [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [3]Stanford Center for Sleep Sciences and Medicine, Redwood City, CA, United States

Quantifying sleep

The body exists in three major neurocognitive states: wake, nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. While the coordination of these various states requires an intricate synchronization of multiple monoaminergic, cholinergic, and GABAergic systems, this alone is not sufficient for regulating the sleep-wake state (Schneider, 2017). Input from multiple other physiologic systems (metabolic, environmental, behavioral, and the like) is integrated via the central circadian pacemaker in order to adapt sleep-wake physiology to organismal needs. In humans, biopsychosocial influences can have a dramatic impact on our "hard-wired" sleep physiology, and the less robust neurocircuitry in late life is more susceptible to disruption. As a result, objective study of sleep is often necessary. Toward this end, sleep is often studied in an artificial environment using polysomnography (PSG), a diagnostic modality that monitors multiple physiologic signals (from brain electrical activity to cardiopulmonary function to leg movements). In many instances, this robust data source is impractical, and alternative strategies seeking a more naturalistic (albeit less accurate) approximation of sleep over time are employed. As such, long-term activity/inactivity monitors (actigraphs) are a valid marker of entrained PSG sleep phase and correlate strongly with entrained endogenous circadian phase (Ancoli-Israel et al., 2003), thereby trading off physiologic detail for a more general picture of day-to-day sleep-wake biorhythms. Both modalities have been used to study sleep across the life span, providing different insights into physiologic changes that accompany healthy aging and disease. Nonetheless, the mainstay of the sleep evaluation relies upon a thorough, sleep-focused history and physical examination, often aided by referral to a sleep specialist who can assist in the decision to pursue further diagnostic testing and its interpretation.

Normal sleep with aging

Several changes occur in sleep with aging. Most of these changes are considered part of the normal aging process. It is well known that sleep in older adults, compared to younger adults, has more nocturnal awakenings and decreased efficiency (i.e., less time in bed spent sleeping), whereas there is an increase in daytime napping (Bliwise, 1993; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Additionally, polysomnographic studies have shown that the proportion of N1 (previously stage 1) increases and N3 (previously stages 3 and 4) decreases with age (Fig. 16.1) (Ohayon et al., 2004). Sleep-wake neurocircuitry has demonstrated a number of changes associated with the normal aging process (Farajnia, Deboer, Rohling, Meijer, & Michel, 2014). Reductions in noradrenergic tone, due to declines in locus coeruleus neuronal counts and projections to the prefrontal cortex, result in diminished monoamine-mediated wakefulness (Manaye, McIntire, Mann, & German, 1995; Mather & Harley, 2016). Other sleep-wake neuronal populations have also demonstrated decreased axonal density, including the cholinergic projections from the nucleus of Meynert and the sleep-wake-stabilizing hypocretinergic (orexinergic) neurons located in the lateral hypothalamus (Brownell & Conti, 2010; Nyakas, Granic, Halmy, Banerjee, & Luiten, 2011; Schneider, 2017). Additionally, there are demonstrable reductions in neuronal populations located in the master circadian pacemaker, the suprachiasmatic nucleus (SCN) (Palomba et al., 2008).

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00016-8

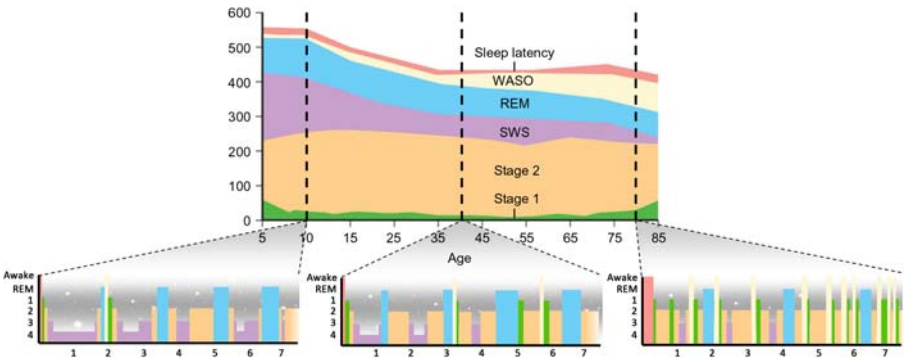


FIGURE 16.1 Sleep changes over the life span. Age-related trends for stage 1 sleep, stage 2 sleep, slow-wave sleep (SWS; stages 3 and 4), rapid eye movement (REM) sleep, wake after sleep onset (WASO), and sleep latency (in minutes) and accompanying examples of hypnograms from three major life epochs.

Circadian changes that accompany normal aging include a shortened natural free-running period (intrinsic biorhythm in the absence of environmental cues), decreased amplitude (difference between peak and minimum activity periods) (Kripke et al., 2005), fragmented rhythms (impingement of more activity into inactive periods and vice versa) (Buysse, Monk, Carrier, & Begley, 2005; Czeisler et al., 1992; Duffy et al., 2002; Luik, Zuurbier, Hofman, Van Someren, & Tiemeier, 2013; Sakurai & Sasaki, 1998; Weitzman, Moline, Czeisler, & Zimmerman, 1982; Yoon et al., 2003), a tendency toward internal desynchronization (Carrier, Monk, Buysse, & Kupfer, 1996; Hofman & Swaab, 2006; Münch, Cajochen, & Wirz-Justice, 2005), and reduced responsiveness to phase-resetting signals, including light and medications used for sleep (Hofman & Swaab, 2006). It is also noted that circadian rhythm, measured with core body temperature, shows phase advance (i.e., earlier sleep-wake periodicity) accompanying the decreased amplitude in older adults (Ancoli-Israel & Ayalon, 2006; Reynolds et al., 1991). However, there appears to be more day-to-day consistency in sleep-wake patterns, despite the diminished strength of the circadian rhythmicity (Musiek et al., 2018). Nearly an hour of phase advance has been demonstrated in the physiologic rhythms of melatonin and cortisol secretion (Tranah et al., 2011). The consequence of reduced circadian amplitude is less consistent periods of sleeping/waking across the 24-hour day, with resultant increased nighttime and decreased daytime activity. Such disruptions of the circadian clock have been linked to neuroinflammation, oxidative stress, and neuronal damage in rodents (Karatsoreos, Bhagat, Bloss, Morrison, & McEwen, 2011; Musiek et al., 2013). The breakdown of the circadian rhythm may be, in part, due to age-related deterioration of the SCN—the location of the body's master clock housed in the hypothalamus (Farajnia et al., 2014). Building upon this, age-related changes in clock gene expression patterns and neurochemical changes in the SCN have been noted in animal models (Hofman & Swaab, 1994, 2006; Kolker et al., 2003; Wyse & Coogan, 2010).

Those individuals with stronger circadian rhythms (reflected in more daytime activity than nighttime activity) report better quality of life (Mormont et al., 2000; Mormont & Waterhouse, 2002). Therefore, while circadian changes are common in old age, dysfunctional circadian rhythmicity may serve as a biomarker of disease. Disturbances in sleep and circadian rhythms are common in neurodegenerative diseases such as Alzheimer's disease, dementia, and Lewy body disease (David et al., 2010; Grace, Walker, & McKeith, 2000; Loewenstein et al., 1982; Neikrug & Ancoli-Israel, 2010). Circadian disturbances are even seen in individuals with mild cognitive impairment (MCI) (Vitiello & Prinz, 1989) and have been suggested to indicate higher risk of developing Alzheimer's disease (Lim, Kowgier, Yu, Buchman, & Bennett, 2013; Tranah et al., 2011). When comparing older individuals with the most robust circadian rhythms to those without strong rhythms, there was an approximately 50% higher likelihood of developing MCI or dementia over about 5 years (Tranah et al., 2011). Among individuals with dementia, circadian dysfunction is a major cause for institutionalization (Bianchetti et al., 1995) and has been shown to predict shorter survival (Gehrman et al., 2004). Circadian rhythm disturbances have also been observed in a variety of mood disorders, from unipolar depression to bipolar depression to seasonal affective disorder (Lamont, Legault-Coutu, Cermakian, & Boivin, 2007; Linkowski et al., 1985). Findings from a number of late-life cohorts (the Rotterdam Study cohort and the Study of Osteoporotic Fractures cohort) have suggested a higher risk of depression in individuals with less stable and more fragmented activity rhythms (Luik et al., 2013; Maglione et al., 2014). Supporting the notion that circadian dysfunction is a core component of late-life depression, several studies have suggested that chronobiologic bright light therapy may be an effective treatment for depression in older adults (Lieverse et al., 2011; Loving, Kripke, Elliott, Knickerbocker, & Grandner, 2005). Finally, alterations in late-life circadian rhythms have also been associated with increased cardiovascular disease (Paudel et al., 2011) and mortality (Paudel et al., 2010; Tranah et al., 2010).

Sleep disturbance and comorbidities

Medical and psychiatric comorbidities are very common in older adults; more than 83% of older adults have at least one medical condition (Foley, Ancoli-Israel, Britz, & Walsh, 2004). Approximately two-thirds of individuals with a major medical condition reported sleep problems, whereas only about one-third of the individuals with multiple medical conditions reported sleep problems (Fig. 16.2) (Foley et al., 2004). Many domains of disease impact sleep quality from chronic pain to genitourinary and gastrointestinal conditions to cardiopulmonary disease. However, it is not just the medical conditions themselves that increase the likelihood of a sleep disturbance, it is also factors related to anatomic and physiologic changes related to medical disorders, environmental influence and changes associated with medical disorders, and treatments of medical disorders that may compound age-dependent sleep change for the worse (Martin, Sforza, Barthélémy, Thomas-Anterion, & Roche, 2014). Even just the limitations on physical activity caused by a number of medical conditions can independently increase the risk of insomnia in older patients (Morgan & Clarke, 1997). Consequently, increased sleep disturbances and poorer quality sleep in older adults may exacerbate existing conditions, worsening prognosis, and are associated with an increased risk of falls, decline in cognition, occurrence of depression and anxiety, and increased mortality (Barczi & Teodorescu, 2017). As such, the bidirectional interplay between sleep health and physical health was demonstrated in a community-based study of over 1200 elderly individuals, in which it was found that the number of physical disorders was associated with the prevalence, incidence, and persistence of insomnia, and that insomnia was associated with increased reporting of physical disorders and diagnoses of depression (Kim et al., 2009). The long-term health consequences of poor sleep were highlighted in a longitudinal study conducted among 185 healthy older adults that showed that decreased sleep efficiency (less than 80%) nearly double the risk of mortality over a 19-year period of follow-up (Dew et al., 2003). Additionally, in a cohort of middle-aged and older adults, not getting a normal amount of nightly sleep (7−8 hours) conferred increased risk of mortality over an average follow-up of 10.8 years (Aurora, Kim, Crainiceanu, O'Hearn, & Punjabi, 2016). In light of the complex interactions between disrupted sleep and overall health, holistic, biopsychosocial strategies targeting the underlying illness and environment and medication optimization or elimination, coupled with behavioral sleep medicine programs and the judicious application of sleep aids are likely needed.

Sleep disturbance and cognition

There is accumulating evidence that sleep quality is closely associated with cognition in older adults. A study based on sleep quality questionnaires showed a correlation of sleep and cognition (Nebes, Buysse, Halligan, Houck, & Monk, 2009; Potvin et al., 2012; Yaffe, Falvey, & Hoang, 2014). Self-reported or actigraphy-measured shorter sleep duration is reportedly associated with worse cognition in older adults (Blackwell et al., 2011b; Potvin et al., 2012; Yaffe et al., 2014). Based upon the body of extant data, there is consensus that ideal sleep duration for older adults is around 7−8 hours (Hirshkowitz et al., 2015). Similar to associations with mortality, it is interesting to note that either excessive or insufficient nightly sleep duration is associated with poorer cognition (Yaffe et al., 2014). It is speculated that the cognitive impairment in shorter sleep duration is due to the cumulative effect from chronic sleep deprivation. However, it remains unclear why longer sleep duration consistently shows association with poorer cognition (Blackwell et al., 2011b; Potvin et al., 2012; Yaffe et al., 2014). Possible explanations include: (1) the involvement of populations with

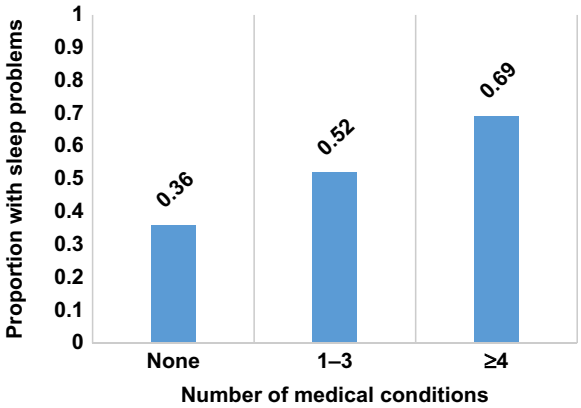


FIGURE 16.2 Prevalence of sleep disorder changes with number of comorbidities. Prevalence of at least one sleep problem, stratified by number of medical conditions (Foley et al., 2004).

subclinical, undiagnosed, and/or untreated sleep disorders; (2) the involvement of populations with other medical conditions affecting both cognition and sleep duration; or (3) the effect of neurodegeneration on arousal circuitry. Nonetheless, the likely explanation in most cases is that excessive sleep is the consequence of some underlying process that also affects cognition, rather than sleep playing some causative role in the cognitive impairment.

Comparatively, it is much clearer that sleep architecture is associated with cognition, including executive or memory functions in younger adults (Aricò et al., 2010; Ferrarelli et al., 2019). In older adults, among several parameters of sleep architecture, longer REM sleep shows more consistent correlation with better cognition (Scullin & Bliwise, 2015; Song et al., 2015). Even though slow-wave sleep (SWS) plays a clear role in sleep-dependent memory consolidation in rats and younger adults (Peigneux et al., 2004; Wilson & McNaughton, 1994), the association of SWS with cognition in older adults has been inconsistent (Scullin, 2013; Scullin & Bliwise, 2015; Song et al., 2015). Mander et al. found a reduction in slow-wave activity [as measured by objective quantification of electroencephalographic (EEG) signals], instead of human-scored SWS itself, to be associated with poorer declarative memory and less overnight retention in older adults compared to younger subjects (Mander et al., 2013), which is in line with the physiologic associations between neurodegenerative biomarkers and low-frequency EEG activity (Holth et al., 2019). While the prevailing hypothesis points to poor quality sleep causing an accumulation of β-amyloid, promulgating a neurotoxicity that culminates in neurodegeneration mediated by phosphorylated tau aggregation, there remains much controversy about the exact pathophysiologic mechanisms and, potentially, the direction of causality (Van Egroo et al., 2019).

Insomnia in late life

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), chronic insomnia is a subjective complaint of difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings that are persistent for a minimum of three nights per week, for at least 3 months (Rodriguez, Dzierzewski, & Alessi, 2015; Suzuki, Miyamoto, & Hirata, 2017). Comparatively, the latest revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) adds dissatisfaction with sleep quality and/or quantity and nonrestorative or poor sleep to the diagnostic criteria (American Psychiatric Association, 2013). Changes in lifestyle, such as working late and evening tech exposure (computers, laptops, phones, and television), have contributed to increased sleep disturbances in individuals, particularly older adults. In fact, the most commonly reported sleep problem in older adults is insomnia, with increased prevalence in older and female populations (Grandner et al., 2012; Ohayon, 2002; Phillips & Mannino, 2005; Uhlig, Sand, Ødegård, & Hagen, 2014; Zhang et al., 2013) and an annual incidence of 5%−8% in older adults (Suzuki et al., 2017). Greater than 50% of individuals over 65 reported at least one sleep complaint, with up to 40% reporting chronic difficulty with initiation and/or maintenance of sleep, in a representative sample of over 9000 individuals from the Established Populations of Epidemiological Studies of the Elderly (Foley et al., 1995). However, despite similar prevalence of insomnia issues (69% with at least one sleep problem, 40% with two or more sleep problems, and 45% experiencing symptoms of insomnia) in a study of older adults in US primary care practices, concerns related to insomnia were recorded in the medical charts only 19% of the time (Reid et al., 2006). In order to reduce the economic and social burden on older adults caused by insomnia, it is crucial to examine sleep quality in older adults during routine clinical visits.

Insomnia often coexists with other chronic medical and/or psychiatric conditions such as depression, chronic pain, chronic obstructive pulmonary disease, and stroke and is higher among older women than among older men (Rodriguez et al., 2015). However, a host of factors contribute to late-life insomnia. Notably, age-related physiologic changes in homeostatic and circadian sleep-wake regulation as well as primary sleep disorders, low physical activity (Morgan & Clarke, 1997), and poor physical and mental health (Reid et al., 2006). Moreover, a host of medications and substances (specifically alcohol, caffeine, and nicotine) have adverse effects on sleep (Table 16.1). Persistent insomnia also results in decreased quality of life, risk of falls, psychological and physical difficulties, economic and social costs, and mortality (Rodriguez et al., 2015). In longitudinal studies, symptoms of insomnia, daytime sleepiness, and sleep medication use have been associated with increased incidence of depression and risk of suicidal ideation (Jaussent et al., 2011; Suh et al., 2013, 2014). Similar associations were found between poor quality sleep (sleep efficiency $<70\%$, prolonged sleep latency, and increased wake time after sleep onset on actigraphic monitoring) and cognitive declined in a large cohort (~ 3000) of women over age 70 (Blackwell et al., 2006). Finally, in another cohort, there was nearly double the risk of mortality over 5 years in individuals with sleep efficiency below 80% or sleep onset latencies longer than 30 minutes (Dew et al., 2003).

The mainstay of therapy for insomnia includes a host of validated psychological and behavioral interventions, often packaged as a cognitive-behavioral therapy for insomnia (CBTi) program (Morgenthaler et al., 2006). These programs

TABLE 16.1 Classes of medications associated with disturbances of sleep and wake.

Classes of medications associated with drowsiness
Antiadrenergics (α and β)
Anticonvulsants
Anticholinergics (antidiarrheal agents, antiemetics, genitourinary antispasmodics)
Antihistamines (particularly first generation)
Antitussives
Barbiturates
Benzodiazepines
Narcotics
Antiparkinsonian agents (e.g., dopamine agonists)
Psychiatric medications: antidepressants (certain MAOIs, certain TCAs, SSRIs) and most antipsychotics
Skeletal muscle relaxants and antispasmodics
Classes of medications associated with insomnia
Acetylcholinesterase inhibitors
COMT inhibitors
Corticosteroids
Nicotinic receptor agonists
Antiparkinsonian agents (e.g., dopamine agonists)
Psychiatric medications (SSRIs, SNRIs, certain TCAs, DNRIs)
Stimulants (amphetamine salts and amphetaminoids)

Notes: Multiple medications influence the sleep-wake and circadian systems; the most common categories of medications that are known to cause excessive daytime sleepiness or insomnia are listed in the table. *COMT*, catechol-O-methyltransferase; *DNRIs*, dopamine–norepinephrine reuptake inhibitors; *MAOIs*, monoamine oxidase inhibitors; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic antidepressants.

have proven efficacy in older adults with primary or comorbid insomnia, as well as in individuals with sedative/hypnotic dependence (Karlin, Trockel, Spira, Taylor, & Manber, 2015). The sleep improvements—including reduced nocturnal wake time accompanying significantly improved sleep efficiency and SWS—of CBTi programs have been demonstrated to be superior to standard sedative/hypnotics (Sivertsen et al., 2006), with prolonged benefits only being noted in individuals administered CBTi (instead of a sedative/hypnotic) (Morin, Colecchi, Stone, Sood, & Brink, 1999). Despite the facts that CBTi is the first-line treatment for chronic insomnia, sedatives/hypnotics are noted to have lower efficacy in older adults, and sedative/hypnotic medications have prominent side effects in older populations, such as daytime sleepiness, impaired cognitive performance, and increased risk of falls, prescription of medications for sleep is at their highest and most chronic in older adults (Glass, Lanctôt, Herrmann, Sproule, & Busto, 2005; Huedo-Medina, Kirsch, Middlemass, Klonizakis, & Siriwardena, 2012). Moreover, alternative medications that are frequently used off-label (antidepressants, antihistamines, or antipsychotics) and over-the-counter supplements with little proven benefit are still considered to have risks that outweigh benefits as treatments primarily for insomnia (National Institutes of Health, 2005).

Excessive daytime sleepiness in late life

Excessive daytime sleepiness (EDS) is also a common complaint in older adults affecting about 20%–30% of the population (Slater & Steier, 2012; Young, Skatrud, & Peppard, 2004). EDS is characterized by the inability to stay awake and alert during the major waking episode (typically daytime), resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep (American Academy of Sleep Medicine, 2014). In a sample of individuals from the general population who reported having EDS, the most likely causes of sleepiness were depression, obesity, age, typical sleep duration, diabetes, and smoking (Bixler et al., 2005). Furthermore, many categories of medications (Table 16.1) (Gonçalves & Togeiro, 2013) are implicated in the etiology of EDS, with nearly 600 medications listed as causing drowsiness as a side effect in the *Physicians' Desk Reference* (Pagel, 2005). In addition to the increasing number of medical conditions and medications, the prevalence of primary sleep disorders also increases with age, thereby increasing the likelihood of EDS caused by insufficient sleep quantity or quality (Ohayon, O'Hara, & Vitiello, 2012; Punjabi, 2008; Roth, 2007). However, even in normal aging, one possible explanation for worsening of EDS in older adults is increased difficulty in staying in one brain state of wake or sleep, potentially sharing pathophysiology with the substantially increased wake after sleep onset that is associated with aging, as is exemplified by the more fragmented

circadian rhythmicity. As such, longitudinal studies in the United States, United Kingdom, and France have all demonstrated an increased risk of global cognitive decline in individuals who reported EDS (but not insomnia), despite being cognitively unimpaired at baseline (Foley et al., 2001; Jaussent et al., 2012; Keage et al., 2012). In fact, in otherwise healthy older individuals, those who self-reported EDS and fatigue were found to have hippocampal volume reductions and more global and regional atrophy through MRI brain volumetric assessments (Carvalho et al., 2017). Additionally, hypersomnia [reflected by sleep durations in excess of those recommended for older adults (Hirshkowitz et al., 2015)] was associated with higher rates of frontotemporal gray matter decline over an 8-year follow-up in cognitively normal older adults (Spira et al., 2016). These findings underscore the importance of assessing for and evaluating EDS in older adults.

For measuring EDS, there are two main strategies: (1) self-reporting questionnaires and (2) objective measurements. Some self-report questionnaires include those that provide a snapshot of sleepiness over a time period, such as the Epworth Sleepiness Scale (Johns, 1991), and those that focus on the current level of sleepiness, such as the Stanford Sleepiness Scale (MacLean, Fekken, Saskin, & Knowles, 1992) or the Karolinska Sleepiness Scale (Miley, Kecklund, & Åkerstedt, 2016). The advantages of these questionnaires include low-cost, ease of administration, and extensive study with normative data. The limitation of self-report questionnaires is that the response depends on the insight into the presence of the symptoms, which individuals are notoriously bad at (Van Dongen, Maislin, Mullington, & Dinges, 2003) doing, and which can be influenced by lifestyle, cultural background (especially method of transportation or nap), and a host of other factors. Comparatively, the multiple sleep latency test provides an objective measure of an individual's propensity for falling asleep, which is more appropriately termed somnolence. It is considered the gold standard for quantifying EDS; however, the test is quite expensive and requires trained technicians and a sleep laboratory for administration. As an alternative measure of hypersomnias (disorders of excessive sleep) that may result in EDS, actigraphs provide a middle ground. While these wrist-worn activity monitors are not as easy to administer as surveys, the relatively low cost of objective quantification of sleep durations and patterns can be useful in elucidating sleep-wake features that may be contributing to EDS (Smith et al., 2018). Moreover, clinical actigraphy is a valid marker of entrained PSG sleep phase and provides meaningful day-over-day information regarding entrained circadian rhythms (Ancoli-Israel et al., 2003).

Sleep-disordered breathing in late life

Sleep-disordered breathing (SDB) is common in older adults. The incidence of SDB ranges from 9% to 60%, depending on the target population, definition of age limit for "older adults," and definition of SDB (Ancoli-Israel et al., 1991; Peppard et al., 2013). However, regardless of the cutoff, there is evidence from population-based studies that the prevalence of obstructive sleep apnea (OSA) generally increases with age (Fig. 16.3) (Bliwise et al., 1987; Tufik, Santos-Silva, Taddei, & Bittencourt, 2010; Young, Peppard, & Gottlieb, 2002). Some population-based studies suggest that at least 1/3 of adults over 65 years of age have an apnea-hypopnea index (AHI) above the normal level of fewer than five breathing disturbances per hour of sleep (Ancoli-Israel et al., 1991; Phillips et al., 1992). And in adult populations over age 50, gender tends to play less of a role as a risk factor for obstructive sleep apnea, a phenomenon explained predominantly by the spike in incidence of female obstructive sleep apnea following menopause (Bixler et al., 2001; Dancey,

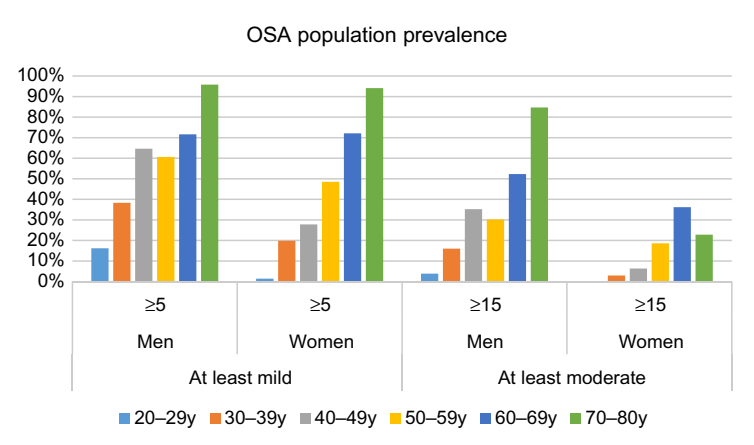


FIGURE 16.3 Epidemiologic data from the São Paulo epidemiologic study. The prevalence of at least mild (AHI ≥ 5) and at least moderate (AHI ≥ 15) obstructive sleep apnea stratified by gender and decade of life in a representative sample of 1042 São Paulo inhabitants. *AHI*, apnea-hypopnea index (Tufik et al., 2010).

Hanly, Soong, Lee, & Hoffstein, 2001; Tishler, Larkin, Schluchter, & Redline, 2003; Young, Finn, Austin, & Peterson, 2003). Another factor that substantially decreases its contribution to OSA risk with advancing age is obesity (Bixler et al., 2001; Tishler et al., 2003), likely resulting in other phenotypic contributions (such as upper airway muscle laxity, arousal threshold, airway patency reflexes, and the like) playing a larger role in airway collapse (Eckert, 2018). Also, the manifestations of SDB appear to differ among older adults, with EDS giving way to sleep quality complaints (Phillips, 2015), increased frequency of nocturic episodes (Fitzgerald, Mulligan, & Parthasarathy, 2006; Kaynak, Kaynak, & Oztura, 2004), and neurocognitive dysfunction, including impaired executive function (Naëgelé et al., 1995), working memory (Thomas, Rosen, Stern, Weiss, & Kwong, 2005), alertness (Mazza et al., 2005), and attention (Verstraeten & Cluydts, 2004).

Of particular concern among our graying population is the accumulating data demonstrating that untreated SDB is associated with higher risk of dementia (Yaffe et al., 2011). One study reported the association of more respiratory disturbances per hour of sleep with worse cognition (Cohen-Zion et al., 2004). While impairments in vigilant attention, alertness, and, to some extent, memory appear to be impacted by the sleep disruptions resulting from OSA, the strongest association between general intellectual and executive functions and OSA appears to be mediated by hypoxemia (Sateia, 2003). Toward this end, a number of studies have reported on the association between more severe oxyhemoglobin desaturation and worse cognition, but not with AHI (Aloia et al., 2003; Blackwell et al., 2011a). While a few studies have demonstrated correction of neurocognitive impairments with optimal adherence to the gold-standard treatment modality, positive airway pressure therapy (Aloia et al., 2003; Weaver & Chasens, 2007), other studies have not demonstrated significant improvements (Quan et al., 2011). Nonetheless, the association between SDB parameters, including AHI or oxygen saturation level, and the risk of developing dementia is not straightforward. Further study is necessary to stratify medical resources to provide appropriate treatment for older patients with SDB. Moreover, despite the lack of strong effects of treatment on neurocognitive outcomes (likely attributable to heterogeneity in clinical populations and in their adherence to therapy), SDB has clear bidirectional links to hypertension (pulmonary and systemic), cardiovascular disease, heart failure, arrhythmias, heart attack, and stroke (Somers et al., 2008). Thus the evaluation for and treatment of such a highly prevalent disorder is of utmost importance in preserving the health of older individuals.

Summary and future directions

Sleep changes are expected to occur with advancing age: advanced circadian phase with diminished amplitude caused by increased sleep fragmentation and decreased daytime activity, due, in part, to loss of neuronal density in the brain structures necessary for regulating sleep-wake and circadian rhythms. Accompanying these natural changes in sleep-wake architecture is an increased burden of sleep disorders such as SDB. Even though some of the sleep changes are considered as a part of normal aging, the increased frequency of sleep disorders is most certainly pathologic, necessitating better clinical recognition, diagnostic pathways, and therapies that account for physiologic changes in late life. Moreover, understanding the delicate interplay between sleep disorders and comorbid medical conditions is essential, given the concomitant increase in major medical disorders, many of which impact sleep either directly or as a consequence of their treatment. In addition, the association between cognition and sleep has been actively investigated in recent years because cognition is one of the most important outcome measures for older adults, particularly in light of the projected burden of Alzheimer's disease in the United States alone (Hebert, Weuve, Scherr, & Evans, 2013). While there is abundant evidence in support of the fact that poor quality or quantity of sleep affects cognitive function in all ages, including executive function, attention, and vigilance, whether addressing our current sleep insufficiency epidemic can attenuate long-term cognitive decline, mainly because the pathophysiology is still largely unknown. Ultimately, finding sensitive sleep biomarkers will aid in the early identification of sleep disorders while also providing effective means to monitor the impact of healthy and disordered sleep on late-life well-being.

References

Aloia, M. S., Ilniczky, N., Di Dio, P., Perlis, M. L., Greenblatt, D. W., & Giles, D. E. (2003). Neuropsychological changes and treatment compliance in older adults with sleep apnea. *Journal of Psychosomatic Research*, *54*, 71–76.

American Academy of Sleep Medicine. (2014). *International classification of sleep disorders* (3rd ed.). Darien: American Academy of Sleep Medicine.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)* (5th ed.). American Psychiatric Publishing.

Ancoli-Israel, S., & Ayalon, L. (2006). Diagnosis and treatment of sleep disorders in older adults. *The American Journal of Geriatric Psychiatry*, *14*, 95–103.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*, *26*, 342–392.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R., & Kaplan, O. (1991). Sleep-disordered breathing in community-dwelling elderly. *Sleep*, *14*, 486–495.

Aricò, D., Drago, V., Foster, P. S., Heilman, K. M., Williamson, J., & Ferri, R. (2010). Effects of NREM sleep instability on cognitive processing. *Sleep Medicine*, *11*, 791–798.

Aurora, R. N., Kim, J. S., Crainiceanu, C., O'Hearn, D., & Punjabi, N. M. (2016). Habitual sleep duration and all-cause mortality in a general community sample. *Sleep*, *39*, 1903–1909.

Barczi, S. R., & Teodorescu, M. C. (2017). Psychiatric and medical comorbidities and effects of medications in older adults. In M. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (6th ed.). Philadelphia: Elsevier, 1484.e6–1495.e6.

Bianchetti, A., Scuratti, A., Zanetti, O., et al. (1995). Predictors of mortality and institutionalization in Alzheimer disease patients 1 year after discharge from an Alzheimer dementia unit. *Dementia*, *6*, 108–112.

Bixler, E. O., Vgontzas, A. N., Lin, H.-M., et al. (2001). Prevalence of sleep-disordered breathing in women. *American Journal of Respiratory and Critical Care Medicine*, *163*, 608–613.

Bixler, E. O., Vgontzas, A. N., Lin, H.-M., Calhoun, S. L., Vela-Bueno, A., & Kales, A. (2005). Excessive daytime sleepiness in a general population sample: The role of sleep apnea, age, obesity, diabetes, and depression. *The Journal of Clinical Endocrinology and Metabolism*, *90*, 4510–4515.

Blackwell, T., Yaffe, K., Ancoli-Israel, S., et al. (2006). Poor sleep is associated with impaired cognitive function in older women: The study of osteoporotic fractures. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*, 405–410.

Blackwell, T., Yaffe, K., Ancoli-Israel, S., et al. (2011a). Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: The Osteoporotic Fractures in Men Sleep Study. *Journal of the American Geriatrics Society*, *59*, 2217–2225.

Blackwell, T., Yaffe, K., Ancoli-Israel, S., et al. (2011b). Association of sleep characteristics and cognition in older community-dwelling men: The MrOS Sleep Study. *Sleep*, *34*, 1347–1356.

Bliwise, D. L. (1993). Sleep in normal aging and dementia. *Sleep*, *16*, 40–81.

Bliwise, D. L., Feldman, D. E., Bliwise, N. G., et al. (1987). Risk factors for sleep disordered breathing in heterogeneous geriatric populations. *Journal of the American Geriatrics Society*, *35*, 132–141.

Brownell, S. E., & Conti, B. (2010). Age- and gender-specific changes of hypocretin immunopositive neurons in C57Bl/6 mice. *Neuroscience Letters*, *472*, 29–32.

Buysse, D. J., Monk, T. H., Carrier, J., & Begley, A. (2005). Circadian patterns of sleep, sleepiness, and performance in older and younger adults. *Sleep*, *28*, 1365–1376.

Carrier, J., Monk, T. H., Buysse, D. J., & Kupfer, D. J. (1996). Amplitude reduction of the circadian temperature and sleep rhythms in the elderly. *Chronobiology International*, *13*, 373–386.

Carvalho, D. Z., St. Louis, E. K., Boeve, B. F., et al. (2017). Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. *Sleep Medicine*, *32*, 236–243.

Cohen-Zion, M., Stepnowsky, C., Johnson, S., Marler, M., Dimsdale, J. E., & Ancoli-Israel, S. (2004). Cognitive changes and sleep disordered breathing in elderly: Differences in race. *Journal of Psychosomatic Research*, *56*, 549–553.

Czeisler, C. A., Dumont, M., Duffy, J. F., et al. (1992). Association of sleep-wake habits in older people with changes in output of circadian pacemaker. *Lancet (London, England)*, *340*, 933–936.

Dancey, D. R., Hanly, P. J., Soong, C., Lee, B., & Hoffstein, V. (2001). Impact of menopause on the prevalence and severity of sleep apnea. *Chest*, *120*, 151–155.

David, R., Zeitzer, J., Friedman, L., et al. (2010). Non-pharmacologic management of sleep disturbance in Alzheimer's disease. *The Journal of Nutrition, Health & Aging*, *14*, 203–206.

Dew, M. A., Hoch, C. C., Buysse, D. J., et al. (2003). Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosomatic Medicine*, *65*, 63–73.

Duffy, J. F., Zeitzer, J. M., Rimmer, D. W., Klerman, E. B., Dijk, D.-J., & Czeisler, C. A. (2002). Peak of circadian melatonin rhythm occurs later within the sleep of older subjects. *American Journal of Physiology-Endocrinology and Metabolism*, *282*, E297–E303.

Eckert, D. J. (2018). Phenotypic approaches to obstructive sleep apnoea—New pathways for targeted therapy. *Sleep Medicine Reviews*, *37*, 45–59.

Farajnia, S., Deboer, T., Rohling, J. H. T., Meijer, J. H., & Michel, S. (2014). Aging of the suprachiasmatic clock. *Neuroscientist*, *20*, 44–55.

Ferrarelli, F., Kaskie, R., Laxminarayan, S., Ramakrishnan, S., Reifman, J., & Germain, A. (2019). An increase in sleep slow waves predicts better working memory performance in healthy individuals. *NeuroImage*, *191*, 1–9.

Fitzgerald, M. P., Mulligan, M., & Parthasarathy, S. (2006). Nocturic frequency is related to severity of obstructive sleep apnea, improves with continuous positive airways treatment. *American Journal of Obstetrics and Gynecology*, *194*, 1399–1403.

Foley, D., Ancoli-Israel, S., Britz, P., & Walsh, J. (2004). Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey. *Journal of Psychosomatic Research*, *56*, 497–502.

Foley, D., Monjan, A., Masaki, K., et al. (2001). Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *Journal of the American Geriatrics Society*, *49*, 1628–1632.

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*, *18*, 425–432.

Gehrman, P., Marler, M., Martin, J. L., Shochat, T., Corey-Bloom, J., & Ancoli-Israel, S. (2004). The timing of activity rhythms in patients with dementia is related to survival. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*, 1050–1055.

Glass, J., Lanctôt, K. L., Herrmann, N., Sproule, B. A., & Busto, U. E. (2005). Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits. *British Medical Journal*, *331*, 1169.

Gonçalves, R., & Togeiro, S. (2013). Drug-induced sleepiness and insomnia: An update. *Sleep Science*, *6*, 36–43.

Grace, J. B., Walker, M. P., & McKeith, I. G. (2000). A comparison of sleep profiles in patients with dementia with Lewy bodies and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *15*, 1028–1033.

Grandner, M. A., Martin, J. L., Patel, N. P., et al. (2012). Age and sleep disturbances among American men and women: Data from the U.S. Behavioral Risk Factor Surveillance System. *Sleep*, *35*, 395–406.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology.*, *80*, 1778–1783.

Hirshkowitz, M., Whiton, K., Albert, S. M., et al. (2015). National Sleep Foundation's sleep time duration recommendations: Methodology and results summary. *Sleep Health*, *1*, 40–43.

Hofman, M., & Swaab, D. F. (2006). Living by the clock: The circadian pacemaker in older people. *Ageing Research Reviews*, *5*, 33–51.

Hofman, M. A., & Swaab, D. F. (1994). Alterations in circadian rhythmicity of the vasopressin-producing neurons of the human suprachiasmatic nucleus (SCN) with aging. *Brain Research*, *651*, 134–142.

Holth, J. K., Fritschi, S. K., Wang, C., et al. (2019). The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science*, *363*, 880–884.

Huedo-Medina, T. B., Kirsch, I., Middlemass, J., Klonizakis, M., & Siriwardena, A. N. (2012). Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: Meta-analysis of data submitted to the Food and Drug Administration. *British Medical Journal*, *345*, e8343.

Jaussent, I., Bouyer, J., Ancelin, M.-L., et al. (2011). Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly. *Sleep*, *34*, 1103–1110.

Jaussent, I., Bouyer, J., Ancelin, M.-L., et al. (2012). Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep*, *35*, 1201–1207.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*, 540–545.

Karatsoreos, I. N., Bhagat, S., Bloss, E. B., Morrison, J. H., & McEwen, B. S. (2011). Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 1657–1662.

Karlin, B. E., Trockel, M., Spira, A. P., Taylor, C. B., & Manber, R. (2015). National evaluation of the effectiveness of cognitive behavioral therapy for insomnia among older versus younger veterans. *International Journal of Geriatric Psychiatry*, *30*, 308–315.

Kaynak, H., Kaynak, D., & Oztura, I. (2004). Does frequency of nocturnal urination reflect the severity of sleep-disordered breathing? *Journal of Sleep Research*, *13*, 173–176.

Keage, H. A. D., Banks, S., Yang, K. L., Morgan, K., Brayne, C., & Matthews, F. E. (2012). What sleep characteristics predict cognitive decline in the elderly? *Sleep Medicine*, *13*, 886–892.

Kim, J.-M., Stewart, R., Kim, S.-W., Yang, S.-J., Shin, I.-S., & Yoon, J.-S. (2009). Insomnia, depression, and physical disorders in late life: A 2-year longitudinal community study in Koreans. *Sleep*, *32*, 1221–1228.

Kolker, D. E., Fukuyama, H., Huang, D. S., Takahashi, J. S., Horton, T. H., & Turek, F. W. (2003). Aging alters circadian and light-induced expression of clock genes in golden hamsters. *Journal of Biological Rhythms*, *18*, 159–169.

Kripke, D. F., Youngstedt, S. D., Elliott, J. A., et al. (2005). Circadian phase in adults of contrasting ages. *Chronobiology International*, *22*, 695–709.

Lamont, E. W., Legault-Coutu, D., Cermakian, N., & Boivin, D. B. (2007). The role of circadian clock genes in mental disorders. *Dialogues in Clinical Neuroscience*, *9*, 333–342.

Lieverse, R., Van Someren, E. J. W., Nielen, M. M. A., Uitdehaag, B. M. J., Smit, J. H., & Hoogendijk, W. J. G. (2011). Bright light treatment in elderly patients with nonseasonal major depressive disorder. *Archives of General Psychiatry*, *68*, 61.

Lim, A. S. P., Kowgier, M., Yu, L., Buchman, A. S., & Bennett, D. A. (2013). Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*, *36*, 1027–1032.

Linkowski, P., Mendlewicz, J., Leclercq, R., et al. (1985). The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *The Journal of Clinical Endocrinology and Metabolism*, *61*, 429–438.

Loewenstein, R. J., Weingartner, H., Gillin, J. C., Kaye, W., Ebert, M., & Mendelson, W. B. (1982). Disturbances of sleep and cognitive functioning in patients with dementia. *Neurobiology of Aging*, *3*, 371–377.

Loving, R. T., Kripke, D. F., Elliott, J. A., Knickerbocker, N. C., & Grandner, M. A. (2005). Bright light treatment of depression for older adults [ISRCTN55452501]. *BMC Psychiatry*, *5*, 41.

Luik, A. I., Zuurbier, L. A., Hofman, A., Van Someren, E. J. W., & Tiemeier, H. (2013). Stability and fragmentation of the activity rhythm across the sleep-wake cycle: The importance of age, lifestyle, and mental health. *Chronobiology International*, *30*, 1223–1230.

MacLean, A. W., Fekken, G. C., Saskin, P., & Knowles, J. B. (1992). Psychometric evaluation of the Stanford Sleepiness Scale. *Journal of Sleep Research*, *1*, 35–39.

Maglione, J. E., Ancoli-Israel, S., Peters, K. W., et al. (2014). Depressive symptoms and circadian activity rhythm disturbances in community-dwelling older women. *The American Journal of Geriatric Psychiatry*, *22*, 349–361.

Manaye, K. F., McIntire, D. D., Mann, D. M. A., & German, D. C. (1995). Locus coeruleus cell loss in the aging human brain: A non-random process. *The Journal of Comparative Neurology*, *358*, 79−87.

Mander, B. A., Rao, V., Lu, B., et al. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nature Neuroscience*, *16*, 357−364.

Martin, M. S., Sforza, E., Barthélémy, J. C., Thomas-Anterion, C., & Roche, F. (2014). Sleep perception in non-insomniac healthy elderly: A 3-year longitudinal study. *Rejuvenation Research*, *17*, 11−18.

Mather, M., & Harley, C. W. (2016). The locus coeruleus: Essential for maintaining cognitive function and the aging brain. *Trends in Cognitive Sciences*, *20*, 214−226.

Mazza, S., Pépin, J.-L., Naëgelé, B., Plante, J., Deschaux, C., & Lévy, P. (2005). Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. *The European Respiratory Journal*, *25*, 75−80.

Miley, A. Å., Kecklund, G., & Åkerstedt, T. (2016). Comparing two versions of the Karolinska Sleepiness Scale (KSS). *Sleep and Biological Rhythms*, *14*, 257−260.

Morgan, K., & Clarke, D. (1997). Risk factors for late-life insomnia in a representative general practice sample. *The British Journal of General Practice*, *47*, 166−169.

Morgenthaler, T., Kramer, M., Alessi, C., et al. (2006). Practice parameters for the psychological and behavioral treatment of insomnia: An update. An American Academy of Sleep Medicine report. *Sleep*, *29*, 1415−1419.

Morin, C. M., Colecchi, C., Stone, J., Sood, R., & Brink, D. (1999). Behavioral and pharmacological therapies for late-life insomnia: A randomized controlled trial. *JAMA*, *281*, 991−999.

Mormont, M.-C., & Waterhouse, J. (2002). Contribution of the rest-activity circadian rhythm to quality of life in cancer patients. *Chronobiology International*, *19*, 313−323.

Mormont, M. C., Waterhouse, J., Bleuzen, P., et al. (2000). Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clinical Cancer Research*, *6*, 3038−3045.

Münch, M., Cajochen, C., & Wirz-Justice, A. (2005). Sleep and circadian rhythms in ageing. *Zeitschrift für Gerontologie und Geriatrie*, *38*, i21−i23.

Musiek, E. S., Bhimasani, M., Zangrilli, M. A., Morris, J. C., Holtzman, D. M., & Ju, Y. S. (2018). Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurology*, *75*, 582−590.

Musiek, E. S., Lim, M. M., Yang, G., et al. (2013). Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. *The Journal of Clinical Investigation*, *123*, 5389−5400.

Naëgelé, B., Thouvard, V., Pépin, J. L., et al. (1995). Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep*, *18*, 43−52.

National Institutes of Health. (2005). National Institutes of Health State of the Science Conference statement on manifestations and management of chronic insomnia in adults, June 13−15, 2005. *Sleep*, *28*, 1049−1057.

Nebes, R. D., Buysse, D. J., Halligan, E. M., Houck, P. R., & Monk, T. H. (2009). Self-reported sleep quality predicts poor cognitive performance in healthy older adults. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *64*, 180−187.

Neikrug, A. B., & Ancoli-Israel, S. (2010). Sleep disturbances in nursing homes. *The Journal of Nutrition, Health & Aging*, *14*, 207−211.

Nyakas, C., Granic, I., Halmy, L. G., Banerjee, P., & Luiten, P. G. M. (2011). The basal forebrain cholinergic system in aging and dementia. Rescuing cholinergic neurons from neurotoxic amyloid-β42 with memantine. *Behavioural Brain Research*, *221*, 594−603.

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*, 97−111.

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, *27*, 1255−1273.

Ohayon, M. M., O'Hara, R., & Vitiello, M. V. (2012). Epidemiology of restless legs syndrome: A synthesis of the literature. *Sleep Medicine Reviews*, *16*, 283−295.

Pagel, J. F. (2005). Medications and their effects on sleep. *Primary Care: Clinics in Office Practice*, *32*, 491−509.

Palomba, M., Nygård, M., Florenzano, F., Bertini, G., Kristensson, K., & Bentivoglio, M. (2008). Decline of the presynaptic network, including GABAergic terminals, in the aging suprachiasmatic nucleus of the mouse. *Journal of Biological Rhythms*, *23*, 220−231.

Paudel, M. L., Taylor, B. C., Ancoli-Israel, S., et al. (2010). Rest/activity rhythms and mortality rates in older men: MrOS Sleep Study. *Chronobiology International*, *27*, 363−377.

Paudel, M. L., Taylor, B. C., Ancoli-Israel, S., et al. (2011). Rest/activity rhythms and cardiovascular disease in older men. *Chronobiology International*, *28*, 258−266.

Peigneux, P., Laureys, S., Fuchs, S., et al. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron*, *44*, 535−545.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology*, *177*, 1006−1014.

Phillips, B., & Mannino, D. (2005). Correlates of sleep complaints in adults: The ARIC study. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *1*, 277−283.

Phillips, B. A. (2015). Obstructive sleep apnea in older adults. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (6th ed., pp. 1496−1502). Philadelphia: Elsevier Health Sciences.

Phillips, B. A., Berry, D. T., Schmitt, F. A., Magan, L. K., Gerhardstein, D. C., & Cook, Y. R. (1992). Sleep-disordered breathing in the healthy elderly. Clinically significant? *Chest*, *101*, 345−349.

Potvin, O., Lorrain, D., Forget, H., et al. (2012). Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. *Sleep*, *35*, 491–499.
Punjabi, N. M. (2008). The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society*, *5*, 136–143.
Quan, S. F., Chan, C. S., Dement, W. C., et al. (2011). The association between obstructive sleep apnea and neurocognitive performance—The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*, *34*, 303–314B.
Reid, K. J., Martinovich, Z., Finkel, S., et al. (2006). Sleep: A marker of physical and mental health in the elderly. *The American Journal of Geriatric Psychiatry*, *14*, 860–866.
Reynolds, C. F., Monk, T. H., Hoch, C. C., et al. (1991). Electroencephalographic sleep in the healthy "old old": A comparison with the "young old" in visually scored and automated measures. *Journal of Gerontology*, *46*, M39–M46.
Rodriguez, J. C., Dzierzewski, J. M., & Alessi, C. A. (2015). Sleep problems in the elderly. *The Medical Clinics of North America*, *99*, 431–439.
Roth, T. (2007). Insomnia: Definition, prevalence, etiology, and consequences. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *3*, S7–S10.
Sakurai, N., & Sasaki, M. (1998). An activity monitor study on the sleep-wake rhythm of healthy aged people residing in their homes. *Psychiatry and Clinical Neurosciences*, *52*, 253–255.
Sateia, M. J. (2003). Neuropsychological impairment and quality of life in obstructive sleep apnea. *Clinics in Chest Medicine*, *24*, 249–259.
Schneider, L. D. (2017). Anatomy and physiology of normal sleep. In M. G. Miglis (Ed.), *Sleep and neurologic disease* (1st ed., pp. 1–28). Elsevier Science.
Scullin, M. K. (2013). Sleep, memory, and aging: The link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychology and Aging*, *28*, 105–114.
Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: Integrating a half century of multidisciplinary research. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *10*, 97–137.
Sivertsen, B., Omvik, S., Pallesen, S., et al. (2006). Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: A randomized controlled trial. *JAMA*, *295*, 2851–2858.
Slater, G., & Steier, J. (2012). Excessive daytime sleepiness in sleep disorders. *Journal of Thoracic Disease*, *4*, 608–616.
Smith, M. T., McCrae, C. S., Cheung, J., et al. (2018). Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, *14*, 1231–1237.
Somers, V. K., White, D. P., Amin, R., et al. (2008). Sleep apnea and cardiovascular disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*, *118*, 1080–1111.
Song, Y., Blackwell, T., Yaffe, K., et al. (2015). Relationships between sleep stages and changes in cognitive function in older men: The MrOS Sleep Study. *Sleep*, *38*.
Spira, A. P., Gonzalez, C. E., Venkatraman, V. K., et al. (2016). Sleep duration and subsequent cortical thinning in cognitively normal older adults. *Sleep*, *39*, 1121–1128.
Suh, S., Kim, H., Yang, H.-C., Cho, E. R., Lee, S. K., & Shin, C. (2013). Longitudinal course of depression scores with and without insomnia in non-depressed individuals: A 6-year follow-up longitudinal study in a Korean cohort. *Sleep*, *36*, 369–376.
Suh, S., Yang, H.-C., Fairholme, C. P., Kim, H., Manber, R., & Shin, C. (2014). Who is at risk for having persistent insomnia symptoms? A longitudinal study in the general population in Korea. *Sleep Medicine*, *15*, 180–186.
Suzuki, K., Miyamoto, M., & Hirata, K. (2017). Sleep disorders in the elderly: Diagnosis and management. *Journal of General and Family Medicine*, *18*, 61–71.
Thomas, R. J., Rosen, B. R., Stern, C. E., Weiss, J. W., & Kwong, K. K. (2005). Functional imaging of working memory in obstructive sleep-disordered breathing. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *98*, 2226–2234.
Tishler, P. V., Larkin, E. K., Schluchter, M. D., & Redline, S. (2003). Incidence of sleep-disordered breathing in an urban adult population: The relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*, *289*, 2230–2237.
Tranah, G. J., Blackwell, T., Ancoli-Israel, S., et al. (2010). Circadian activity rhythms and mortality: The study of osteoporotic fractures. *Journal of the American Geriatrics Society*, *58*, 282–291.
Tranah, G. J., Blackwell, T., Stone, K. L., et al. (2011). Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Annals of Neurology*, *70*, 722–732.
Tufik, S., Santos-Silva, R., Taddei, J. A., & Bittencourt, L. R. A. (2010). Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Medicine*, *11*, 441–446.
Uhlig, B. L., Sand, T., Ødegård, S. S., & Hagen, K. (2014). Prevalence and associated factors of DSM-V insomnia in Norway: The Nord-Trøndelag Health Study (HUNT 3). *Sleep Medicine*, *15*, 708–713.
Van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, *26*, 117–126.
Van Egroo, M., Narbutas, J., Chylinski, D., et al. (2019). Sleep-wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease. *Sleep*.
Verstraeten, E., & Cluydts, R. (2004). Executive control of attention in sleep apnea patients: Theoretical concepts and methodological considerations. *Sleep Medicine Reviews*, *8*, 257–267.

Vitiello, M. V., & Prinz, P. N. (1989). Alzheimer's disease. Sleep and sleep/wake patterns. *Clinics in Geriatric Medicine*, *5*, 289–299.

Weaver, T. E., & Chasens, E. R. (2007). Continuous positive airway pressure treatment for sleep apnea in older adults. *Sleep Medicine Reviews*, *11*, 99–111.

Weitzman, E. D., Moline, M. L., Czeisler, C. A., & Zimmerman, J. C. (1982). Chronobiology of aging: Temperature, sleep-wake rhythms and entrainment. *Neurobiology of Aging*, *3*, 299–309.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, *265*, 676–679.

Wyse, C. A., & Coogan, A. N. (2010). Impact of aging on diurnal expression patterns of CLOCK and BMAL1 in the mouse brain. *Brain Research*, *1337*, 21–31.

Yaffe, K., Falvey, C. M., & Hoang, T. (2014). Connections between sleep and cognition in older adults. *Lancet Neurology*, *13*, 1017–1028.

Yaffe, K., Laffan, A. M., Harrison, S. L., et al. (2011). Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*, *306*, 613–619.

Yoon, I.-Y., Kripke, D. F., Elliott, J. A., Youngstedt, S. D., Rex, K. M., & Hauger, R. L. (2003). Age-related changes of circadian rhythms and sleep-wake cycles. *Journal of the American Geriatrics Society*, *51*, 1085–1091.

Young, T., Finn, L., Austin, D., & Peterson, A. (2003). Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *American Journal of Respiratory and Critical Care Medicine*, *167*, 1181–1185.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine*, *165*, 1217–1239.

Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. *JAMA*, *291*, 2013.

Zhang, J., Lamers, F., Hickie, I. B., He, J.-P., Feig, E., & Merikangas, K. R. (2013). Differentiating nonrestorative sleep from nocturnal insomnia symptoms: Demographic, clinical, inflammatory, and functional correlates. *Sleep*, *36*, 671–679.

Chapter 17

Aging of persons with neurodevelopmental disabilities

Lauren A. Anker[1,2], Christina F. Chick[1,2] and Joachim F. Hallmayer[1,2]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [2]Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States

A growing body of research informs our understanding of aging in individuals with neurodevelopmental or intellectual disorders, including autism spectrum disorder (ASD) and Down syndrome (DS). Due to diagnostic, medical, and technological advances, as well as improvements in formal and informal support, adults with neurodevelopmental disorders are living longer than ever before. This has resulted in a dramatic increase in the population of older adults living with neurodevelopmental disorders (Bittles et al., 2002; Coppus et al., 2008; Roux, Shattuck, Rast, Rava, & Anderson, 2015). Although neurodevelopmental diagnoses are typically made in childhood, features of neurodevelopmental disorders exist throughout the lifespan and significantly impact an individual's functional abilities in late life (Bittles et al., 2002; Brugha et al., 2011; Coppus et al., 2008). Functional and cognitive abilities, which vary widely within this population, play an important role in determining life expectancy as well as quality of life during the aging process (Eaves & Ho, 2008).

In this chapter, we will provide an overview of research findings regarding the aging process in older adults with a neurodevelopmental disorder. Given the variability within this population, both between and within diagnostic categories, we will focus on ASD and DS as two illustrative examples. We begin by reviewing demographic trends and population characteristics, including life expectancy. Next, we provide an overview of cognitive abilities, physical health, mental health, and functional abilities in older adulthood. We also consider the impact of formal and informal support systems on outcomes in late life. Lastly, we discuss directions for future research that will facilitate understanding and support of aging individuals with neurodevelopmental disorders.

Features and diagnostic criteria of neurodevelopmental disorders

Neurodevelopmental disorders affect the development of the nervous system, leading to abnormal brain function. People with neurodevelopmental disorders exhibit disability in one or all domains of adaptive function, and their level of functioning can differ across domains (e.g., conceptual, social, and practical; DSM-5). Conceptual abilities involve language and other cognitive functions, such as reasoning and memory. Social abilities involve empathy and judgment, the ability to form social relationships, and the understanding of social dynamics. Practical abilities refer to independence in the self-care domain, as well as the ability to carry out tasks related to organization and management of day-to-day activities, including finances.

Neurodevelopmental disorders are a large category that includes communication, motor, and intellectual disorders. Communication disorders include language disorder, speech sound disorder, social (pragmatic) communication disorder, and childhood-onset fluency disorder (stuttering), as well as specific learning disorders. Motor disorders include developmental coordination disorder, stereotypic movement disorder, and tic disorder. Intellectual developmental disorders (IDD) refer to significantly below-average intelligence, as well as deficits in adaptive abilities, with onset of impairments manifesting prior to age 18 (ICD-11). When providing a diagnosis of IDD, a specifier is used to signify mild, moderate, severe, or profound severity (DSM-5). A specifier can also be used to classify impairments that are "associated with a known medical or genetic condition or environmental factor." This includes disorders such as DS, low birth weight, and fetal alcohol syndrome. It is common for neurodevelopmental disorders to cooccur. For example, a significant number of individuals on the autism spectrum have a cooccurring IDD, and individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) frequently have a secondary learning disability (DSM-5).

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00017-X

Terminology for describing IDD has changed over time. The use of IDD as a diagnostic term originates with the International Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11), released in 2015. Prior to the ICD-11, IDD was classified under mental retardation. The ICD-11 also reclassified IDD as a health condition or a disorder, rather than a disability (Girimaji & Pradeep, 2018). In a previous version of the ICD (ICD-6, released in 1956), IDD was classified as a "mental deficiency" (APA: Intellectual Disability, 2013). These changes in diagnostic terminology have made it challenging to track the trajectory of neurodevelopmental disorders over the lifespan.

Given the diversity of diagnoses that fall under the umbrella of neurodevelopmental disorders, as well as the variability of individual experiences within each diagnostic category, it would not be feasible to provide an in-depth review of all associated diagnoses here. Instead, we will focus on two disorders as illustrative examples: ASD and DS.

Autism spectrum disorder

Generally characterized by restrictive and repetitive behaviors and sensitivity to their environment, people on the autism spectrum exhibit deficiencies in behavior and communication that manifest in the first 2 to 3 years of life (Szatmari et al., 2016). As the current concept of autism emerged only in the 1940s, until the late 1980s, autism was considered a rare disorder. The rate of diagnosing persons with autism drastically increased in the 1990s (Piven, Rabins, & Autism in Older Adults Working Group, 2011). In 2013, the diagnostic criteria for ASD in the DSM-5 were restructured; Asperger's disorders, pervasive developmental disorder not otherwise specified (PDD-NOS), and childhood disintegrative disorder were combined into a single diagnosis of ASD.

ASD occurs more frequently in males; for every four males on the autism spectrum there is one female (Werling & Geschwind, 2013). However, current and past ASD research used to develop and determine criteria has focused on the presentation of features in males, leading to a possible underdiagnosis in females (Dworzynski, Ronald, Bolton, & Happe, 2012). Cooccurring IDD is present in around 30% of individuals on the autism spectrum (Christensen et al., 2018), and a specifier is used to indicate with or without accompanying intellectual impairment in DSM-5. Additionally, attention problems are present in 30%−40% of individuals on the autism spectrum (Matson & Cervantes, 2014). Other specifiers include with or without accompanying language impairment, associated with a known medical or genetic condition or environmental factor associated with another neurodevelopmental, mental, or behavioral disorder, and with catatonia (DSM-5). When providing an ASD diagnosis an accompanying severity level is determined ranging from Level 1 (requiring support) to Level 3 (requiring very substantial support; DSM-5).

Down syndrome

DS is caused by trisomy 21 (i.e., a whole or partial third copy of chromosome 21). Physical features of DS include craniofacial dysmorphia, hypotonia (i.e., weak muscle tone), short stance, atypical gait, and congenital heart defects (Arumugam et al., 2016; Kazemi, Salehi, & Kheirollahi, 2016). All individuals with DS have some degree of intellectual disability, which is most apparent in short-term verbal memory and in some aspects of language processing (Chapman, 1999; Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). Although physical features of DS are apparent at birth, features of motor, communication, and intellectual functioning typically do not become apparent until 1 year of age. There is considerable interindividual variability in the extent to which intellectual, physical, and psychiatric features of DS are expressed, which is thought to be due to variability in chromosomal patterns of gene expression (Letourneau & Antonarakis, 2012). Increases in maternal age and prenatal screening have affected the rate of live births of babies with DS. Improvements in medical treatment and in service availability have dramatically increased the lifespan of people with DS, resulting in a growing population of older adults with DS (Larsen & Kirkevold, 2008).

Chromosome 21 encodes genes related to multiple disorders, including epilepsy and Alzheimer's dementia, for which the prevalence is higher among adults with DS than in the general population. One of the genes on chromosome 21 codes for the amyloid precursor protein (APP). People with DS, who have three copies of chromosome 21, display an early buildup of beta-amyloid plaques; many show neurological pathology typical of Alzheimer's dementia by age 30 (Rumble et al., 1989). Although not all adults with DS develop dementia, the average age of onset is earlier in DS than in the general population, and the prevalence is much higher (McCarron et al., 2017). Trisomy 21 may also contribute to other medical conditions that frequently cooccur with DS, including obstructive sleep apnea (OSA) and seizure disorders (Bayen, Possin, Yingjia, de Langavant, & Yaffe, 2018). Some research has indicated that depression is more prevalent in adults with DS, although specialized diagnostic criteria are required given that depression and other psychiatric disorders present differently in people with DS than in neurotypical people (Cooper, Smiley, Allan, & Morrison, 2018; Walker, Dosen, Buitelaar, & Janzing, 2011).

Demographic trends

Obtaining an accurate estimate of the prevalence of neurodevelopmental disorders is challenging for multiple reasons. First, as a definitional problem, there is no consensus for defining the lower boundary of old age in this population. Most studies on aging use 55, 60, or 65, but some studies use 85 as a cut-off. The US Census Bureau has used "aged 65 years and over" to report on aging in the US population. Second, all counts are restricted to those older persons with developmental disorders who are known to the developmental disabilities service system in each state. Similarly, for children with developmental disorders, data are only collected on children registered to receive services.

The US Census Bureau reported in 2016 that there are an estimated 49.2 million adults aged 65 and older living in the United States, and the older adult population is projected at reaching 70 million individuals over the next two decades (U.S. Census Bureau, 2010). This growing older adult population is the consequence of dramatic reductions of mortality rates (Ballaban-Gil, Rapin, Tuchman, & Shinnar, 1996; National Center for Health Statistics, 2001; Kobayashi, Murata, & Yoshinaga, 1992; Manton & Gu, 2001) in combination with the rapidly growing human population (Schoeni, Freedman, & Wallace, 2001).

With the projected doubling of the older adult population in 2050, the projected number of adults aging with a disability is staggering (Ortman, Velkoff, & Hogan, 2014). The number of adults with an intellectual or developmental disability over the age of 65 is predicted to double to 1.2 million within the next 10 years (Heller, Stafford, Davis, Sedlezky, & Gaylord, 2010; Piven et al., 2011). In the last 15 years, the estimated prevalence of neurodevelopmental disorders among children aged 13−17 has increased from around 14% in 2008 to around 31% today. The largest driver of growth has been the rising prevalence of ADHD, which is reported at around 40% of children aged 13−17, an estimated increase of 33% in the last 15 years (Boyle et al., 2011; CDC, 2018). The prevalence of specific learning disability is estimated around 8% in 2008, and prevalence of other developmental delays is 4% (CDC, 2018).

Autism spectrum disorder

The prevalence of ASD has increased by 15% since 2012 (CDC, 2018). Among children aged 13−17, the prevalence of ASD nearly quadrupled from 1999 to 2008, likely reflecting increased awareness and updated diagnostic criteria (Boyle et al., 2011). An estimated 650,000 older adults (age 65 +) are on the autism spectrum in the United States, with predicted costs of 3.2 million (Ganz, 2007) for each individual with ASD across the lifetime. This highlights the importance of preparing for the large cohort of individuals diagnosed from 1990 to 2000 to reach old age.

Down syndrome

People with DS comprise between 10% and 18% of the population living with an intellectual disorder (Glasson, Sullivan, Petterson, Montgomery, & Bittles, 2002; Mantry et al., 2008). The worldwide prevalence of DS is estimated to range between six and eight per 10,000 (Besser, Shin, Kucik, & Correa, 2007; Mantry et al., 2008) or approximately 5.8 million people (CDC, 2006). In the United States, the prevalence is estimated to be about eight in 10,000 or approximately 250,000 people (Presson et al., 2013). Worldwide, the rate of live DS births varies by country and according to societal mores. On the one hand, the rate of childbirth by mothers over age 35 is increasing in developed countries (Loane et al., 2013), and higher maternal age is the primary risk factor for DS (Perkins, 2017). On the other hand, increasing availability of genetic testing and pregnancy termination may reduce the rate of live births (Presson et al., 2013; Weijerman et al., 2008). Worldwide, the live-birth prevalence of DS is between 10 and 14 per 10,000 (Bittles, Bower, Hussain, & Glasson, 2006, as cited by Torr, Strydom, Patti, & Jokinen, 2010; Presson et al., 2013; Weijerman et al., 2008). In the United States, the live-birth prevalence is about 14 per 10,000 or 6000 babies per year (Centers for Disease Control and Prevention, 2017; Diamandopoulos & Green, 2018). The number of people aged 40 and over living with DS has been predicted to double between 2008 and 2045 (Larsen & Kirkevold, 2008).

Life expectancy

Over the past decades, advances in technology and health care have facilitated a marked increase in life expectancy for adults with neurodevelopmental disorders (Ballaban-Gil et al., 1996; National Center for Health Statistics, 2001; Kobayashi et al., 1992; Manton & Gu, 2001). Adults with IDD are consistently living into their late 60s and older (Bittles et al., 2002).

Autism spectrum disorder

In the past decades, there has been a marked increase in life expectancy of persons on the autism spectrum. The predicted mean age of death for people on the autism spectrum is mid-50s to late 60s (Hirvikoski et al., 2016), and the first person to be formally diagnosed as on the autism spectrum, Donald Triplett, is 86 years old in the year 2019 (Perkins, 2017). Nonetheless, middle-aged adults with ASD have one to five times higher mortality rates than the general population (Gillberg, Billstedt, Sundh, & Gillberg, 2010). Multiple factors contribute to this. First, up to 30% of persons on the autism spectrum have an intellectual disability, which is associated with reduced lifespan (Happé & Charlton, 2012; Hirvikoski et al., 2016). Second, cooccurring medical conditions and psychiatric disorders are more common in adults on the autism spectrum compared to the general population (Croen et al., 2015), and the cause of death is most frequently related to an epileptic event or accident (Gillberg et al., 2010; Mouridsen, Brønnum-Hansen, Rich, & Isager, 2008; Shavelle, Strauss, & Pickett, 2001). Epilepsy rates are higher in women on the autism spectrum than in men on the autism spectrum (Spence & Schneider, 2009), which could explain the higher mortality rates for women with ASD (Gillberg et al., 2010; Mouridsen et al., 2008; Shavelle et al., 2001). Third, the rates of suicide among persons with ASD are over 400 times higher than in the general population (Croen et al., 2015). In contrast, mortality due to smoking, alcohol use, and cancer is significantly less in adults on the autism spectrum than in the general population (Croen et al., 2015).

Down syndrome

Less than a century ago, the life expectancy of a baby born with DS was 9 years (Bittles & Glasson, 2004; Penrose, 1933, 1949). This was largely due to congenital heart defects, respiratory infections, and other medical illnesses for which treatments have since been developed (Torr et al., 2010). Today, in developed countries, the mean age of death is over 60 years (Glasson et al., 2002; Hithersay et al., 2019; Ng, Flygare Wallén, & Ahlström, 2017). In a large Australian cohort study, 25% of adults with DS were between 57 and 62 years of age at time of death (Bittles et al., 2006; Glasson et al., 2002). There are documented cases of individuals with DS living into their eighth decade (Glasson et al., 2002; Krinsky-McHale et al., 2008).

Nevertheless, people with DS die an average of 13 years before neurotypical people (Ng et al., 2017), and DS has the shortest lifespan of all intellectual disorders (Bittles, Bower, Hussain, & Glasson, 2007; CDC, 2006). A study of over 118,000 people with intellectual disorders in California (United States) found that mortality rates for individuals with DS were similar to those of individuals with other types of intellectual disability until age 35, after which mortality rates increased much more steeply for those with DS. After age 35, the mortality rate doubled every 6.4 years for people with DS, whereas it doubled every 9.6 years for people with other types of intellectual disability (Strauss & Eyman, 1996). Life expectancy is considerably shorter for ethnic and racial minorities (Day, Strauss, Shavelle, & Reynolds, 2005; Friedman, 2001; Leonard, Bower, Petterson, & Leonard, 2000), although more research is needed in order to understand the factors that contribute to this discrepancy (CDC, 2006; Torr et al., 2010).

The most common causes of death differ for adults with DS compared to neurotypical adults or those with other intellectual disorders. Severe intellectual disorder, dementia, psychiatric disorders, and physical comorbidities are all risk factors for mortality in adults with DS (Torr et al., 2010). A prospective longitudinal study of adults with DS over age 35 found that dementia was associated with a fivefold increase in mortality rate, and that dementia was the proximate cause of death in 70% of deaths observed (Hithersay et al., 2019). Another prospective longitudinal study of over 500 adults with DS found that epilepsy, visual impairment, restricted mobility, and dementia at baseline predicted increased likelihood of death (Coppus et al., 2008). Based on an analysis of death certificate records from Australian adults with DS over the age of 40, Bittles et al. (2006) found that pneumonia was the proximate cause of death in over 40% of cases. As noted by Torr et al. (2010), death certificates typically list proximate causes (e.g., pneumonia) but not underlying causes (e.g., Alzheimer's) of death, which is a limitation of this type of study. Cognitive decline, as well as sensory and musculoskeletal impairments, limits quality of life and contributes to functional decline (Covelli, Raggi, Meucci, Paganelli, & Leonardi, 2016; Torr et al., 2010), which may explain their association as risk factors for earlier death in adults with DS. For this reason, frequent screenings for sensory impairment are recommended as standard-of-care for adults with DS (Torr et al., 2010).

Cognitive abilities

As in the general population, most persons with neurodevelopmental disorders maintain their cognitive abilities and even show evidence of intellectual development throughout their adult years (Howlin, Goode, Hutton, & Rutter, 2014;

Howlin, Moss, Savage, & Rutter, 2013; Whitehouse, Line, Watt, & Bishop, 2009, Whitehouse, Watt, Line, & Bishop, 2009), with declines manifested only after age 60 or 70.

Autism spectrum disorder

The literature shows nuanced results regarding cognitive changes over time in older adults with ASD. Whereas the overall level of functioning across cognitive domains in persons on the autism spectrum is relatively stable over time, there can be variations in trajectories of individual cognitive domains (Farley et al., 2009). In adults with high-functioning autism, changes with age were less in fluency and more pronounced in visual memory performance compared to healthy controls (Geurts & Vissers, 2012). Overall, verbal ability tends to increase, whereas visual memory and reasoning abilities tend to decrease in these individuals over time (Geurts & Vissers, 2012; Howlin, Goode, Hutton, & Rutter, 2004; Howlin, Mawhood, & Rutter, 2000; Mawhood, Howlin, & Rutter, 2000). With age, sustained attention, working memory, and fluency decline, consistent with the pattern of nonASD adults (Geurts & Vissers, 2012). Although there is a high prevalence of Alzheimer's dementia in older adults with developmental disorders overall, the prevalence rate is not high in persons on the autism spectrum (Coppus et al., 2008; Janicki & Dalton, 2000).

Down syndrome

All people with DS have some degree of intellectual disability, with IQs averaging 50 and ranging between 30 and 70 (Chapman, 1999). However, intellectual deficits in DS are more severe in some domains than in others. Language-processing deficits are primarily observed in morphosyntax (Joffe & Varlokosta, 2007; Levorato, Roch, & Beltrame, 2009). In spite of impaired verbal short-term memory, people with DS typically show intact visuospatial short-term memory (though some studies have found deficits in visuospatial memory; Baddeley & Jarrold, 2007; Frenkel & Bourdin, 2009; Lanfranchi, Carretti, Spano, & Cornoldi, 2009). Additionally, despite deficits in explicit long-term memory, people with DS typically have intact implicit long-term memory (Carlesimo, Marotta, & Vicari, 1997). Vision and hearing impairments, as well as language-processing impairments, can compound information-processing deficits (Evenhuis, Sjoukes, Koot, & Kooijman, 2009; Lott & Dierssen, 2010; Vicari, 2001).

Other physical health conditions common in adults with DS, including epilepsy and hypothyroidism, can also affect cognitive function (Correia et al., 2009). Severity of epileptic seizures is associated with degree of cognitive impairment (Kumada et al., 2005) and with rapid cognitive decline (Menendez, 2005; Puri, Ho, & Signh, 2001). Although the evidence in humans is correlational, mouse models suggest that seizures contribute to diminished cognitive function, as induced seizures led to impaired neuronal and neurotransmitter function (Holmes, 2009; Lott & Dierssen, 2010). Alternatively, seizures and cognitive decline may be caused by the same underlying neuropathology (Cabrejo et al., 2006; Westmark, Westmark, Bear, Hildebrandt, & Malter, 2008). These effects are compounded by the fact that many antiepileptic medications further impair cognitive functioning (Mula & Trimble, 2009; Tsiouris, Patti, Tipu, & Raguthu, 2002).

Although not all adults with DS develop dementia, dementia emerges at earlier ages and occurs with higher prevalence in adults with DS than in neurotypical adults. Estimates of prevalence among adults with DS aged 45 and above range from 15% to 45% (McCarron et al., 2017; Prasher & Krishnan, 1993), and the duration typically ranges from 3 to 6 years (Lai & Williams, 1989; Prasher & Krishnan, 1993). In contrast, the prevalence of dementia among neurotypical adults below the age of 65 is between 2% and 10% (Prince & Jackson, 2009). A prospective, 20-year longitudinal study of adults with DS found that the risk for dementia increased from 23% at age 50 to 45% at age 55 to 88% at ages 65 and above (McCarron et al., 2017). The mean age of onset was 55 years (median = 56 years). The risk for developing dementia, age of onset, and duration do not appear to vary according to severity of intellectual disability (McCarron, McCallion, Reilly, & Mulryan, 2014; McCarron et al., 2017; Strydom et al., 2010).

The neurological phenotype of DS is thought to contribute to the disproportionately high risk for developing dementia in this population. DS is associated with increased expression of the gene coding for APP, which is also coded on chromosome 21 (Rumble et al., 1989). APP is a precursor to the amyloid-Beta protein, which has been associated with the development of Alzheimer's disease. One study found deposits of Beta-amyloid protein in the hippocampal region of the brain of an eight-year-old with DS (Leverenz & Raskind, 1998). Beta-amyloid deposits begin in the superficial layers of the frontal lobe and are found in deeper layers of the cortex with increasing age (Azizeh et al., 2000). Positron emission tomography studies have found increased glucose metabolism in frontotemporal areas of the brains of young adults with DS, suggesting that their brains may compensate for the presence of Beta-amyloid prior to dementia onset (Lott, 2012). Indeed, although Alzheimer's pathology (i.e., buildup of Beta-amyloid) is present in the brains of virtually

all adults with DS, not all adults with DS develop dementia. This has supported the hypothesis that a compensatory mechanism may protect against loss of cognitive function in some individuals with DS (Lott, 2012).

Given the early onset of dementia in adults with DS, there has been a concerted effort to identify cognitive and behavioral changes that presage the progression to dementia in this population. Preclinical and prodromal symptoms of dementia in adults with DS differ from those in neurotypical adults. A recent literature review found that declines in executive function, as well as onset of behavioral and psychological symptoms of dementia, preceded clinical dementia onset—and often preceded memory loss of any kind—in adults with DS (Lautarescu, Holland, & Zaman, 2017). In contrast, short-term memory loss is often the first symptom to appear in neurotypical adults (Lautarescu et al., 2017). A separate review found that both cognitive tests and informant-based measures were suitable for early detection of progression to dementia in adults with DS (Elliott-King et al., 2016). In contrast, a cohort study of 283 adults with DS found that tests of memory, verbal fluency, sustained attention, and motor coordination were more sensitive in detecting early decline than were informant-based measures (Firth et al., 2018). A separate cohort study of 312 adults with DS found that, among cognitive functions, measures of memory and attention were most sensitive in tracking cognitive decline associated with both aging and Alzheimer progression. Specifically, measures of memory and attention were most sensitive in distinguishing preclinical from prodromal dementia, whereas only memory measures distinguished between prodromal and clinical dementia (Startin et al., 2019).

Physical health

Individuals with neurodevelopmental disorders, particularly those with IDD, are more likely to have multiple cooccurring medical issues (Scepters et al., 2005). The most common of these medical issues are epilepsy, gastrointestinal conditions, poor oral health, cardiovascular disease (CVD), and other related cardiovascular conditions (Bodde & Seo, 2009; Draheim, 2006; Krahn, Hammond, & Turner, 2006; Pezzementi & Fisher, 2005; Reichard & Stolze, 2011; Reichard, Stolze, & Fox, 2011; Traci, Seekins, Szali-Petree, & Ravesloot, 2002; Tyler, Schramm, Karafa, Tang, & Jain, 2010).

Autism spectrum disorder

A recent review of patient medical records from a large medical provider in Northern California (Kaiser Permanente) established that all chronic medical diagnoses were substantially more common in adults on the autism spectrum (Croen et al., 2015). Specifically, higher rates of obesity, hypertension, and gastrointestinal problems occurred in the population of older adults on the autism spectrum, compared to age-matched peers without ASD (Croen et al., 2015). This replicates a 2010 study that found higher rates of obesity and diabetes in adults on the autism spectrum (Heller et al., 2010). Older adults with ASD also had an increased risk for stroke in later life, as well as a higher predisposition for developing CVD and Parkinson's disease; this was not attributable to higher rates of tobacco use (Croen, 2019; Croen et al., 2015).

Croen and colleagues (2015, 2019) found that the medical profile of persons with ASD changes over the lifetime. Compared to children on the autism spectrum, adults on the autism spectrum have higher rates of allergy and autoimmune problems. In early adulthood, individuals with ASD had a higher occurrence of gastrointestinal distress (GI) problems, immune disorders, and sleep disturbance compared to same-aged individuals with a diagnosis. However, after age 50, rates of sleep disturbance, seizure, and epilepsy disorders no longer distinguished individuals with ASD from same-aged nonautistic peers.

Down syndrome

Adults with DS have a high prevalence of cardiovascular, neurological, metabolic, and endocrine disorders (Bayen et al., 2018). A study of over 1000 Scottish adults with intellectual disorders, including 186 with DS, found that individuals with DS had a mean of 11.68 physical health conditions (Kinnear et al., 2018). More than 95% of adults with DS had multimorbidity (i.e., more than one physical health condition), which is similar to the rate among adults with other intellectual disorders (Kinnear et al., 2018). Kinnear and colleagues found that obesity, visual and hearing impairments, skin and nail disorders, and constipation were the most common conditions among adults with DS. The rate of epileptic seizures among adults with DS, though higher than that of the general population, is lower than that among all intellectual disorders (Mcdermott et al., 2005). Rates of hypertension, ataxia, cerebral palsy, and osteoporosis are also lower in adults with DS than in adults with other intellectual disorders (Kinnear et al., 2018).

For adults with DS, a diagnosis of dementia increases the risk for multimorbidity. Bayen et al. (2018) conducted a study of 2015 California Medicare records, in which they compared adults over age 45 who had DS with and without

dementia. They found that a diagnosis of dementia was associated with an increased incidence of hypothyroidism, anemia, dyslipidemia, weight loss, chronic renal failure, tumors, and hematologic diseases. Older age is associated with all of these disorders, and it is unclear whether these conditions reflect general neurodegeneration, or whether there is a causal relationship between dementia and physical comorbidities. Bayen and colleagues report that the prevalence of cardiovascular and cerebrovascular diseases, as well as diabetes, obesity, osteoporosis, rheumatism, tobacco use, and ulcer, liver, or chronic pulmonary disease, did not differ between those with and without dementia. The most common physical conditions in this sample were hypothyroidism (45.8%), epilepsy (29.5%), anemia (29.3%), hypertension (22.3%), dyslipidemia (21.9%), chronic pulmonary disease (18.8%), congestive heart failure (12.2%), diabetes (11.5%), and chronic renal failure (10.1%). Another recent study found a higher incidence of dental and gastrointestinal problems among adults with both DS and dementia, compared to those with only DS (Esbensen, Johnson, Amaral, Tan, & Macks, 2016). Other studies have reported an association between dementia and epileptic seizures (Lott & Lai, 1982; McVicker, Shanks, & McClelland, 1994; Prasher & Krishnan, 1993; Puri et al., 2001). It is estimated that between 9% and 26% of adults with DS experience epileptic seizures, with a mean onset at age 37 (Esbensen, Seltzer, and Greenberg, 2007; Johannsen, Christensen, Goldstein, Nielsen, & Mai, 1996; Mcdermott et al., 2005; McVicker et al., 1994; Puri et al., 2001). It appears that late-onset seizures (i.e., those occurring after age 30) may be associated with dementia, although dementia does not account for the overall high rate of seizure activity in adults with DS (Menendez, 2005).

OSA is both more common and more severe in adults with DS than in the general adult population. Whereas over 90% of adults with DS have sleep-disordered breathing (Trois et al., 2009), the general population prevalence is only 2%–4% (Young, 1993). Both higher age and higher body mass index are associated with more severe OSA in adults with DS (Resta et al., 2003). OSA is also associated with more severe hypoxia in DS than in the general population. OSA is also interwoven with the other medical comorbidities experienced by adults with DS. On the one hand, these comorbidities, including hypothyroidism, gastroesophageal reflux disease, hypotonia, and obesity may contribute to the severity of OSA (Lal, White, Joseph, van Bakergem, & LaRosa, 2015). For example, the high rate of obesity among adults with DS may also contribute to OSA; one study found that the degree of obesity predicted the degree of apnea-hypopnea in adults with DS (Trois et al., 2009). On the other hand, OSA may also exacerbate these comorbidities. For example, OSA may compound cognitive deficits in adults with DS, who already have an intellectual disability and are at high risk for developing dementia. Prospective studies have found that, among adults with DS, higher ratings of sleep disruption were associated with greater executive function difficulties (Chen, Spano, & Edgin, 2013), and sleep-disordered breathing was associated with very low scores on the Mini-Mental State Examination and the Raven's Progressive Matrices, two neurocognitive assessment tools (Andreou, Galanopoulou, Gourgoulianis, Karapetsas, & Molyvdas, 2002). Thus, the sleep-disordered breathing may increase the tendency of adults with DS to develop dementia and other neurodegenerative conditions (Lal et al., 2015).

Mental health

Individuals with neurodevelopmental disorders, specifically those with IDD, have higher rates of psychiatric disorders (Traci et al., 2002). Despite the high prevalence of cooccurring medical and psychiatric issues, individuals with a developmental disability rarely get effective mental health treatment for secondary mental health problems (Farley et al., 2009; Roux et al., 2015), which can lead to various negative outcomes (Farley et al., 2009; Gillberg, Helles, Billstedt, & Gillberg, 2016).

Autism spectrum disorder

Croen and colleagues (2015) found that more than half of adults on the autism spectrum had a cooccurring psychiatric disorder. In particular, they observed significantly increased rates of bipolar disorder, obsessive-compulsive disorder, schizophrenia, and suicide attempts in the older adult population who were on the autism spectrum (Croen et al., 2015). Rates of depression and anxiety were over twice the rates of individuals without ASD (Croen et al., 2015). The high rate of cooccurring medical and mental health problems is likely due to a combination of lifestyle, diet, and communication differences that influence access to health care, as well as possible genetic overlap between developmental disorders and major medical diagnoses (Croen et al., 2015).

Down syndrome

Aside from Alzheimer's and other forms of dementia, the most common psychiatric disorders in adults with DS are mood disorders, anxiety, and problem behaviors. Bipolar disorder, psychosis, schizophrenia, and personality disorders

are rare in this population (Grieco et al., 2015; Tasse et al., 2016; Walker et al., 2011). Depressed or anxious mood may be more prevalent in adults with DS than in neurotypical adults, although they are not necessarily more prevalent than in adults with other intellectual disorders (Cooper et al., 2018; Walker et al., 2011).

A challenge with assessing the prevalence of psychiatric disorders in adults with DS is that the clinical presentation and phenomenology of these disorders differ from that of neurotypical adults. The most common symptom of depression in adults with DS is loss of interest, which was reported in over 90% of subjects in two separate studies (Cooper & Collacott, 1994; Myers & Pueschel, 1995). Other symptoms reported by these studies include depressed mood, tearfulness, sleeping disorders, fatigue, psychomotor retardation, loss of appetite, aggression or tantrums, agitation, anxiety, memory deficits, and visual or auditory hallucinations. An additional challenge in diagnosing depression in adults with DS is the overlap with symptoms of other disorders common in this population, including dementia, hypothyroidism, and sleep disorders (Roizen & Patterson, 2003). Indeed, symptoms of depression, including apathy and withdrawal, are considered prodromal to the development of dementia in this population (Adams & Oliver, 2010; Ball, Holland, Treppner, Watson, & Huppert, 2008). Although thoughts of guilt, worthlessness, or death are common symptoms of depression in neurotypical adults, adults with DS typically do not express such thoughts (Smiley & Cooper, 2003). Adults with DS frequently have impairments in expressive language, which limits their ability to communicate cognitive symptoms of depression during diagnostic interviews (Walker et al., 2011). Diagnostic overshadowing, in which health care professionals misattribute emotional symptoms to the intellectual disability rather than diagnosing a separate psychiatric disorder (Reiss, Levitan, & Szyszko, 1982) is yet another barrier to diagnosis of depression or other mood disorders in adults with DS.

Given these diagnostic challenges, separate diagnostic criteria, which rely on observable characteristics and behavior as opposed to self-report, have been developed for use with people who have intellectual disorders. These include the Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation (DC-LD; Smiley & Cooper, 2003) and the Diagnostic Manual-Intellectual Disability (DM-ID; Fletcher, Loschen, Stavrakaki, & First, 2007). These alternative diagnostic criteria are recommended for use with adults with DS (Chapman & Hesketh, 2000; Ypsilanti, Grouios, Alevriadou, & Tsapkini, 2005). One study applied multiple diagnostic criteria to a sample of adults with DS and found that employing ID-specific criteria resulted in higher prevalence estimates for depression (Mantry et al., 2008).

Despite the recommended use of alternative diagnostic criteria in clinical settings, most research studies have assessed rates of depression and other psychiatric disorders according to population-general diagnostic criteria, such as the DSM and ICD. Based on these criteria, studies have reported that the prevalence of depression in people with DS is between 0% and 11% (Walker et al., 2011), with one study reporting a 2-year incidence of up to 5.2% in adults (Mantry et al., 2008). The prevalence of depression in adults with DS has been reported to be comparable to that of adults with other intellectual disorders (Burt, Loveland, & Lewis, 1992; Walker et al., 2011). Some studies found higher incidence rates of depression in adults with DS compared to adults with other intellectual disorders (Collacott, Cooper, & McGrother, 1992; Cooper & Collacott, 1994) Mantry et al. (2008) reported lower prevalence and incidence of depression in the DS cohort when compared with other adults with ID. A retrospective study of adults with DS found that the age of depression onset ranged from 11 to 50 years, with a mean age of 29.5 (Cooper & Collacott, 1994). Of those who experienced depression, a majority (81%) experienced a single episode, whereas 19% experienced recurrent depression. The incidence of depression and other mood or psychiatric disorders in adults with DS increases with age, particularly past the age of 35 (Tasse et al., 2016).

A variety of treatment modalities, including pharmacotherapy (particularly serotonergic agents; Byrne & Seyfort, 1998; Myers & Pueschel, 1995), electroconvulsive therapy (Lazarus, Jaffe, & Dubin, 1990; Warren, Holroyd, & Folstein, 1989), and psychotherapy (Willner, 2005), have been found effective in treating depression in adults with DS. Additionally, cognitive behavioral therapy is both feasible (Lindsay, Howells, & Pitcaithly, 1993) and effective (McCabe, McGillivray, & Newton, 2006) in treating adults with both a mild intellectual disability and depression, though research is needed to assess feasibility and efficacy in DS specifically.

Functional abilities

Functional abilities refer to the performance of routine daily living activities that are expected of adults living independently of a caregiver. Most studies conclude that, in people with a neurodevelopmental disorder, overall cognitive functioning, social ability, and language skills do not change substantially over time; however, declines or improvements in specific domains do occur (Magiati, Tay, & Howlin, 2014). Persons without IDD continue to develop new functional abilities throughout their adult years, but the acquisition of new skills levels off and begins to decline in older age

(Billstedt, Gillberg, & Gillberg, 2005, 2007; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Gillespie-Lynch et al., 2012).

Autism spectrum disorder

In older adults on the autism spectrum without a cooccurring intellectual disability, certain characteristics of ASD are reported to improve with age, specifically communication (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Shattuck et al., 2007), repetitive and restrictive behaviors and interests, social functioning, and eye gaze (Bastiaansen et al., 2011). While behavioral therapy and other treatments improve overall functional abilities, the consensus appears to be that abilities in social and functional support will never rarely improve to the level of nonautistic individuals (Brugha et al., 2011; Seltzer et al., 2004; Shattuck et al., 2007).

Down syndrome

About half of adults with DS engage in a vocational activity (Tasse et al., 2016). Tasse and colleagues found that the diagnosis of a comorbid psychiatric disorder did not affect the likelihood of having a job, though they included sheltered work programs in this analysis. Esbensen and colleagues (2016) found that adults with both DS and dementia were less likely to be engaged in vocational or educational activities than were those who had DS without dementia.

Considerable evidence suggests that the decline of functional abilities is associated with mortality in adults with DS (Chaney & Eyman, 2000; Esbensen, Seltzer, & Greenberg, 2007), although other studies have found no relation (Glasson et al., 2002; Strauss & Eyman, 1996). Esbensen and colleagues (2016) found that the presence of dementia was associated with lower functional abilities among adults with DS, although dementia status did not predict level of social activities.

The majority of adults with DS live in the home of a family member (Stancliffe et al., 2012; Tasse et al., 2016). Given that older maternal age is a primary risk factor for DS, and that adults with DS experience aging-related health problems several decades before their neurotypical counterparts, adults with DS are often in need of care from parents who are, themselves, in advanced stages of late life (i.e., senescence). This has led to a high prevalence of adults with DS living with their adult siblings (Hodapp, Burke, Finley, & Urbano, 2016). One study reports that adults with DS and a comorbid psychiatric disorder were five times as likely as those without a comorbid psychiatric disorder to live in an intermediate care facility (Tasse et al., 2016). Another study found that adults with both DS and dementia were more likely to receive full in-residence support than were adults with DS but without dementia, either with or without a psychiatric disorder (Esbensen et al., 2016). Esbensen and colleagues found that adults with DS but without dementia were most likely to live with family members.

Service use and availability

Physical and mental health are important for fostering both independence and quality of life, as articulated by the United Nations Convention on the Rights of Persons with Disabilities (UN General Assembly, 2007). However, people with developmental and intellectual disorders often do not receive the level of medical care that they require and experience poorer health outcomes as compared to adults without disabilities (Minihan et al., 2011; Pharr & Bungum, 2012). Older adults with a neurodevelopmental disorder are less likely to use medical services (Haveman, 2019) and preventive dental services (Pezzementi & Fisher, 2005). Additionally, access to community mental health services can be insufficient among those with an intellectual disorder and a comorbid psychiatric disorder (Ward, Nichols, & Freedman, 2010). Women with intellectual or developmental disabilities are less likely to receive preventative screenings such as mammograms (Greenwood, Wang, Bowen, & Wilkinson, 2014; Parish, Swaine, Luken, Rose, & Dababnah, 2012, 2014; Swaine, Parish, Luken, Son, & Dickens, 2014) and are less educated about sexual and reproductive health (Rurangirwa, Van Naarden Braun, Schendel, & Yeargin-Allsopp, 2006). Aging with a neurodevelopmental disorder that involves cognitive impairments, communication impairments, or congenital insensitivity to pain poses additional challenges and can limit the ability to effectively engage with the medical system (Haveman, 2019; Roux et al., 2015).

Service use in people with a developmental disability is particularly important due to their need for supportive care in managing daily activities and physical and mental health throughout the lifespan. However, older people with a developmental disorder are significantly less likely to marry or have children, and therefore lack the most basic supports that are provided to older persons by members of their nuclear family. Additionally, advancing age and functional

impairments may interfere with the ability to develop meaningful relationships with friends who could provide support (Tobin, Drager, & Richardson, 2014). For these reasons, people with neurodevelopmental disorders often depend on their aging parents or siblings for this support. Older persons with developmental disorders may be especially vulnerable and isolated; in addition to continued informal support from their family of origin and from friends, they also have substantial need for formal supports.

Autism spectrum disorder

Despite their higher need for medical and mental health services, persons on the autism spectrum face challenges that make it difficult to seek or receive the services they need. For example, on average, adults with a developmental disability are less likely to see their primary care physician when compared with the typically developing population. Additionally, they are less likely to receive routine care and preventive care. For example, women on the autism spectrum saw OBGYNs less frequently than nonautistic women (Zerbo et al., 2018). Communicating symptoms to providers can be challenging, and environmental stimuli can make it difficult for a person on the autism spectrum to tolerate an examination. Behavioral problems and cooperation could impact a clinician's ability to examine, test, or provide necessary medical procedures such as injections (Heller et al., 2010). In addition, there are many complexities inherent in transitioning out of pediatric care and entering primary care as an adult with a neurodevelopmental disorder. Persons on the autism spectrum often have difficulty embracing change or initially trusting new people (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). Additionally, there is a lack of knowledgeable providers trained in working with this population (Henderson, Lynch, Wilkinson, & Hunter, 2007; Kerr, Dunstan, & Thapar, 1996; Kirby & Hegarty, 2010). In a survey of medical providers in a large Californian health care system, only 13% of providers said that they had the training, comfort, support, and tools to adequately treat patients on the autism spectrum (Zerbo, Massolo, Qian, & Croen, 2015).

The functional trajectory of persons on the autism spectrum is related to their environmental supports and personal interventions. The level of both formal (e.g., state-funded) and informal (e.g., family) support is more important than the level of disability in predicting quality of life for adult men on the autism spectrum (Renty & Roeyers, 2007; Tobin et al., 2014). However, as individuals with ASD become adults, they are eligible for fewer state-funded services, particularly if they do not have an intellectual disability (Seltzer et al., 2003). Adults who are on the autism spectrum but who do not have an intellectual disability are frequently ineligible for state-funded services such as sheltered workshops or day activities (Taylor & Seltzer, 2011). One study found that 26% of young adults on the autism spectrum did not receive any services (Roux et al., 2015), despite the importance of supportive services for positive outcomes in this community (Eaves & Ho, 2008). As this population is expected to exceed half a million in the next decade (Shattuck et al., 2012), increased services targeting older adulthood are needed (Bishop-Fitzpatrick, Minshew, & Eack, 2014; Mahan & Kozlowski, 2011).

There are many interventions targeted toward individuals with an intellectual disability. In 2011, 86% of persons with an intellectual disability had sheltered workshop or supported employment. In contrast, only 20% of persons on the autism spectrum without an intellectual disability were employed, which is much lower than the rate of employment among individuals with an intellectual disability (Taylor & Seltzer, 2011). The lack of employment opportunities can impact that individual's ability to thrive in his or her environment and highlights the importance and need for more opportunities for individuals on the autism spectrum who do not have an intellectual disability or who do not qualify for supportive services (Shattuck et al., 2007).

Formal supports

In California, regional centers are the biggest formal provider of services and support to individuals on the autism spectrum and individuals with hearing, speaking, and learning disorders. Each client has an Individualized Education Program (IEP) targeted at insuring supportive services, behavioral services, residential placements, and other services such as transportation and day services. The regional center pays for community-based services and is available for all individuals, provided they were given a diagnosis prior to age 18.

A common service provided by the regional center is Applied Behavior Analysis (ABA). ABA is then contracted out to specialists to provide in-home or local personalized care targeting behavioral interventions on a consistent schedule matched to the needs of the individual. While behavioral therapy can improve overall functional abilities, the consensus is that abilities in social functioning remain stable throughout the individual's lifespan (Brugha et al., 2011).

Special education services for persons on the autism spectrum and other neurodevelopmental disorders end after completing high school or at age 22, whichever occurs first. While an IEP will suggest the next steps to support a transition away from services received early in life, referrals are often limited to suggested recommendations. Individuals who have a developmental disability and continue onto higher education can use Section 504 accommodations through the office of disability at their individual schools. Job assistance programs and supportive higher educational programs have begun to emerge, but those are generally separate from the majority of individuals in the formal system.

Down syndrome

Considerable evidence suggests that the decline of functional abilities is associated with mortality in adults with DS (Chaney & Eyman, 2000; Esbensen et al., 2007), although other studies have found no relation (Glasson et al., 2002; Strauss & Eyman, 1996). Esbensen and colleagues (2016) found that the presence of dementia was associated with lower functional abilities among adults with DS, although dementia status did not predict level of social activities. Among adults with DS, those with dementia are more likely to need and receive self-care support (Esbensen et al., 2016).

About half of adults with DS engage in a vocational activity (Tasse et al., 2016). Tasse and colleagues found that the diagnosis of a comorbid psychiatric disorder did not affect the likelihood of having a job, though they included sheltered work programs in this analysis. Esbensen and colleagues (2016) found that adults with both DS and dementia were less likely to be engaged in vocational or educational activities than were those who had DS without dementia.

The high prevalence of multimorbidity among adults with DS, combined with the importance of physical and mental health to independent functioning, suggests that adults with DS need more frequent health screenings compared to the general adult population. Annual hearing and vision checks, as well as annual screenings for other disorders, have been recommended for adults with DS (Evenhuis, Theunissen, Denkers, Verschuure, & Kemme, 2001; van Allen, Fung, & Jurenka, 1999). In many developed countries, eligibility for geriatric health services begins at age 60 or 65. However, given that adults with DS experience aging-related health problems about two decades before neurotypical adults, this system does not account for atypical aging experienced by adults with DS. Some have argued for policy amendments to provide geriatric health services to people with DS starting at age 40; others have argued for specialized training of primary care doctors, including geriatricians, in the needs of adults with DS and other intellectual disorders (Torr et al., 2010). Multiple studies report that adults with DS have difficulty accessing mental health care services, which has been attributed in part to a lack of integration between services for intellectual disability and those for mental health (Maatta, Maatta, Taanila, Kaski, & Iivanainen, 2011; Morgan, Leonard, Bourke, & Jablensky, 2008). In particular, depression is undertreated in adults with DS (Walker et al., 2011). As we have discussed, it can be challenging to diagnose dementia or other neuropsychiatric disorders in individuals with an underlying intellectual disorder; both dementia and psychiatric disorders, including depression, may present differently in adults with DS than in neurotypical adults, necessitating modified diagnostic criteria.

Additionally, the high prevalence of multimorbidity in adults with DS frequently requires coordinated care among a team of specialists (Capone et al., 2017). These diagnostic and treatment challenges, combined with perceived and actual obstacles to communication between patients with DS and their providers, argue for specialized training to treat aging adults with DS. Indeed, primary care providers often report that they feel inadequately prepared to treat adults with DS (Pace, Shin, & Rasmussen, 2011). There is also little guidance around palliative care for adults with DS (McCallion, Ferretti, & McCarron, 2017).

Family and informal supports

Informal supports

For many persons with neurodevelopmental disorders that require assistance in daily activities, the majority of caregiving is provided through supportive family members. This type of informal support is essential for developing and maintaining social relationships, academic achievement, and navigating the formal support system.

Regardless of informal or formal placement for living arrangement, the individual's family remains extremely involved in daily care (Krauss, Seltzer, & Jacobson, 2005). One option for families is conservatorship, which is common at age 18, which facilitates help from parents or another authority; limited conservatorship is common in adults on the autism spectrum, where only delegated rights are given to the conservator. Participating in conservatorship has

reportedly good outcomes (Kirby, Schneider, Diener, & Henderson, 2019). Recently, medical insurance will still cover individuals over 26 on their parents' insurance if that individual is conserved.

Autism spectrum disorder

Often, mothers of children on the autism spectrum serve as the primary advocate and caregiver. They frequently hold working positions out of the home but earn significantly less than parents without a child on the spectrum (Zuleyha, Marcus & Mandell, 2012).

Down syndrome

The majority of adults with DS live in the home of a family member (Stancliffe et al., 2012; Tasse et al., 2016). Given that older maternal age is a primary risk factor for DS, and that adults with DS experience aging-related health problems several decades before their neurotypical counterparts, adults with DS are often in need of care from parents who are, themselves, in advanced stages of late life (i.e., senescence). This has led to a high prevalence of adults with DS living with their adult siblings (Hodapp et al., 2016). One study reports that compared to those without a comorbid psychiatric disorder, adults with DS with comorbid diagnosis of a psychiatric disorder were five times as likely to live in an intermediate care facility (Tasse et al., 2016). Another study found that adults with both DS and dementia were more likely to receive full in-residence support than were adults with DS but without dementia, either with or without a psychiatric disorder (Esbensen et al., 2016). Esbensen and colleagues found that adults with DS but without dementia were most likely to live with family members. Living in an institutional care facility is also associated with functional decline in adults with DS (Patti, Amble, & Flory, 2010).

Summary and future directions

This chapter has provided an overview of the current research on aging in persons with neurodevelopmental disorders, with a focus on ASD and DS. Improved medical technology, increased rates of service seeking and delivery to this population, and the push for social inclusion have changed the landscape for individuals currently aging with a neurodevelopmental disorder. Previously, developmental disorders have been approached through the lens of a disability model. As more value is placed on the worth of neurodiversity in our society, there is the potential for higher quality of life and better treatment outcomes for individuals with developmental disorders (Kapp, Gillespie-Lynch, Sherman, & Hutman, 2013). The trend toward strength-based research can inform and develop supportive therapy programs. Although research on persons with neurodevelopmental disorders has grown by leaps and bounds over the past few decades, there is still a great deal that is not understood about the characteristics of this population and the extent to which they are similar to and different from the larger population of older Americans.

Many issues regarding aging in the population with developmental disorders warrant additional investigation. Five stand out as particularly important. First, there is a great interest in sex differences in the features, characteristics, and outcomes in adults with neurodevelopmental disorders, specifically in persons on the autism spectrum. Future research could benefit understanding better how autism is manifested in women and considering sex as an important biological variable. In addition, it is possible that sex, gender identity, and gender expression plays a role in the diagnosis of people with autism. Most existing research has been conducted on male samples. If the diagnostic criteria are established for males, and if the preferred interests of women are more socially acceptable, this may lead to underdiagnoses of ASD in women.

Second, there exists a gap in research relating to individuals with a neurodevelopmental disorder and a cooccurring intellectual disability. Many research studies fail to include individuals with IQ lower than 70. This occurs particularly in ASD research, despite half of the ASD population having an intellectual disability.

Third, there is considerable work to do in order to optimize health care and service delivery to adults with neurodevelopmental disorders. As we have discussed, adults with neurodevelopmental disorders are significantly more likely to have cooccurring medical conditions and/or psychiatric disorders, despite the myriad of barriers to treatment that exist. Therefore, it becomes necessary to understand the social, health care access, and biological factors underlying these observations (Croen et al., 2015), with the goal of improving how physicians integrate and manage chronic disease in adolescence and adults on the autism spectrum.

Fourth, there is a need for additional real-world implementation studies focused on strength-based outcomes and a prioritization of health care to improve well-being and physical health (Warner, Parr, & Cusack, 2018). Additionally,

many research studies only include families who have insurance, which likely results in an underestimation of the extent of the current problems occurring in the formal support system.

Fifth, research on the long-term outcomes of early interventions for neurodevelopmental disorders is warranted. Research on childhood neurodevelopmental disorders has given rise to a myriad of early interventions, which have been delivered to subsets of the eligible population. The lasting effects of behavioral therapy and interventions provided by the supportive services industry are largely unknown. Studies have reported minor changes within cognitive and functional domains in the short term, although overall cognitive abilities remain relatively stable.

While ASD and DS are two of the most prevalent neurodevelopmental disorders, there are many other neurodevelopmental disorders, each with their own considerations during the aging process. There remains a great need for research on the functional abilities, health care needs, and barriers to treatment of persons with neurodevelopmental disorders in late life. Such research will ultimately inform clinicians, caregivers, and policymakers. As society gains additional understanding of this growing aging population, it is hoped that more targeted treatments will be developed to address the needs of individuals with neurodevelopmental disorders across their lifespan.

References

Adams, D., & Oliver, C. (2010). The relationship between acquired impairments of executive function and behavior change in adults with Down syndrome. *Journal of Intellectual Disability Research*, *54*(5), 393–405. Available from https://doi.org/10.1111/j.1365-2788.2010.01271.x.

American Psychiatric Association: Intellectual Disability. (2013). *DSM-5 intellectual disability fact sheet*.

Andreou, G., Galanopoulou, C., Gourgoulianis, K., Karapetsas, A., & Molyvdas, P. (2002). Cognitive status in Down syndrome individuals with sleep disordered breathing deficits (SDB). *Brain and Cognition*, *50*, 145–149.

Arumugam, A., Raja, K., Venugopalan, M., Chandrasekaran, B., Sampath, K.K., Muthusamy, H., & Shanmugam, N. (2016). Down syndrome—A narrative review with a focus on anatomical features. *Clinical Anatomy 29*(5), 568–577. https://doi.org/10.1002/ca.22672

Azizeh, B. Y., Head, E., Ibrahim, M. A., Torp, R., Tenner, A. J., Kim, R. C., … Cotman, C. W. (2000). Molecular dating of senile plaques in the brains of individuals with Down syndrome and in aged dogs. *Experimental Neurology*, *163*, 111–122.

Baddeley, A., & Jarrold, C. (2007). Working memory and Down syndrome. *Journal of Intellectual Disability Research*, *51*(pt 12), 925–931.

Ball, S. L., Holland, A. J., Treppner, P., Watson, P. C., & Huppert, F. A. (2008). Executive dysfunction and its association with personality and behaviour changes in the development of Alzheimer's disease in adults with Down syndrome and mild to moderate learning disabilities. *British Journal of Clinical Psychology*, *47*, 1–29.

Ballaban-Gil, K., Rapin, I., Tuchman, R., & Shinnar, S. (1996). Longitudinal examination of the behavioral, language, and social changes in a population of adolescents and young adults with autistic disorder. *Pediatric Neurology*, *15*(3), 217–223.

Bastiaansen, J. A., Thioux, M., Nanetti, L., van der Gaag, C., Ketelaars, C., Minderaa, R., & Keysers, C. (2011). Age-related increase in inferior frontal gyrus activity and social functioning in autism spectrum disorder. *Biological Psychiatry*, *69*(9), 832–838.

Bayen, E., Possin, K. L., Yingjia, C., de Langavant, L. C., & Yaffe, K. (2018). Prevalence of aging, dementia, and multimorbidity in older adults with Down syndrome. *JAMA Neurology*, *75*(11), 1399–1406. Available from https://doi.org/10.1001/jamaneurol.2018.2210.

Besser, L. M., Shin, M., Kucik, J. E., & Correa, A. (2007). Prevalence of down syndrome among children and adolescents in metropolitan Atlanta. *Birth Defects Research*, *79*, 765–774.

Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13-to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders*, *35*(3), 351–360.

Billstedt, E., Gillberg, C., & Gillberg, C. (2007). Autism in adults: Symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. *Journal of Child Psychology and Psychiatry*, *48*(11), 1102–1110.

Bishop-Fitzpatrick, L., Minshew, N. J., & Eack, S. M. (2014). *A systematic review of psychosocial interventions for adults with autism spectrum disorders. Adolescents and adults with autism spectrum disorders* (pp. 315–327). New York, NY: Springer.

Bittles, A. H., Bower, C., Hussain, R., & Glasson, E. J. (2006). The four ages of Down syndrome. *European Journal of Public Health*, *17*(2), 221–225. Available from https://doi.org/10.1093/eurpub/ckl103.

Bittles, A. H., & Glasson, E. J. (2004). Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Developmental Medicine & Child Neurology*, *46*(4), 282–286.

Bittles, A. H., Petterson, B. A., Sullivan, S. G., Hussain, R., Glasson, E. J., & Montgomery, P. D. (2002). The influence of intellectual disability on life expectancy. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *57*(7), M470–M472.

Bodde, A. E., & Seo, D. C. (2009). A review of social and environmental barriers to physical activity for adults with intellectual disabilities. *Disability and Health Journal*, *2*(2), 57–66. Available from https://doi.org/10.1016/j.dhjo.2008.11.004.

Boyle, C. A., Boulet, S., Schieve, L., Cohen, R. A., Blumberg, S. J., Yeargin-Allsopp, M., … Kogan, M. D. (2011). Trends in the prevalence of developmental disabilities in US children, 1997–2008. *Pediatrics*, *127*(6), 1034–1042.

Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., … Meltzer, H. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of General Psychiatry*, *68*(5), 459–465.

Burt, D. B., Loveland, K. A., & Lewis, K. R. (1992). Depression and the onset of dementia in adults with mental retardation. *American Journal of Mental Retardation*, *96*(5), 502–511.

Byrne, C., & Seyfort, B. (1998). Complications in the diagnosis and treatment of depression in persons with Down syndrome. *The NADD Bulletin*, *1*, 103−106.

Cabrejo, L., Guyant-Marechal, L., Laqurriere, A., Vercelletto, M., De la Fourniere, F., Thomas-Anterion, C., … Hannequin, D. (2006). Phenotype associated with APP duplication in five families. *Brain*, *129*, 2966−2976.

Capone, G. T., Chicoine, B., Bulova, P., Stephens, M., Hart, S., Crissman, B., … Smith, D. (2017). Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. *American Journal of Medical Genetics*, *176a*, 116−133. Available from https://doi.org/10.1002/ajmg.a.38512.

Carlesimo, G. A., Marotta, L., & Vicari, S. (1997). Long-term memory in mental retardation: Evidence for a specific impairment in subjects with Down's syndrome. *Neuropsychologia*, *35*(1), 71−79.

Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I. C., & Gillberg, C. (2008). Asperger syndrome and autism: A comparative longitudinal follow-up study more than 5 years after original diagnosis. *Journal of Autism and Developmental Disorders*, *38*(1), 72−85.

Centers for Disease Control and Prevention. (2006). *Data and statistics on down syndrome*. <https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/data.html> Accessed 06.11.17.

Centers for Disease Control and Prevention. (2018). *Data & statistics on autism spectrum disorder*. <https://www.https://www.cdc.gov/ncbddd/autism/data.html> Accessed 06.11.17.

Chaney, R. H., & Eyman, R. K. (2000). Patterns in mortality over 60 years among persons with mental retardation in a residential facility. *Mental Retardation*, *38*, 289−293.

Chapman, R. S., & Hesketh, L. J. (2000). Behavioral phenotype of individuals with Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*, 84−95.

Chapman, R. S. (1999). Language and cognitive development in children and adolescents with Down syndrome. In J. F. Miller, L. A. Leavitt, & M. Leddy (Eds.), *Improving the communication of people with Down syndrome* (pp. 41−60). Baltimore: Brookes.

Chen, C. C., Spano, G., & Edgin, J. O. (2013). The impact of sleep disruption on executive function in Down syndrome. *Research in Developmental Disabilities*, *34*, 2033−2039.

Christensen, D. L., Baio, J., Braun, K. V., Bilder, D., Charles, J., Constantino, J. N., … Yeargin-Allsopp, M. (2018). Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR Surveillance Summaries*, *65*(13), 1−23.

Collacott, R. A., Cooper, S. A., & McGrother, C. (1992). Differential rates of psychiatric disorders in adults with Down's syndrome compared with other mentally handicapped adults. *British Journal of Psychiatry*, *161*, 671−674.

Cooper, S. A., & Collacott, R. A. (1994). Clinical features and diagnostic criteria of depression in Down's syndrome. *British Journal of Psychiatry*, *165*(3), 399−403.

Cooper, S. A., Smiley, E., Allan, L., & Morrison, J. (2018). Incidence of unipolar and bipolar depression, and mania in adults with intellectual disabilities: Prospective cohort study. *The British Journal of Psychiatry*, *212*, 295−300.

Coppus, A. M. W., Evenhuis, H. M., Verberne, G. J., Visser, F. E., Oostra, B. A., Eikelenboom, P., … van Duijn, C. M. (2008). Survival in elderly persons with Down syndrome. *Journal of the American Geriatrics Society*, *56*, 2311−2316.

Correia, N., Mullally, S., Cooke, G., Tun, T. K., Phelan, N., Feeney, J., … Gibney, J. (2009). Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *The Journal of Clinical Endocrinology and Metabolism*, *94*(10), 3789−3797. Available from https://doi.org/10.1210/jc.2008-2702.

Covelli, V., Raggi, A., Meucci, P., Paganelli, C., & Leonardi, M. (2016). Ageing of people with Down's syndrome: A systematic literature review from 2000 to 2014. *International Journal of Rehabilitation Research*, *39*(1), 20−28. Available from https://doi.org/10.1097/MRR.0000000000000147.

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. *Autism*, *19*(7), 814−823.

Croen, L. A., Qian, Y., Ashwood, P., Daniels, J. L., Fallin, D., Schendel, D., & Zerbo, O. (2019). Family history of immune conditions and autism spectrum and developmental disorders: Findings from the study to explore early development. *Autism Research*, *12*(1), 123−135. Available from https://doi.org/10.1002/aur.1979.

Day, S. M., Strauss, D. J., Shavelle, R. M., & Reynolds, R. J. (2005). Mortality and causes of death in persons with Down syndrome in California. *Developmental Medicine & Child Neurology*, *47*, 171−176.

Diamandopoulos, K., & Green, J. (2018). Down syndrome: An integrative review. *Journal of Neonatal Nursing*, *24*(5), 235−241. Available from https://doi.org/10.1038/nrg1525.

Draheim, C. C. (2006). Cardiovascular disease prevalence and risk factors of persons with mental retardation. *Mental Retardation and Developmental Disabilities Research Reviews*, *12*(1), 3−12.

Dworzynski, K., Ronald, A., Bolton, P., & Happe, F. (2012). How different are girls and boys above and below the diagnostic threshold for autism spectrum disorders? *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(8), 788−797. Available from https://doi.org/10.1016/j.jaac.2012.05.018.

Eaves, L. C., & Ho, H. H. (2008). Young adult outcome of autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*(4), 739−747.

Elliott-King, J., Shaw, S., Bandelow, S., Devshi, R., Kassam, S., & Hogervorst, E. (2016). A critical literature review of the effectiveness of various instruments in the diagnosis of dementia in adults with intellectual disabilities. *Alzheimer's & Dementia*, *30*(4), 126−148.

Esbensen, A. J., Johnson, E. B., Amaral, J. L., Tan, C. M., & Macks, R. (2016). Differentiating aging among adults with Down syndrome and comorbid dementia or psychopathology. *American Journal on Intellectual and Developmental Disabilities*, *121*(1), 13–24. Available from https://doi.org/10.1352/1944-7558-121.1.13.

Esbensen, A. J., Seltzer, M. M., & Greenberg, J. S. (2007). Factors predicting mortality in midlife adults with and without Down syndrome living with family. *Journal of Intellectual Disability Research*, *51*(pt 12), 1039–1050.

Evenhuis, H. M., Sjoukes, L., Koot, H. M., & Kooijman, A. C. (2009). Does visual impairment lead to additional disability in adults with intellectual disabilities? *Journal of Intellectual Disability Research*, *53*(1), 19–28. Available from https://doi.org/10.1111/j.1365-2788.2008.01114.x.

Evenhuis, H. M., Theunissen, M., Denkers, I., Verschuure, H., & Kemme, H. (2001). Prevalence of visual and hearing impairment in a Dutch institutionalized population with intellectual disability. *Journal of Intellectual Disability Research*, *45*(pt 5), 457–464.

Farley, M. A., McMahon, W. M., Fombonne, E., Jenson, W. R., Miller, J., Gardner, M., ... Coon, H. (2009). Twenty year outcome for individuals with autism and average or near average cognitive abilities. *Autism Research*, *2*(2), 109–118.

Firth, N. C., Startin, C. M., Hithersay, R., Hamburg, S., Wijeratne, P. A., Mok, K. Y., ... Strydom, A. (2018). Aging related cognitive changes associated with Alzheimer's disease in Down syndrome. *Annals of Clinical and Translational Neurology*, *5*(6), 741–751. Available from https://doi.org/10.1002/acn3.571.

Fletcher, R., Loschen, E., Stavrakaki, C., & First, M. (2007). *Diagnostic manual intellectual disability (DM-ID): A clinical guide for diagnosis of mental disorders in persons with intellectual disability*. Kingston, NY: National Association for the Dually Diagnosed.

Frenkel, S., & Bourdin, B. (2009). Verbal, visual, and spatio-sequential short-term memory: Assessment of the storage capacities of children and teenagers with Down's syndrome. *Journal of Intellectual Disability Research*, *53*(2), 152–160. Available from https://doi.org/10.1111/j.1365-2788.2008.01139.x.

Friedman, J. M. (2001). Racial disparities in median age at death of persons with Down syndrome—United States, 1968–1997. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*, *50*, 463–465.

Ganz, M. L. (2007). The lifetime distribution of the incremental societal costs of autism. *Archives of Pediatrics & Adolescent Medicine*, *161*(4), 343–349.

Geurts, H. M., & Vissers, M. E. (2012). Elderly with autism: Executive functions and memory. *Journal of Autism and Developmental Disorders*, *42*(5), 665–675.

Gillberg, C., Billstedt, E., Sundh, V., & Gillberg, I. C. (2010). Mortality in autism: A prospective longitudinal community-based study. *Journal of Autism and Developmental Disorders*, *40*(3), 352–357.

Gillberg, I. C., Helles, A., Billstedt, E., & Gillberg, C. (2016). Boys with Asperger syndrome grow up: Psychiatric and neurodevelopmental disorders 20 years after initial diagnosis. *Journal of Autism and Developmental Disorders*, *46*(1), 74–82.

Gillespie-Lynch, K., Sepeta, L., Wang, Y., Marshall, S., Gomez, L., Sigman, M., & Hutman, T. (2012). Early childhood predictors of the social competence of adults with autism. *Journal of Autism and Developmental Disorders*, *42*(2), 161–174.

Girimaji, S. C., & Pradeep, A. J. V. (2018). Intellectual disability in international classification of Diseases-11: A developmental perspective. *Indian Journal of Social Psychiatry*, *34*(5), 68.

Glasson, E. J., Sullivan, S. G., Petterson, B. A., Montgomery, P. D., & Bittles, A. H. (2002). The changing survival profile of people with Down's syndrome: Implications for genetic counseling. *Clinical Genetics*, *62*(5), 390–393.

Greenwood, N. W., Wang, C. T., Bowen, D., & Wilkinson, J. (2014). Testing the feasibility of a DVD-based intervention to promote preparedness for mammography in women with intellectual disabilities. *Journal of Cancer Education*, *29*(1), 99–105. Available from https://doi.org/10.1007/s13187-013-0554-1.

Grieco, J., Pulsifer, M., Seligsohn, K., Skotko, B., & Schwartz, A. (2015). Down syndrome: Cognitive and behavioral functioning across the lifespan. *American Journal of Medical Genetics Part C*, *169*, 135–149.

Happé, F., & Charlton, R. A. (2012). Aging in autism spectrum disorders: A mini-review. *Gerontology*, *58*(1), 70–78.

Haveman, M. (2019). Aging and physical health. In V. Prasher, & M. Janicki (Eds.), *Physical health of adults with intellectual and developmental disabilities*. Cham: Springer.

Holmes, G. (2009). The long term effects of Neonatal seizures. *Clinics in Perinatology*, *36*(4), 901–914. Available from https://doi.org/10.1016/j.clp.2009.07.012.

National Center for Health Statistics. (2001). *Health, United States, 2001: With urban and rural health chart book*. (DHHS publication no. 01-1232). Hyattsville, MD: National Center for Health Statistics.

Heller, T., Stafford, P., Davis, L. A., Sedlezky, L., & Gaylord, V. (2010). People with intellectual and developmental disabilities growing old: An overview. *Impact: Feature Issue on Aging and People with Intellectual and Developmental Disabilities*, *23*(1), 2–3.

Henderson, A., Lynch, S., Wilkinson, S., & Hunter. (2007). Adults with Down syndrome: The prevalence of complications and health care in the community. *British Journal of General Practice*, *57*(534), 50–55.

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. *British Journal of Psychiatry*, *208*(3), 232–238.

Hithersay, R., Startin, C. M., Hambur, S., Mok, K. Y., Hardy, J., Fisher, E. M. C., ... Strydom, A. (2019). Association of dementia with mortality among adults with Down syndrome older than 35 years. *JAMA Neurology*, *76*(2), 152–160. Available from https://doi.org/10.1001/jamaneurol.2018.3616.

Hodapp, R. M., Burke, M. M., Finley, C. I., & Urbano, R. C. (2016). Family caregiving of aging adults with Down syndrome. *Journal of Policy and Practice in Intellectual Disabilities*, *13*(2), 181–189. Available from https://doi.org/10.1111/jppi.12153.

Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2004). Adult outcome for children with autism. *Journal of Child Psychology and Psychiatry*, *45*(2), 212–229.

Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2014). Cognitive and language skills in adults with autism. *Journal of Child Psychology and Psychiatry*, *45*, 212–229.

Howlin, P., Mawhood, L., & Rutter, M. (2000). Autism and developmental receptive language disorder—A follow-up comparison in early adult life. II: Social, behavioural, and psychiatric outcomes. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *41*(5), 561–578.

Howlin, P., Moss, P., Savage, S., & Rutter, M. (2013). Social outcomes in mid-to later adulthood among individuals diagnosed with autism and average nonverbal IQ as children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(6), 572–581.

Janicki, M. P., & Dalton, A. J. (2000). Prevalence of dementia and impact on intellectual disability services. *Mental Retardation*, *38*(3), 276–286.

Joffe, V., & Varlokosta, S. (2007). Patterns of syntactic development in children with Williams syndrome and Down's syndrome: Evidence from passives and wh-questions. *Clinical Linguistics and Phonetics*, *21*(9), 705–727.

Johannsen, P., Christensen, J. E., Goldstein, H., Nielsen, V. K., & Mai, J. (1996). Epilepsy in Down syndrome—Prevalence in three age groups. *Seizure*, *5*(2), 121–125.

Kapp, S. K., Gillespie-Lynch, K., Sherman, L. E., & Hutman, T. (2013). Deficit, difference, or both? Autism and neurodiversity. *Developmental psychology*, *49*(1), 59.

Kazemi, M., Salehi, M., & Kheirollahi, M. (2016). Down syndrome: Current status, challenges and future perspectives. *International Journal of Molecular and Cellular Medicine*, *5*(13), 125–133.

Kerr, M., Dunstan, F., & Thapar, A. (1996). Attitudes of general practitioners to caring for people with learning disability. *British Journal of Clinical Psychology*, *46*(403), 92–94.

Kim, J. A., Szatmari, P., Bryson, S. E., Streiner, D. L., & Wilson, F. J. (2000). The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. *Autism*, *4*, 117–132.

Kirby, S., & Hegarty, J. (2010). Breast awareness within an intellectual disability setting. *European Journal of Oncology Nursing*, *14*(4), 328–336. Available from https://doi.org/10.1016/j.ejon.2010.03.005.

Kinnear, D., Morrison, J., Allan, L., Henderson, A., Smiley, E., & Cooper, S. A. (2018). Prevalence of physical conditions and multimorbidity in a cohort of adults with intellectual disabilities with and without Down syndrome: Cross-sectional study. *BMJ Open*, *8*(2). Available from https://doi.org/10.1136/bmjopen-2017-018292.

Kirby, A. V., Schneider, M., Diener, M., & Henderson, J. (2019). "Who is going to pay for the Wi-Fi?" Exploring adulthood from the perspectives of autistic youth. *Autism in Adulthood*, *1*(1), 37–43.

Kobayashi, R., Murata, T., & Yoshinaga, K. (1992). A follow-up study of 201 children with autism in Kyushu and Yamaguchi areas, Japan. *Journal of Autism and Developmental Disorders*, *22*(3), 395–411.

Krahn, G. L., Hammond, L., & Turner, A. (2006). A cascade of disparities: Health and health care access for people with intellectual disabilities. *Mental Retardation and Developmental Disabilities Research Reviews*, *12*(1), 70–82.

Krauss, M. W., Seltzer, M. M., & Jacobson, H. T. (2005). Adults with autism living at home or in non-family settings: Positive and negative aspects of residential status. *Journal of Intellectual Disability Research*, *49*, 111–124.

Krinsky-McHale, S. J., Devenny, D. A., Gu, H., Jenkins, E. C., Kittler, P., Murty, V. V., … Silverman, W. (2008). Successful aging in a 70-year-old man with Down syndrome: A case study. *Intellectual and Developmental Disabilities*, *46*, 215–228.

Kumada, T., Ito, M., Miyajima, T., Fujii, T., Okuno, T., Go, T., … Hamada, Y. (2005). Multi-institutional study on the correlation between chromosomal abnormalities and epilepsy. *Brain & Development*, *27*(2), 127–134.

Lai, F., & Williams, R. S. (1989). A prospective study of Alzheimer's disease in Down's syndrome. *Archives of Neurology*, *46*, 849–853.

Lal, C., White, D. R., Joseph, J. E., van Bakergem, K., & LaRosa, A. (2015). Sleep disordered breathing in Down syndrome. *Chest*, *147*(2), 570–579. Available from https://doi.org/10.1378/chest.14-0266.

Lanfranchi, S., Carretti, B., Spano, G., & Cornoldi, C. (2009). A specific deficit in visuospatial simultaneous working memory in Down syndrome. *Journal of Intellectual Disability Research*, *53*(5), 474–483.

Larsen, F., & Kirkevold, O. (2008). The aging population with Down syndrome in Norway, 1969–2045. *Journal of Intellectual Disability Research*, *52*, 644.

Lautarescu, B. A., Holland, A. J., & Zaman, S. H. (2017). The early presentation of dementia in people with Down syndrome: A systematic review of longitudinal studies. *Neuropsychology Review*, *27*, 31–45.

Lazarus, A., Jaffe, R. L., & Dubin, W. R. (1990). Electroconvulsive therapy and major depression in Down's syndrome. *Journal of Clinical Psychiatry*, *51*(10), 422–425.

Leonard, S., Bower, C., Petterson, B., & Leonard, H. (2000). Survival of infants born with Down's syndrome: 1980–96. *Paediatric and Perinatal Epidemiology*, *14*, 163–171.

Letourneau, A., & Antonarakis, S.E. (2012). Genomic determinants in the phenotypic variability of Down syndrome. In M. Dierssen, & R. de la Torre (Eds.), *Progress in Brain Research* (pp. 15–28).

Leverenz, J. B., & Raskind, M. A. (1998). Early amyloid deposition in the medial temporal lobe of young Down syndrome patients: A regional quantitative analysis. *Experimental Neurology*, *150*, 296–304.

Levorato, M. C., Roch, M., & Beltrame, R. (2009). Text comprehension in Down syndrome: The role of lower and higher level abilities. *Clinical Linguistics and Phonetics*, *23*(4), 285–300. Available from https://doi.org/10.1080/02699200802673259.

Lindsay, W. R., Howells, L., & Pitcaithly, D. (1993). Cognitive therapy for depression with individuals with intellectual disabilities. *British Journal of Clinical Psychology*, *66*(pt 2), 135–141.

Loane, M., Morris, J. K., Addor, M. C., Arriola, L., Budd, J., Doray, B., & Melve, K. K. (2013). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: Impact of maternal age and prenatal screening. *European Journal of Human Genetics*, *21*, 27–33.

Lott, I.T. (2012). Neurological phenotypes for Down syndrome across the life span. *Progress in Brain Research*, *197*, 101–121.

Lott, I. T., & Dierssen, M. (2010). Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurology*, *9*(6), 623–633. Available from https://doi.org/10.1016/S1474-4422(10)70112-5.

Lott, I. T., & Lai, F. (1982). Dementia in Down's syndrome: Observations from a neurology clinic. *Applied Research in Mental Retardation*, *3*(3), 233–239.

Maatta, T., Maatta, T. T., Taanila, A., Kaski, M., & Iivanainen, M. (2011). Mental health, behaviour and intellectual abilities of people with Down syndrome. *Down Syndrome Research and Practice*, *11*(1), 37–43.

Magiati, I., Tay, X. W., & Howlin, P. (2014). Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. *Clinical Psychology Review*, *34*(1), 73–86.

Mahan, S., & Kozlowski, A. M. (2011). *Adults with autism Spectrum disorders. International handbook of autism and pervasive developmental disorders* (pp. 521–538). New York, NY: Springer.

Manton, K. G., & Gu, X. (2001). Changes in the prevalence of chronic disability in the United States black and nonblack population above age 65 from 1982 to 1999. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(11), 6354–6359.

Mantry, D., Cooper, S. A., Smiley, E., Morrison, J., Allan, L., Williamson, A., & Jackson, A. (2008). The prevalence and incidence of mental ill-health in adults with Down syndrome. *Journal of Intellectual Disability Research*, *52*, 141–155.

Matson, J. L., & Cervantes, P. E. (2014). Commonly studied comorbid psychopathologies among persons with autism spectrum disorder. *Research in Developmental Disabilities*, *35*, 952–962.

Mawhood, L., Howlin, P., & Rutter, M. (2000). Autism and developmental receptive language disorder—A comparative follow-up in early adult life. I: Cognitive and language outcomes. *Journal of Child Psychology and Psychiatry*, *41*(5), 547–559.

McCallion, P., Ferretti, H. B., & McCarron, M. (2017). Epidemiological issues in intellectual disability and aging research. In V. P. Prasher, & M. P. Janicki (Eds.), *Physical health of adults with intellectual and developmental disabilities* (pp. 9–26). Switzerland: Springer.

McCarron, M., McCallion, P., Reilly, E., Dunne, P., Carroll, R., & Mulryan, N. (2017). A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *Journal of Intellectual Disability Research*, *61*(9), 843–852. Available from https://doi.org/10.1111/jir.12390.

McCarron, M., McCallion, P., Reilly, E., & Mulryan, N. (2014). A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome. *Journal of Intellectual Disability Research*, *58*, 61–70.

Mcdermott, S., Moran, R., Platt, T., Wood, H., Isaac, T., & Dasari, S. (2005). Prevalence of epilepsy in adults with mental retardation and related disabilities in primary care. *American Journal of Mental Retardation*, *110*(1), 48–56.

McCabe, M. P., McGillivray, J. A., & Newton, D. C. (2006). Effectiveness of treatment programmes for depression among adults with mild/moderate intellectual disability. *Journal of Intellectual Disability Research*, *50*(4), 239–247. Available from https://doi.org/10.1111/j.1365-2788.2005.00772.x.

McVicker, R. W., Shanks, O. E., & McClelland, R. J. (1994). Prevalence and associated features of epilepsy in adults with Down's syndrome. *British Journal of Clinical Psychology*, *164*(4), 528–532.

Menendez, M. (2005). Down syndrome, Alzheimer's disease and seizures. *Brain & Development*, *27*(4), 246–252.

Minihan, P. M., Robey, K. L., Long-Bellil, L. M., Graham, C. L., Hahn, J. E., Woodard, L., & Eddey, G. E. (2011). Desired educational outcomes of disability-related training for the generalist physician: Knowledge, attitudes, and skills. *Academic Medicine*, *86*(9), 1171–1178. Available from https://doi.org/10.1097/ACM.0b013e3182264a25.

Morgan, V. A., Leonard, H., Bourke, J., & Jablensky, A. (2008). Intellectual disability co-occurring with schizophrenia and other psychiatric illness: Population-based study. *British Journal of Psychiatry*, *193*, 364–372.

Mouridsen, S. E., Brønnum-Hansen, H., Rich, B., & Isager, T. (2008). Mortality and causes of death in autism spectrum disorders: An update. *Autism*, *12*(4), 403–414.

Mula, M., & Trimble, M. R. (2009). Antiepileptic drug-induced cognitive adverse effects: Potential mechanisms and contributing factors. *CNS Drugs*, *23*(2), 121–137. Available from https://doi.org/10.2165/00023210-200923020-00003.

Myers, B. A., & Pueschel, S. M. (1995). Major depression in a small group of adults with Down syndrome. *Research in Developmental Disabilities*, *16*(4), 285–299.

Ng, N., Flygare Wallén, E., & Ahlström, G. (2017). Mortality patterns and risk among older men and women with intellectual disability: A Swedish national retrospective cohort study. *BMC Geriatrics*, *17*(1), 269. Available from https://doi.org/10.1186/s12877-017-0665-3.

Ortman, J. M., Velkoff, V. A., & Hogan, H. (2014). *An aging nation: The older population in the United States* (pp. 25–1140). Washington, DC: United States Census Bureau, Economics and Statistics Administration, US Department of Commerce.

Pace, J. E., Shin, M., & Rasmussen, S. A. (2011). Understanding physicians' attitudes toward people with Down syndrome. *American Journal of Medical Genetics*, *155A*(6), 1258–1263. Available from https://doi.org/10.1002/ajmg.a.34039.

Parish, S. L., Swaine, J. G., Luken, K., Rose, R. A., & Dababnah, S. (2012). Cervical and breast cancer-screening knowledge of women with developmental disabilities. *Intellectual & Developmental Disabilities*, *50*, 79–91.

Patti, P., Amble, K., & Flory, M. (2010). Placement, relocation and end of life issues in aging adults with and without Down's syndrome: A retrospective study. *Journal of Intellectual Disability Research*, *54*, 538–546.

Penrose, L. S. (1933). Mental defect, London: Sidgwick & Jackson Ltd *Journal of Mental Science*, *80*(328), 114–115.

Penrose, L. S. (1949). The incidence of Mongolism in the general population. *Journal of Mental Science*, *95*, 685–688.

Perkins, A. (2017). The lowdown on Down syndrome. *Wolters Kluwer Health*, *15*, 40–46.

Pezzementi, M. L., & Fisher, M. A. (2005). Oral health status of people with intellectual disabilities in the southeastern United States. *Journal of the American Dental Association*, *136*(7), 903–912.

Pharr, J. R., & Bungum, T. (2012). Health disparities experienced by people with disabilities in the United States: A behavioral risk factor surveillance system study. *Global Journal of Health Science*, *4*, 99–108. Available from https://doi.org/10.5539/gjhs.v4n6p99.

Piven, J., Rabins, P., & Autism in Older Adults Working Group. (2011). Autism spectrum disorders in older adults: Toward defining a research agenda. *Journal of the American Geriatrics Society*, *59*(11), 2151–2155.

Prasher, V. P., & Krishnan, V. H. R. (1993). Age of onset and duration of dementia in people with Down's syndrome: Integration of 98 reported cases in the literature. *International Journal of Geriatric Psychiatry*, *8*, 915–922.

Presson, A. P., Partyka, G., Jensen, K. M., Devine, O. J., Rassmussen, S. A., McCabe, L. L., & McCabe, E. R. B. (2013). Current estimate of Down syndrome population prevalence in the United States. *Journal of Pediatrics*, *163*(4), 1163–1168. Available from https://doi.org/10.1016/j.jpeds.2013.06.013.

Prince, M., & Jackson, J. (2009). *World Alzheimer's Report London* (pp. 1–96). United Kingdom: Alzheimer's Disease International.

Puri, B. K., Ho, K. W., & Signh, I. (2001). Age of seizure onset in adults with Down's syndrome. *International Journal of Clinical Practice*, *55*(7), 442–444.

Reichard, A., & Stolze, H. (2011). Diabetes among adults with cognitive limitations compared to individuals with no cognitive disabilities. *Journal of Intellectual and Developmental Disability*, *49*(3), 141–154. Available from https://doi.org/10.1352/1934-9556-49.2.141.

Reichard, A., Stolze, H., & Fox, M. H. (2011). Diabetes among adults with cognitive limitations compared to individuals with no cognitive disabilities. *Disability and Health Journal*, *4*(2), 59–67. Available from https://doi.org/10.1016/j.dhjo.2010.05.003.

Reiss, S., Levitan, G. W., & Szyszko, J. (1982). Emotional disturbance and mental retardation: Diagnostic overshadowing. *American Journal of Mental Deficiency*, *86*(6), 567–574.

Renty, J., & Roeyers, H. (2007). Individual and marital adaptation in men with autism spectrum disorder and their spouses: The role of social support and coping strategies. *Journal of Autism and Developmental Disorders*, *37*(7), 1247–1255.

Resta, O., Barbaro, M. P. F., Giliberti, T., Caratozzolo, G., Cagnazzo, M. G., Scarpelli, F., & Nocerino, M. C. (2003). Sleep related breathing disorders in adults with Down syndrome. *Down Syndrome Research and Practice*, *8*(3), 115–119.

Roizen, N. J., & Patterson, D. (2003). Down's syndrome. *Lancet*, *361*(9365), 1281–1289.

Roux, A.M., Shattuck, P.T., Rast, J.E., Rava, J.A., & Anderson, K.A. (2015). *National autism indicators report: Transition into young adulthood*. Life Course Outcomes Research Program, AJ Drexel Autism Institute, Drexel University, Philadelphia, PA.

Rumble, B., Retallack, R., Hilbich, C., Simms, G., Multhaup, G., Martins, R., & Masters, C. L. (1989). Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. *The New England Journal of Medicine*, *320*(22), 1446–1452.

Rurangirwa, J., Van Naarden Braun, K., Schendel, D., & Yeargin-Allsopp, M. (2006). Healthy behaviors and lifestyles in young adults with a history of developmental disabilities. *Research in Developmental Disabilities*, *27*(4), 381–399.

Scepters, M., Keer, M., O'Hara, D., Bainbridge, D., Cooper, S. A., Davis, R., & Wehmeyer, M. (2005). Reducing health disparity in people with intellectual disabilities: A report from the health issues special interest research group of the International Association of Intellectual Disability. *Journal of Policy and Practice in Intellectual Disabilities*, *2*(3–4), 249–255.

Schoeni, R. F., Freedman, V. A., & Wallace, R. B. (2001). Persistent, consistent, widespread, and robust? Another look at recent trends in old-age disability. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *56*(4), S206–S218.

Seltzer, M. M., Krauss, M. W., Shattuck, P. T., Orsmond, G., Swe, A., & Lord, C. (2003). The symptoms of autism spectrum disorders in adolescence and adulthood. *Journal of Autism and Developmental Disorders*, *33*(6), 565–581.

Seltzer, M. M., Shattuck, P., Abbeduto, L., & Greenberg, J. S. (2004). Trajectory of development in adolescents and adults with autism. *Mental Retardation and Developmental Disabilities Research Reviews*, *10*(4), 234–247.

Shattuck, P. T., Roux, A. M., Hudson, L. E., Taylor, J. L., Maenner, M. J., & Trani, J. F. (2012). Services for adults with an autism spectrum disorder. *The Canadian Journal of Psychiatry*, *57*(5), 284–291.

Shattuck, P. T., Seltzer, M. M., Greenberg, J. S., Orsmond, G. I., Bolt, D., Kring, S., . . . Lord, C. (2007). Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *37*(9), 1735–1747.

Shavelle, R. M., Strauss, D. J., & Pickett, J. (2001). Causes of death in autism. *Journal of Autism and Developmental Disorders*, *31*(6), 569–576.

Smiley, E., & Cooper, S. A. (2003). Intellectual disabilities, depressive episode, diagnostic criteria and diagnostic criteria for psychiatric disorders for use with adults with learning disabilities/mental retardation (DC-LD). *Journal of Intellectual Disability Research*, *47*, 62–71.

Spence, S. J., & Schneider, M. T. (2009). The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatric Research*, *65*(6), 599.

Stancliffe, R. J., Lakin, K. C., Larson, S. A., Engler, J., Taub, S., Fortune, J., & Bershadsky, J. (2012). Demographic characteristics, health conditions, and residential service use in adults with Down syndrome in 25 US states. *Intellectual and Developmental Disabilities*, *50*, 92–108.

Startin, C. M., Hamburg, S., Hithersay, R., Al-Janabi, T., Mok, K. Y., Hardy, J., . . . Strydom, A. (2019). Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome. *Alzheimer's & Dementia*, *15*, 245–257.

Strauss, D., & Eyman, R. K. (1996). Mortality of people with mental retardation in California with and without Down syndrome, 1986–1991. *American Journal on Mental Retardation*, *100*(6), 643–653.

Strydom, A., Shooshtari, S., Lee, L., Raykar, V., Torr, J., Tsiouris, J., ... Maaskant, M. (2010). Dementia in older adults with intellectual disabilities—Epidemiology, presentation, and diagnosis. *Journal of Policy and Practice in Intellectual Disabilities*, *7*(2), 96–110.

Swaine, J. G., Parish, S. L., Luken, K., Son, E., & Dickens, P. (2014). Test of an intervention to improve knowledge of women with intellectual disabilities about cervical and breast cancer screening. *Journal of Intellectual Disability Research*, *58*, 651–663.

Szatmari, P., Chawarska, K., Dawson, G., Georgiades, S., Landa, R., Lord, C., ... Halladay, A. (2016). Prospective longitudinal studies of infant siblings of children with autism: Lessons learned and future directions. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(3), 179–187. Available from https://doi.org/10.1016/j.jaac.2015.12.014.

Tasse, M. J., Macho, P. N., Havercamp, S. M., Benson, B. A., Allain, D. C., Manickam, K., & Davis, S. (2016). Psychiatric conditions prevalent among adults with Down syndrome. *Journal of Policy and Practice in Intellectual Disabilities*, *2*, 173–180. Available from https://doi.org/10.1111/jppi.12156.

Taylor, J. L., & Seltzer, M. M. (2011). Employment and post-secondary educational activities for young adults with autism spectrum disorders during the transition to adulthood. *Journal of Autism and Developmental Disorders*, *41*(5), 566–574.

Tobin, M. C., Drager, K. D., & Richardson, L. F. (2014). A systematic review of social participation for adults with autism spectrum disorders: Support, social functioning, and quality of life. *Research in Autism Spectrum Disorders*, *8*(3), 214–229.

Torr, J., Strydom, A., Patti, P., & Jokinen, N. (2010). Aging in Down syndrome: Morbidity and mortality. *Journal of Policy and Practice in Intellectual Disabilities*, *7*(1), 70–81.

Traci, M. A., Seekins, T., Szali-Petree, A., & Ravesloot, C. (2002). Assessing secondary conditions among adults with developmental disabilities: A preliminary study. *Mental Retardation*, *40*(2), 119–131.

Trois, M. S., Capone, G. T., Lutz, J. A., Melendres, M. C., Schwartz, A. R., Collop, N. A., & Marcus, C. L. (2009). Obstructive sleep apnea in adults with Down syndrome. *Journal of Clinical Sleep Medicine*, *15*, 317–323.

Tsiouris, J. A., Patti, P. J., Tipu, O., & Raguthu, S. (2002). Adverse effects of phenytoin given for late-onset seizures in adults with Down syndrome. *Neurology*, *59*(5), 779–780.

Tyler, C. V., Schramm, S. C., Karafa, M., Tang, A. S., & Jain, A. K. (2010). Electronic health record analysis of the primary care of adults with intellectual and other developmental disabilities. *Journal of Policy and Practice in Intellectual Disabilities*, *7*, 204–210.

U.S. Census Bureau. *Table 2a: Projected population of the United States, by age and sex: 2000 to 2050.* <www.census.gov/population/www/projections/usinterimproj/natprojtab02a.pdf> Accessed 19.05.10.

UN General Assembly (2007). *Convention on the rights of persons with disabilities: Resolution/adopted by the General Assembly*, A/RES/61/106, <http://www.refworld.org/docid/45f973632.html> Accessed 19.03.16.

van Allen, M. I., Fung, J., & Jurenka, S. B. (1999). Health care concerns and guidelines for adults with Down syndrome. *American Journal of Medical Genetics*, *89*(2), 100–110.

Vicari, S. (2001). Implicit versus explicit memory function in children with Down and Williams syndrome. *Down Syndrome Research and Practice*, *7*(1), 35–40.

Walker, J. C., Dosen, A., Buitelaar, J. K., & Janzing, J. G. E. (2011). Depression in Down syndrome: A review of the literature. *Research in Developmental Disabilities*, *32*, 1432–1440.

Ward, R. L., Nichols, A. D., & Freedman, R. I. (2010). Uncovering healthcare inequalities among adults with intellectual and developmental disabilities. *Health & Social Work*, *35*, 280–290.

Warner, G., Parr, J. R., & Cusack, J. (2018). Workshop report: Establishing priority research areas to improve the physical health and well-being of autistic adults and older people. *Autism in Adulthood*, *1*(1), 6–12. Available from https://doi.org/10.1089/aut.2018.0003.

Warren, A. C., Holroyd, S., & Folstein, M. F. (1989). Major depression in Down's syndrome. *British Journal of Psychiatry*, *155*, 202–205.

Weijerman, M. E., Van Furth, A. M., Noordegraaf, A. V., Van Wouwe, J. P., Broers, C. J., & Gemke, R. J. (2008). Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: A national study. *Journal of Pediatrics*, *152*, 15–19.

Werling, D. M., & Geschwind, D. H. (2013). Sex differences in autism spectrum disorders. *Current Opinion in Neurology*, *26*, 146–153.

Westmark, C. J., Westmark, P. R., Bear, A. M., Hildebrandt, S. M., & Malter, J. S. (2008). Seizure susceptibility and mortality in mice that overexpress amyloid precursor protein. *International Journal of Clinical and Experimental Pathology*, *1*(2), 157–168.

Whitehouse, A. J., Line, E. A., Watt, H. J., & Bishop, D. V. (2009). Qualitative aspects of developmental language impairment relate to language and literacy outcome in adulthood. *International Journal of Language & Communication Disorders*, *44*(4), 489–510.

Whitehouse, A. J., Watt, H. J., Line, E. A., & Bishop, D. V. (2009). Adult psychosocial outcomes of children with specific language impairment, pragmatic language impairment and autism. *International Journal of Language & Communication Disorders*, *44*(4), 511–528.

Willner, P. (2005). The effectiveness of psychotherapeutic interventions for people with learning disabilities: A critical overview. *Journal of Intellectual Disability Research*, *49*(1), 73–85.

Young, T. (1993). Analytic epidemiology studies of sleep disordered breathing—What explains the gender difference in sleep disordered breathing? *Sleep*, *16*(8), S1–S2.

Ypsilanti, A., Grouios, G., Alevriadou, A., & Tsapkini, K. (2005). Expressive and receptive vocabulary in children with Williams and Downs syndromes. *Journal of Intellectual Disability Research*, *49*(5), 353–364.

Zerbo, O., Massolo, M. L., Qian, Y., & Croen, L. A. (2015). A study of physician knowledge and experience with autism in adults in a large integrated healthcare system. *Journal of Autism and Developmental Disorders*, *45*(12), 4002–4014.

Zerbo, O., Qian, Y., Ray, T., Sidney, S., Rich, S., Massolo, M., & Croen, L. (2018). *Autism in Adulthood*, *1*(1), 18–27. Available from https://doi.org/10.1089/aut.2018.0004.

Zuleyha, C., Marcus, S. C., & Mandell, D. S. (2012). Implications of childhood autism for parental employment and earnings. *Pediatrics*, *129*(4), 617–623.

Further reading

A.J. Drexel Autism Institute. (2015). *Life course outcomes research program.* Philadelphia, PA: Drexel University.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th Ed.). Arlington, VA.

Anonymous. (2013). Strengthening connections between Down syndrome and AD. *The Lancet Neurology*, *12*(10), 931. Available from https://doi.org/10.1016/S1474-4422(13)70228-X.

Caraci, F., Iulita, F. M., Pentz, R., Aguilar, L. F., Orciani, C., Barone, C., … Cuello, C. A. (2017). Searching for new pharmacological targets for the treatment of Alzheimer's disease in Down syndrome. *European Journal of Pharmacology*, *817*, 7–19.

Carulla, L. S., Reed, G. M., Vaez-Azizi, L. M., Cooper, S. A., Leal, R. M., Bertelli, M., … Girimaji, S. C. (2011). Intellectual developmental disorders: Towards a new name, definition and framework for "mental retardation/intellectual disability" in ICD-11. *World Psychiatry*, *10*(3), 175–180.

Cipriani, G., Danti, S., Carlesi, C., & Di Fiorino, M. (2018). Aging with Down syndrome: The dual diagnosis: Alzheimer's disease and Down syndrome. *American Journal of Alzheimer's Disease & Other Dementias*, *33*(4), 253–262. Available from https://doi.org/10.1177/1533317518761093.

Dekker, A. D., Strydom, A., Coppus, A. M. W., Nizetic, D., Vermeiren, Y., Naudé, P. J. W., … de Deyn, P. P. (2015). Behavioural and psychological symptoms of dementia in Down syndrome: Early indicators of clinical Alzheimer's disease*? Cortex*, *73*, 36. Available from https://doi.org/10.1016/j.cortex.2015.07.032.

Environmental Protection Agency. *America's children and the environment*.

Flatt, T. (2012). A new definition of aging? *Frontiers in genetics*, *3*, 148.

Fombonne, E. (2005). The epidemiology of pervasive developmental disorders. In M. F. Casanova (Ed.), *Recent developments in autism research* (pp. 1–25). New York: Nova Science Publishers Inc.

Freedman, V. A., & Martin, L. G. (1998). Understanding trends in functional limitations among older Americans. *American Journal of Public Health*, *88*(10), 1457–1462.

Hartley, D., Blumenthal, T., Carrillo, M., DiPaolo, G., Esralew, L., Gardiner, K., … Wisniewski, T. (2015). Down syndrome and Alzheimer's disease: Common pathways, common goals. *Alzheimers Dement*, *11*(6), 700–709. Available from https://doi.org/10.1016/j.jalz.2014.10.007.

Head, E., Silverman, W., Patterson, D., & Lott, I. T. (2012). Aging and Down syndrome. *Current Gerontology and Geriatrics Research*, *2012*, 1–6. Available from https://doi.org/10.1155/2012/412536.

Horvath, S., Garagnani, P., Bacalini, M. G., Pirazzini, C., Salvioli, S., Gentilini, D., … Franceschi, C. (2015). Accelerated epigenetic aging in Down Syndrome. *Aging Cell*, *14*, 491–495.

Howlin, P., & Moss, P. (2012). Adults with autism spectrum disorders. *The Canadian Journal of Psychiatry*, *57*(5), 275–283.

Janicki, M. P., Henderson, C. M., Rubin, I. L., & Neurodevelopmental Conditions Study Group. (2008). Neurodevelopmental conditions and aging: Report on the Atlanta study group charrette on neurodevelopmental conditions and aging. *Disability and Health Journal*, *1*(2), 116–124.

Jasien, J. M., Daimon, C. M., Wang, R., Shapiro, B. K., Martin, B., & Maudsley, S. (2014). The effects of aging on the BTBR mouse model of autism spectrum disorder. *Frontiers in Aging Neuroscience*, *6*, 225.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217–250.

Kim, J. A., Szatmari, P., Bryson, S. E., Streiner, D. L., & Wilson, F. J. (2000). The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. *Autism*, *4*, 117–132.

Krahn, G. L., & Drum, C. E. (2007). Translating policy principles into practice to improve health care access for adults with intellectual disabilities: A research review of the past decade. *Mental Retardation and Developmental Disabilities Research Reviews*, *13*(2), 160–168.

Krauss, M. W., Gulley, S., Sciegaj, M., & Wells, N. (2003). Access to specialty medical care for children with mental retardation, autism, and other special health care needs. *Mental Retardation*, *41*(5), 329–339.

Maddox, B. B., & Gaus, V. L. (2018). Community mental health services for autistic adults: Good news and bad news. *Autism in Adulthood*, *1*(1), 13–17. Available from https://doi.org/10.1089/aut.2018.0006.

Marriage, S., Wolverton, A., & Marriage, K. (2009). Autism spectrum disorder grown up: A chart review of adult functioning. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *18*(4), 322.

Mukaetova-Ladinska, E. B., & Stuart-Hamilton, I. (2015). Adults with autism spectrum disorder (ASD): Service user perspective on ageing transition (s). *Journal of Autism*, *2*(1), 1–11.

Murphy, C. M., Wilson, C. E., Robertson, D. M., Ecker, C., Daly, E. M., Hammond, N., … McAlonan, G. M. (2016). Autism spectrum disorder in adults: Diagnosis, management, and health services development. *Neuropsychiatric Disease and Treatment*, *12*, 1669.

National Institute of Mental Health. (2018). *Autism spectrum disorder*. <https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml> Accessed 28.05.19.

Newman, L., Wagner, M., & Knockey, A.M. (2011) *The post-high school outcomes of young adults with disabilities up to 8 years after high school—A report from the National Longitudinal Transition Study-2 (NLTS2) (NCSER 2011-3005)*. Menlo Park, CA: SRI International. <www.nlts2.org/reports>.

Patterson, D., & Costa, A. C. S. (2005). Down syndrome and genetics—A case of linked histories. *Nature Reviews Genetics*, *6*(2), 137–147.

Perkins, E. A., & Berkman, K. A. (2012). Into the unknown: Aging with autism spectrum disorders. *American Journal on Intellectual and Developmental Disabilities*, *117*(6), 478–496.

Perkins, E. A., & Moran, J. A. (2010). Aging adults with intellectual disabilities. *JAMA*, *304*(1), 91–92.

Prasher, V. P., Mahmood, H., & Mitra, M. (2016). Challenges faced in managing dementia in Alzheimer's disease in patients with Down syndrome. *Degenerative Neurological and Neuromuscular Disease*, *6*, 85–94.

Rafii, M. S., & Santoro, S. L. (2019). Prevalence and severity of Alzheimer disease in individuals with Down syndrome. *JAMA Neurology*, *76*(2), 142–143.

Raznahan, A., Cutter, W., Lalonde, F., Robertson, D., Daly, E., Conway, G. S., ... Murphy, D. D. (2010). Cortical anatomy in human X monosomy. *Neuroimage*, *49*(4), 2915–2923.

Rose, M. R. (1991). *Evolutionary biology of aging*. Oxford, UK and New York, NY: Oxford University Press.

Sabbagh, M., & Edgin, J. (2016). Clinical assessment of cognitive decline in adults with Down syndrome. *Current Alzheimer Research*, *13*, 30–34.

Silverman, W. (2007). Down syndrome: Cognitive phenotype. *Mental Retardation and Developmental Disabilities Research Reviews*, *13*(3), 228–236.

Sinai, A., Mokrysz, C., Bernal, J., Bohnen, I., Bonell, S., Courtenay, K., & Strydom, A. (2018). Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. *Journal of Alzheimer's Disease*, *61*, 717–728. Available from https://doi.org/10.3233/JAD-170624.

Szatmari, P., Bartolucci, G., Bremner, R., Bond, S., & Rich, S. (1989). A follow-up study of high-functioning autistic children. *Journal of Autism and Developmental Disorders*, *19*(2), 213–225.

Thapar, A., Pine, D. S., Scott, S., Snowling, M. J., & Taylor, E. A. (Eds.), (2017). *Rutter's child and adolescent psychiatry*. John Wiley & Sons.

Wright, S. D., Brooks, D. E., DAstous, V., & Grandin, T. (2013). The challenge and promise of autism spectrum disorders in adulthood and aging: A systematic review of the Literature (1990-2013). *Autism Insights*, *5*, 21–73.

Zigman, W. B. (2013). Atypical aging in Down syndrome. *Developmental Disabilities Research Reviews*, *18*, 51–67.

This page intentionally left blank

Chapter 18

Bereavement and grief

Danielle K. Glorioso[1,2], Alana Iglewicz[1,3] and Sidney Zisook[1,3]

[1]Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA, United States, [2]Sam and Rose Stein Institute for Research on Aging, University of California San Diego School of Medicine, La Jolla, CA, United States, [3]Veterans Affairs San Diego Healthcare System, San Diego, CA, United States

Introduction

Throughout their lives, individuals face a myriad of losses capable of triggering grief. In late life, people grieve the loss of their youth, of opportunities, independence, health, mobility, functional abilities, and mental capacities, to name a few. Manifestations of grief vary from loss to loss, situation to situation, person to person, and moment to moment and may involve all aspects of the grieving person's being. This chapter will focus on grief following a particular form of loss, *bereavement*, which refers to the death of someone close.

For older adults especially, bereavement is a fact of life. In 2017 alone, there were over 2.8 million deaths in the United States, an increase of more than 69,000 from 2016 (Heron, 2019). Each of these deaths leave close family and friends to grieve, resulting in over 10 million bereaved individuals each year. Death of a spouse is thought to be the most common loss in older adults, with nearly one-third of those aged 65 and older being widowed (https://www.census.gov/). But loss of children, siblings, and close friends also are common.

Given the frequency of bereavement in late life and the toll it takes on the bereaved survivor's health and well-being, it is vital that health care clinicians are able to understand characteristics, boundaries, and dimensions of "normal" grief, be familiar with risk factors and clinical features of complicated grief (CG), can recognize and assess other health problems that may be triggered by bereavement and often coexist with grief, and are able to intervene promptly and appropriately when indicated. This chapter aims to provide health care clinicians working with older individuals with tools to understand "normal" grief and bereavement, CG, common mental health consequences of bereavement, and evidence-based treatment approaches.

Terminology: bereavement, grief, and mourning

The terms bereavement, grief, and mourning often are confused with each other and/or are used interchangeably. We think of them as different aspects of the experience of the death of a loved one.

Bereavement is sometimes used interchangeably with grief, sometimes to connote the period after a loss during which the grief is experienced and mourning occurs, and sometimes as the state of having someone with whom we are emotionally attached die (Zisook et al., 2014). In this chapter, we use the latter definition. The death of a loved one, bereavement, is considered one of the most difficult challenges faced in a lifetime. Bereavement differs from many other adverse life events and losses in that it is discrete, dateable, irreversible, and heralds a period of intense emotional pain and disruption of daily life activities that is both expected as well as socially sanctioned. In addition to the loss itself, bereavement often requires one to redefine goals and plans in order to restore a meaningful and satisfying life with, at times, new responsibilities and roles. In addition, the stress of bereavement can precipitate or worsen general medical or psychiatric disorders. Although social expectations and ritualizing vary widely across cultures, there is usually an expectation that a person will adapt to loss with appropriate support from family and friends (Hamilton, 2016).

Grief is the natural, universal all-encompassing response to bereavement. Although grief occurs in response to other meaningful (nonbereavement) losses, this chapter focuses upon grief in response to the death of a loved one. Grief is not just an emotion but rather encompasses a myriad of thoughts, feelings, behaviors, and physiologic reactions that are triggered by emotionally meaningful losses. The pattern and intensity of grief varies over time as the bereaved person

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00018-1

adapts to the loss. The experience of grief is influenced by widely varying cultural and religious rituals and is unique to each person and each loss.

Mourning is the term sometimes used to signify the public display of grief and/or the period of time that allows people to adapt to the loss (Stroebe, Hansson, & Schut, 2008). For this chapter, mourning refers to the process of adapting to a loss and integrating grief (Shear, 2018). Adaptation entails accepting the finality and consequences of the loss, finding a way to maintain and recognize continuing bonds and meaningful relationships with the deceased and re-envisioning the future with room for joy and meaning in a world without the deceased. When mourning is successful, the painful and disruptive experience of acute grief is transformed into an experience of integrated grief that is bittersweet and in the background (Shear, Frank, & Houck, 2005; Zisook & Shear, 2009). The bereaved ultimately know that they have grieved and can return to their customary daily activities, re-experience pleasure, and seek the companionship and love of others. Like grief, mourning is influenced by cultural and religious rituals that vary widely.

Historical background

Beginning with Freud's *Mourning and Melancholia* (1959), several descriptions of normal grief and bereavement have appeared in the psychiatric literature. Freud identified four distinguishing features of "normal" grief: (1) a profoundly painful dejection, (2) loss of the capacity to adopt new love objects, (3) the inhibition of activity or turning away from activity not connected with thoughts of the loved person, and (4) loss of interest in the outside world in so far as it does not recall the deceased. Furthermore, Freud distinguished mourning from melancholia by the absence of ambivalent feelings about the deceased and significant disturbances in self-esteem in the bereaved.

In his seminal study of bereavement after the Coconut Grove fire in Boston, Massachusetts, Erich Lindemann (1944) described six components of acute grief among survivors: (1) intense somatic distress, occurring in waves and lasting from 20 minutes to 1 hour, manifested by a tight throat, choking and sighing, an empty feeling in the abdomen, weakness, tenseness, and mental pain, commonly accompanied by withdrawal from friends, relatives, or others because visits may provoke these somatic disturbances; (2) preoccupying thoughts of the deceased; (3) guilt and self-accusations of having mistreated or neglected the dead; (4) irritation and anger directed at themselves, the deceased, friends, relatives, doctors, the world, or God; (5) restlessness, agitation, aimlessness, and lack of motivation, accompanied by abandonment of usual habit patterns; and (6) identification phenomena: a pathological adoption of traits and behaviors of the deceased (especially those of the final illness). Acute anguish lasts weeks or months, gradually giving way to a return of well-being and the ability to go on.

Building on Freud and Lindemann's work, Engle (1961) proposed that grief is a disease state with a predictable course and specific symptoms. Focused primarily on psychopathological symptoms, Clayton (1990) subsequently found crying, sleep disturbances, and depressed mood as cardinal symptoms of bereavement and that many bereaved individuals suffer from a major depressive syndrome within the first 13 months of the death of their loved one. In her study, the depression of bereavement was distinguished by the absence of disturbed self-esteem, guilt, motor retardation, fear of losing one's mind, suicide attempts, past personal or family history of depression, or seeking professional help for the depression.

Kübler-Ross, Wessler, and Avioli widely discussed stages of death and dying (1972) have been applied by some to "normal" grief (Hamilton, 2016). While many of the themes noted in her five stages (denial, anger, bargaining, depression, and acceptance) often are seen in the bereaved, most research has not supported the theory that grief resolves in discreet stages (Bonanno & Boerner, 2007; Silver & Wortman, 2007; Zisook & Shear, 2009). In fact, there are as many ways to grieve as there are people grieving. Most grief researchers and clinicians do not view grief as a process that is ever fully completed or resolved for most individuals; however, during the course of mourning and integration of the loss, people come to terms with the loss and find a new way to live a meaningful life while still carrying their loved one with them symbolically and psychologically in their "hearts," memories, and deeds. To a great extent, prevailing conceptualizations of acute grief have moved away from staging grief and toward a multidimensional (Shuchter & Zisook, 1986) or dual-process model of grief (Stroebe & Schut, 2010).

Two forms of "normal" grief: acute and integrated

Acute grief

Acute grief describes the period wherein people often, but not always, experience heightened, intense, and painful emotions. Shortly after the death, bereaved individuals often report feelings that may include shock, despair, disbelief,

denial, and numbness (Bonanno & Field, 2001; Bonanno & Kaltman, 2001). As the reality of the death sets in, a broad spectrum of emotional, cognitive, social, and behavioral disruptions, ranging from barely noticeable alterations to profound anguish and dysfunction, may ensue. When grief's perturbations appear mild or minimal, clinicians may mistakenly label the lack of observable grief or mourning as pathological, suggesting vulnerability to delayed intense grief or medical complications. However, there is little empirical validation of this assumption and significant data to refute it (Bonanno & Field, 2001; Bonanno & Kaltman, 2001; Stroebe et al., 2000). On the other end of the spectrum, bereavement can be one of the most gut-wrenching and painful experiences an individual ever faces. Some bereaved describe the emotions as a large cloak weighing 1000 pounds that they wear. Initially, the weight of acute grief may feel ever present, hard to live with, difficult to carry, and unending. But soon, there is some respite, as the intense misery manifests in fits and starts, with attention oscillating to and from the painful reality of the death. Some of the many painful feelings and thoughts that characterize acute grief include yearning and longing, intense sadness and crying, anger, anxiety, loneliness, guilt, blame, depersonalization, a preoccupation with thoughts and memories of the deceased person, insistent memories, disturbed neurovegetative functions, difficulty concentrating, and relative disinterest in other people and in activities of daily life (Bonanno & Field, 2001; Bonanno & Kaltman, 2001). The bereaved individual may feel they are on an emotional roller coaster, and typically find the intense, uncontrollable emotionality of acute grief disconcerting or even shameful or frightening. If these reactions are prominent, a person may attempt to avoid reminders or over-control stimuli, which can interfere with the normal grief progression. Yet, grief is not only about pain. In an uncomplicated grief process, painful experiences are intermingled with positive feelings, such as relief, joy, peace, and happiness that emerge after the loss of an important person.

Acute grief may last for days, weeks, or months. During the height of this period, individuals may find it difficult to experience sustained joy, to see meaning in a life absent their loved one, and may feel overwhelmed (Zisook et al., 2014). However, over time, mourning rituals and the support of family and friends facilitate passage through acute grief to a place where the reality and permanence of the loss are understood. A comfortable place for the lost loved one is found in the bereaved person's heart, memories and deeds, and well-being and the ability to get on with living are restored.

Integrated grief

For most people, grief is never fully completed. Instead, as the bereaved gradually adapt to their loss, acute grief evolves into an attenuated form which we call "integrated grief." In integrated grief, the sense of disbelief lessens, intense emotionality subsides, thoughts and memories recede into the background, and well-being is restored (Shear et al., 2005). The deceased loved one rests peacefully in the bereaved person's heart along with a renewed sense of purpose, meaning, and connection to others. Painful memories reside in the background and may temporarily emerge at special times, such as anniversaries, birthdays, and other special occasions. But, for the most part, these are well-accepted and do not interfere with daily life. Embracing these opportunities to "remember" helps maintain the connection to the person who has died. For many, adapting to the death of a loved one is accompanied by postloss growth, such as discovering heretofore untapped inner resources and strengths, pride in overcoming the trauma of loss, abilities to take on new tasks and roles, reprioritizing one's values and relationships, developing a greater sense of appreciation for what one has, openness to new possibilities in life, wisdom, and finding new paths to maintaining connections to one's inner self and to others (Zisook et al., 2014).

Complicated grief

The natural trajectory from acute to integrated grief does not occur for everybody. For a small but meaningful subset of bereaved individuals, perhaps as high as 7%, the smooth passage described above is blocked and successful adaptation to the loss does not occur (Kersting, Brähler, Glaesmer, & Wagner, 2011). Instead, the condition we call CG ensues. Also known as Prolonged Grief Disorder in ICD-11 (World Health Organization, 2018) and Persistent Complex Bereavement Disorder in DSM-5 (American Psychiatric Association, 2013), CG is the response that occurs when the mourning process gets derailed and acute grief does not transition into integrated grief. The exact criteria and best name for this condition are still works in progress (Cozza et al., 2019). One prominent research group prefers the term "Prolonged Grief" and has proposed its own criteria set (Prigerson & Maciejewski, 2017). Our group favors the term "Complicated Grief" (Reynolds, Cozza, & Shear, 2017). What each of these conceptualizations have in common is that the grief is unusually intense, lasts well beyond the period expected by social and cultural norms, and is accompanied by impairments in daily functioning. The phrase "time heals all wounds" does not apply to those with CG, as those

with CG become stuck in an acute phase of grief, perhaps indefinitely (Shear et al., 2011). The identification of CG is of great consequence because this syndrome occurs with relative frequency and characterizes a population at high risk for ongoing distress, suffering, and both medical and psychiatric comorbidity (Germain, Caroff, Buysse, & Shear, 2005; Lannen, Wolfe, Prigerson, Onelov, & Kreicbergs, 2008; Latham & Prigerson, 2004; Ott, 2003; Simon et al., 2007). CG can be diagnosed by history alone, and when properly managed, can carry an excellent prognosis.

It is still not clear why some develop CG while others do not. Risk factors for developing CG include a current or past history of anxiety and mood disorders, lack of perceived support, multiple losses, insecure attachments in childhood, as well as life stressors that can complicate coping (Shear et al., 2005; Shear & Mulhare, 2008). It is believed that the type of loss may increase the risk of CG with those that have lost a child (Meert et al., 2010) and a loved one to a violent death or to suicide (Boelen & van den Bout, 2005; Mitchell, Kim, Prigerson, & Mortimer-Stephens, 2004) being at a higher risk of developing CG. Older adults grieving the death of a spouse are at greater risk for developing CG than are young adults (Ott, Lueger, & Kelber, 2007; Robbins-Welty et al., 2018; Supiano & Luptak, 2014). However, these estimates are not exact as many individuals go undiagnosed by clinicians.

Assessing CG can be aided with the self-report measure, the Inventory of Complicated Grief (ICG). The ICG is a 19-question instrument developed by Prigerson et al. (1995) to assess indicators of pathological grief, such as anger and disbelief. Each question is written in the first person as a statement about the bereaved with five response options, ranging from "Never" to "Always." Clients who score over 25 are considered at high risk for requiring clinical care. This tool has demonstrated internal consistency and validity and thus provides an easily administered assessment of CG.

The treatment of choice for CG is grief-focused psychotherapy. The most widely researched therapy for CG, simply called complicated grief therapy (CGT), is a manualized, 16-week intervention designed to identify and resolve complications of grief and to facilitate adaptation to loss. The treatment includes two key areas of focus: (1) loss (i.e., helping patients find a way to think about the death that does not evoke intense feelings of anger, guilt, or anxiety); and (2) restoration (restoring effective functioning by generating enthusiasm and creating plans for the future) (Shear et al., 2005). Developed from attachment theory and utilizing elements of cognitive-behavioral therapy, interpersonal therapy (IPT), and motivational interviewing, CGT includes techniques similar to prolonged exposure (repeatedly telling the story of the death and in vivo exposure activities) combined with cognitive reappraisal and gestalt therapy (imaginal conversation with the deceased). CGT also utilizes daily grief monitoring, setting and monitoring aspirational goals, working with memories and techniques geared to cut through avoidance (Wetherell, 2012). CGT is the most extensively tested method available to help people with CG and has been found to be more effective than IPT (Shear et al., 2005). A second large randomized controlled trial replicated the efficacy of CGT compared to IPT in a sample of bereaved individuals aged 50 and older (mean age 66 years) (Shear et al., 2014). A third large, multisite, randomized controlled clinical trial of CGT, which also tested the efficacy of antidepressant medications, confirmed the robust efficacy of CGT but was not able to demonstrate any independent or additional benefits from antidepressant medications (Shear et al., 2016). The latter study did find that antidepressants helped alleviate depressive symptoms in bereaved individuals with CG, but only in those also receiving CGT.

Other individual and grief-focused therapies may also help individuals with CG (Currier, Neimeyer, & Berman, 2008; Wittouck, Van Autreve, De Jaegere, Portzky, & van Heeringen, 2011). Medications clearly are not first-line treatments. CG often occurs concomitantly with major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Treating the cooccurring condition is extra-challenging in the face of CG and may not result in optimal results. Therefore, we recommend clinical attention be given to both conditions. Unfortunately, there is little in the psychiatric literature to inform ideal treatment approaches in these circumstances. The first step is a careful and comprehensive evaluation to make sure each condition is identified, and the patient knows both will be addressed. Whether to focus on both simultaneously or sequentially, and if the latter, in what order, are open questions that may need to be decided on a case-by-case basis, considering the person's preferences, resources, severity of each condition, and previous therapeutic experiences.

Depression in the context of grief

The relationship between grief and depression is complex and controversial (Zisook, Pies, & Iglewicz, 2013). Bereavement not only brings on an acute grief reaction in almost everyone, but also may trigger a variety of health conditions, including the onset or exacerbation of MDD (Alexopoulos, 2005; Stroebe, Schut, & Stroebe, 2007; Zisook, Reynolds, et al., 2010; Zisook, Simon, et al., 2010). Many of the symptoms and clinical features of grief and MDD overlap, resulting in clinicians being faced with the clinical dilemma of distinguishing between normal grief due to the loss of a loved one and symptoms and depression that time will heal versus MDD, a serious condition requiring clinical

attention. Thus when presented with an acutely bereaved patient with prominent depressive symptoms, the clinician may face several questions: Is the patient experiencing normal grief or clinical depression? Should these symptoms be treated or left to resolve on their own in what many believe to be a restorative process? And, if intervention is appropriate, which therapeutic domain maximizes the probability of a successful outcome? These issues, perplexing in any clinical encounter, pose an additional set of challenges when the patient is elderly as the loss may be accompanied by a host of factors associated with aging, such as poor health, impaired cognitive abilities, declining income, decreasing independence, and the loss of social and occupational roles, to name a few.

To help sort out some of the questions raised above, the DSM-III (American Psychiatric Association, 1980) introduced the Bereavement Exclusion (BE) for the diagnosis of MDD. The BE was meant to help clarify the distinction between uncomplicated grief and MDD and to protect against normal sadness or grief being mistaken for depression, mislabeled as an illness, pathologized and/or inappropriately treated. Thus the BE disallowed the diagnosis of MDD during the first 2 months of bereavement unless the depressive symptoms and dysfunction were particularly severe, defined by symptoms of morbid worthlessness, psychomotor retardation, suicidal ideation, psychotic features, or marked disability. However, subsequent studies found that the BE was largely misunderstood and misapplied and that major depressive syndromes occurring in the context of bereavement were essentially identical to other, nonbereavement-related major depressive episodes in risk factors, including familial and genetic factors, associated clinical features, chronicity and course, and treatment response (Shear et al., 2014: Zisook et al., 2012).

To remove what the DSM-5 mood disorders task force felt had become a systematic roadblock to the diagnosis of this potentially life-altering and costly mental disorder, the BE was eliminated in DSM-5 (American Psychiatric Association, 2013). Instead of the BE, the revised diagnostic criteria for MDD in DSM-5 promote the exercise of clinical judgment "based on the individual's history of the cultural norms for the expression of distress in the context of loss."

As a footnote to the diagnostic criteria for MDD, the DSM-5 provided guidelines to help differentiate grief that is not complicated by cooccurring MDD from MDD (Zisook, Reynolds, et al., 2010; Zisook, Simon, et al., 2010). For example, in ordinary grief, the predominant effects are emptiness and loss as opposed to the persistent depressed mood and anhedonia of MDD. In grief, the dysphoria decreases in intensity over days to weeks and occurs in waves, the so-called pangs of grief, which are associated with thoughts or reminders of the deceased. In MDD, on the other hand, the dysphoria tends to be persistent and is not tied to specific thoughts or images. Furthermore, grief is characterized by a preoccupation with thoughts and memories of the deceased whereas in MDD the preoccupation is with self-critical or pessimistic ruminations. Similarly, self-esteem is preserved in grief, while feelings of worthlessness and self-loathing predominate one's view of oneself in MDD. Thoughts of death and dying in grief are generally focused on the deceased and possibly about joining or reuniting with their loved one, while thoughts about dying in MDD more often are focused on ending one's life because of feeling worthless, undeserving of life, or unable to cope with the pain and misery of depression. There are other differences, as well. Bereaved individuals often retain the capacity to laugh, to appreciate the comfort and support of relatives and neighbors sharing warm memories of the deceased, to be consoled, and to recognize that what they are going through will lessen in time (American Psychiatric Association, 2013).

Recognizing that bereavement may sometimes be a focus of clinical attention, the DSM-5 categorizes "Uncomplicated Bereavement" with a V-code under the category of "Other Problems Related to Primary Support Group" (V62.82). "As part of their reaction to a loss, some grieving individuals present with symptoms characteristic of major depressive disorder—for example, feelings of sadness and associated symptoms such as insomnia, poor appetite, and weight loss. The bereaved individual typically regards the depressed mood as 'normal,' although the individual may seek professional help for relief of associated symptoms such as insomnia or anorexia. The duration and expression of 'normal' bereavement vary considerably among different cultural groups" (American Psychiatric Association, 2013).

There are no hard and fast rules or evidence-based guidelines on how to best treat MDD when it is associated with bereavement. Based on both data supporting that such depressions cooccurring with bereavement respond to standard antidepressant treatments (Hensely, 2006; Jacobs, Nelson, & Zisook, 1987; Pasternak et al., 1991; Reynolds, Frank, & Perel, 1999; Zisook, Shuchter, & Pedrelli, 2001) and in our clinical experience, we recommend treatment of bereavement-related depression, perhaps as soon as it is diagnosed if very severe, life-threatening or part of a lifetime recurrent course of illness, but as early as 6−8 weeks after the loss in others. Whether the treatment should be psychotherapy, medications, or both rests upon factors similar to treating any nonbereavement-related MDD (ref: APA guidelines). In the only randomized, placebo-controlled study on bereavement-related major depression, Reynolds et al. (1999) found that nortriptyline was more effective than placebo in achieving remission of major depressive episodes, that interpersonal therapy was not more effective than placebo, and that the combination of medication and

psychotherapy was associated with the highest retention rates, but not necessarily with greater clinical effectiveness than medication alone.

With regard to medications, there is no reason to think that any one class of medications is more effective than others for the treatment of bereavement-related depression. As with treating other, nonbereavement-related depressions, selection should be based on patient preferences, past or family history of response, side effect and safety profiles, and, to a lesser extent, on clinical subtype (Kennedy et al., 2009). Issues surrounding the pharmacologic treatment of older, nonbereaved individuals who have MDD also apply when treating older, depressed patients who have lost a loved one. Clinicians should consider beginning with lower doses of antidepressant medications in this population than in their younger counterparts. Concerns surrounding polypharmacy are relevant in this group as the elderly often take multiple medications for various ailments. Special attention should be paid to compliance issues: older individuals may suffer from visual or hearing losses and not perceive instructions properly or they may have problems with memory and easily forget when and how much medication should be taken (Alexopoulos, Katz, Carpenter, & Docherty, 2001; Kok & Reynolds, 2017). Clinicians should, whenever possible, involve family members or other caregivers when treating older, bereaved individuals.

There is a similar paucity of data on which specific form of psychotherapy is best suited for MDD in the context of bereavement. IPT makes some theoretical sense as a treatment of choice, as grief is one of the key foci of IPT. One small case report series suggests the potential effectiveness of interpersonal psychotherapy for bereavement-related depression following loss of a spouse in late life (Miller, Frank, Cornes, & Imber, 1994), while another randomized trial was not able to demonstrate efficacy of IPT for older bereaved individuals with prominent depressive symptoms (Reynolds et al., 1999). In our clinical experience, each of the evidence-based psychotherapies effective for the treatment of MDD is about equally likely to be effective for bereavement-related MDD. The choice of which treatment for which patient is similar to the choice in nonbereavement-related depression (Scogin, Welsh, Hanson, Stump, & Coates, 2005). Nonspecific therapeutic factors play a vital role and attention to the loss and its consequences is an important component whatever approach the clinician takes.

Posttraumatic stress disorder

Like MDD, PTSD commonly cooccurs with bereavement—especially with CG. The symptoms of PTSD also overlap with several of the key symptoms of CG. Subsequently, differentiating between these two diagnoses can be challenging. In this section, cooccurring PTSD and CG will be explored, followed by guidance on how to differentiate between these two conditions. Certain kinds of deaths are inherently "unnatural" and traumatizing. These include many deaths that are sudden and/or unexpected, such as by suicide, homicide, and accident. The traumatizing effect is compounded when the bereaved person found, saw, and/or had to clean up the mutilated body of their loved one (Bui, 2018). Thus it is not surprising that individuals who lost a loved one to suicide or to other sudden, violent means of deaths are at higher risk of developing PTSD than are other bereaved individuals (Mitchell & Terhorst, 2017; Zisook, Chentsova-Dutton, & Shuchter, 1998). When cooccurring PTSD is present, it is pivotal that both the PTSD and the CG are addressed clinically.

Yet, importantly, most individuals with CG do not have cooccurring PTSD (Simon et al., 2007). Furthermore, differentiating between PTSD and CG can be fraught with challenges, even for seasoned clinicians. Overlapping symptoms of PTSD and CG include preoccupation, re-experiencing, hyperarousal, and withdrawal (Hibberd, Elwood, & Galovski, 2010; Shear et al., 2011). Helping to differentiate between these two conditions, the qualitative aspects of these symptoms differ from one another. The preoccupying emotion of PTSD is fear, whereas those of grief are sadness and yearning. The re-experiencing of PTSD centers around thoughts and images of the traumatic event, whereas with grief, it centers around thoughts and images of the loved one's death. Hyperarousal in PTSD is related to the threat of danger, whereas in CG it is related to the loss of interpersonal regulators (Shear et al., 2011; Shear & Shair, 2005). Avoidance serves a different utility in PTSD and in CG. With PTSD, avoidance serves to prevent the recurrence of danger. In contrast, with CG, avoidance serves to forestall painful feelings and thoughts related to the loss of the loved one (Shear et al., 2011). Knowing these qualitative differences allows clinicians to differentiate between PTSD and CG when only one of these conditions is present. However, in order to ensure optimal treatment outcomes, the authors recommend that mental health professionals think in terms of "and/or" rather than just "or" when it comes to both grief and depression as well as grief and PTSD. For the latter, this is especially the case when the death was violent and unexpected.

Bereavement and medical morbidity

Typical grief is associated with some medical morbidity. Scientific evidence exists for the "broken heart syndrome" or "Takotsubo cardiomyopathy"—a physiologic reaction to severe physical or emotional stress (Prasad, Lerman, & Rihal, 2008). Grief is an example of an emotional stress that can precipitate this condition. People who develop Takotsbuo cardiomyopathy are at higher risk for arrhythmias, cardiogenic shock, and resultant death, laying the foundation for the expression "die of a broken heart" (Fagundes et al., 2018; Graff, Fenger-Grøn, & Christensen, 2016). However, most people who develop Takotsubo cardiomyopathy recover from it. Takotsubo cardiomyopathy aside, on the whole, typical grief is not associated with excessive morbidity and mortality. Partly, this relates to an increase in riskier health behaviors, such as increased use of alcohol and/or cigarettes (Zisook, Shuchter, & Lyons, 1987). It also relates to increased rates of insomnia and its negative sequelae (Hardison, Neimeyer, & Lichstein, 2005; Simon et al., 2007). Individuals with CG have elevated rates of cardiac disease, hypertension, cerebrovascular events, and even cancer (Prigerson et al., 1997). Compounding these factors, individuals suffering from CG tend to underutilize health resources despite having elevated rates of health problems. Health risks increase around the time of an anniversary of a loved one's death, especially for widows and widowers. For example, widows and widowers have higher rates of headaches, cardiac problems, and flu symptoms near the anniversary of their spouses' death (Prigerson et al., 1997). In addition to these medical morbidities, CG is associated with pronounced psychiatric morbidity which includes a much higher rate of not only MDD and PTSD, but also suicidal ideation and suicidal behaviors (Latham & Prigerson, 2004).

Cognition

It is important to recognize cognition as a factor when evaluating grief and depression in older adults. The cognitive changes common during bereavement include intrusive thoughts, emotional numbness, distractibility, poor concentration, confusion, forgetfulness, and lack of clarity and coherence (Clayton, Halikes, & Maurice, 1971; Shuchter & Zisook, 1993; Ward, Mathias, & Hitchings, 2007; Xavier, Ferraz, Trentini, Freitas, & Moriguchi, 2002). Some studies have found evidence of cognitive decline, including memory disturbance, to accompany bereavement in older adults (Aartsen, Van Tilburg, Smits, Comjis, & Knipscheer, 2005; Rosnick, Small, & Burton, 2010), but this finding has not been consistently reproduced. On the other hand, CG has been more consistently associated with impaired cognitive functioning (Hall et al., 2014) and cognitive decline in middle-aged and older individuals (Pérez, Ikram, Direk, & Tiemeier, 2018).

Suicide bereavement

What used to be a topic that most would avoid, suicide has grown to be front-page news with high-profile suicides being increasingly acknowledged. Suicide is a public health crisis and is the only one of the top 10 causes of death in the United States that is increasing in prevalence each year. In fact, suicide deaths in the United States have increased over 30% from 1999 to 2017, with older adults accounting for roughly 18% of the suicide losses. Those over 60 years of age are considered to be at greatest risk of suicide loss. Rates are particularly high among older men, with men aged 85 and older having the highest rate of any group in the country (Centers for Disease Control and Prevention, 2017). Key risk factors for suicide in older adults include having other mental disorders, physical illness or disability, previous attempts, access to means, becoming a widow/widower, and the loss of loved ones other than a spouse (Bonnewyn, Shah, & Demyttenaere, 2009). Thus clinicians working with older adults must understand not only how to fully assess suicide risk for bereaved older adults but also how to address those who have lost someone to suicide.

Researchers are mixed on whether there is a distinct difference between the grief and mourning processes in suicide survivors compared to those bereaved by other causes of death (Jordan, 2001). But certain issues common to grief, in general, appear amplified in intensity and duration: feelings of loss, sadness, loneliness, self-blame and guilt, confusion, rejection, abandonment, shame, anger, and the effects of stigma and trauma (Tal Young et al., 2012). Furthermore, survivors of suicide loss are at higher risk of developing CG and may be more likely to experience MDD or PTSD (Jordan, 2008; Kristensen, Weisæth, & Heir, 2012; Tal Young et al., 2012).

Suicide survivors may require different support and treatment to cope with their loss than those bereaved by other modes of death. For example, survivors of suicide have a real need to answer the question, "why." Given most believe that the suicide was preventable, people often ruminate over putting the pieces of the puzzle together in order to make sense of what happened. This includes replaying every past conversation, thinking through things the bereaved could have done differently and looking for clues to better understand "why." Survivors will need time to work through

learning to live with the questions they will never satisfactorily answer. Additionally, since guilt is such a common and distressing theme in the suicide bereaved, clinicians must help the bereaved find a way to forgive themselves and provide the same compassion for themselves they would offer to others. No matter how many exigencies one can anticipate and provide for, and how loving the relationship may have been, when someone close dies by suicide, there are always regrets, often accompanied by a misguided, overinflated sense of responsibility, self-blame, and guilt. A bereaved person may believe they contributed to the death or suffering of the deceased, blaming themselves for many "transgressions," including improper feeding, inadequate support, failing to prevent unhealthy behavior or lifestyle, or not pushing the physician hard enough to detect or treat the disorder. The survivor may dwell on missed opportunities to do or say something that might have helped with suffering or completed some unfinished business. They become their own accuser, prosecutor, judge, and jury. It often helps to clarify the difference between blame and responsibility, as this distinction is a key piece for survivors in coming to terms with the loss and moving toward integration.

For many, there is great stigma around suicide loss (Kristensen et al., 2012). This may be magnified for older adults as they grew up in a generation where suicide was not often talked about. Stigma may also be the result of cultural and religious beliefs. Some cultures and religions have an unfavorable view of suicide, such as the Roman Catholic religion that objectively views suicide as a sin of the commandment "thou shall not kill." For those who are connected to a religious faith, the loss may directly conflict with the teachings of their faith. Stigma serves as a barrier to accepting or receiving support from others, magnifying shame and isolation, and disrupting grief (Mitchell et al., 2004). Clinicians can help break such barriers by opening the dialogue in an accepting, nonjudgmental, and patient manner; employing empathic listening; and providing psycho-education about common themes experienced by people who lose loved ones to suicide. If a clinician has lost a loved one to suicide, self-disclosing this information with thoughtfulness and care can be especially therapeutic.

Both individual and group support can make a huge impact on suicide survivors and may even prevent the development of CG (Jordan & McMenamy, 2004). For suicide survivors with CG, we have found that CGT can be effective for grief symptoms and also to reduce suicide risk, depressive symptoms, anxiety, and dysfunction (Zisook et al., 2018).

Clinical recommendations

Most bereaved individuals do not require any formal or professional treatment. Most often, time, support from family and friends, and the natural restorative powers of grief and mourning are all it takes for healing to proceed. For many, but not all, spiritual/religious practices may help ease the pain and provide meaning and sustenance. On occasion, especially in the absence of adequate support from relatives and friends, or after a particularly taxing loss, support groups may provide additional benefit (McMenamy, Jordan, & Mitchell, 2008; Ott et al., 2007; Zisook, Reynolds, et al., 2010; Zisook, Simon, et al., 2010).

Older adults struggling with loss commonly seek help from their primary care provider for emotional distress (Bergman & Haley, 2009; Caserta & Lund, 1992). Ghesquiere, Shear, and Duan (2013) examined bereavement in older adults with major depression and CG to learn whether physician support, support groups, or other religious supports were associated with a reduction in grief. They found that support groups helped reduce grief severity and support from a religious leader helped reduce depression severity. Interestingly, support from a primary care doctor was not associated with a decrease in anxiety, depression, or grief severity.

Clinicians working with someone struggling with acute grief should focus on providing a supportive, validating environment, be as comfortable as possible with sitting with a client's heightened emotional distress, utilize empathic listening, and monitor their client regularly (Prigerson & Jacobs, 2001; Shear, Muldberg, & Periyakoil, 2017). Additionally, it is important for clinicians to avoid causing their client's ancillary pain by saying terminology that the bereaved may find hurtful or triggering. Phrases to avoid include: "your loved one is in a better place"; "I know how you feel"; "you will move on"; "everything happens for a reason"; "he wouldn't want you to be sad"; or "time heals all wounds." While well-meaning, phrases like this can cause more harm than good to a grieving individual. Instead, phrases like: "I am deeply sorry for your loss"; "would you like to talk about your loved one"; and "I can't imagine what you are going through, but I am here to listen" are preferable.

For CG, we recommend a referral to a specialist, whenever possible, who is skilled in providing targeted, grief-focused therapy. As described above, there are several evidence-based therapies to choose from, but one that has been found specifically useful for older adults is CGT (Shear et al., 2014). The Center for Complicated Grief (https://complicatedgrief.columbia.edu/professionals/complicated-grief-professionals/overview/) maintains a list of therapists throughout the United States who have been trained in the use of CGT. For any individual with CG, we recommend a careful

assessment for commonly associated conditions, such as MDD and PTSD as well as for suicide risk, and appropriately targeted treatments when they are present.

Tending to those in tremendous pain can be difficult for clinicians and health care providers as the intensity of the work can take a toll and create vicarious trauma and compassion fatigue. Mental health professionals are called upon to be compassionate, understanding, and empathic; yet, there is a need to control their own emotional needs and responsiveness in dealing with their clients. Providers may be exposed to hearing the traumatic stories of loss and extreme suffering (Sorenson, Bolick, Wright, & Hamilton, 2016). Clinicians are encouraged to put in place a routine of self-care that includes processing with colleagues, regular supervision, and self-reflection. Working with the bereaved can also be extremely meaningful and rewarding as having the opportunity to facilitate transformation and integration of the loss provides clinicians with a bird's eye view of healing and growth.

Conclusion

Despite—or perhaps because of—the pain, disability, and life disruption associated with bereavement, many individuals experience enormous growth and development throughout the grief process. As Thomas Mann (1875−1955) said, "A man's dying is more the survivors' affair than his own." For although the shattering impact of losing a loved one should never be minimized, many individuals emerge from the experience with a renewed sense of who they are and with an expanded repertoire of competencies. However, a substantial minority of bereaved individuals may find their loss precipitating the onset, persistence, or exacerbation of a psychiatric disorder. In such cases, the problem should not be rationalized or minimized. Psychiatric disturbances that emerge in the context of bereavement, including CG, MDD, and PTSD, warrant full clinical attention. More studies are needed in the area of late-life bereavement. A particular dearth of literature exists in the area of treatment strategies geared toward this population. In the meantime, an integrative approach combining patient support, family education, psychotherapy, and when called for by cooccurring conditions, evidence-based, targeted pharmacological interventions is ideal.

References

Aartsen, M. J., Van Tilburg, T., Smits, C. H., Comjis, H. C., & Knipscheer, K. C. (2005). Does widowhood affect memory performance of older persons? *Psychological Medicine*, *35*, 217−226. Available from https://doi.org/10.1017/S0033291704002831.

Alexopoulos, G. S. (2005). Depression in the elderly. *The Lancet*, *365*(9475), 1961−1970.

Alexopoulos, G. S., Katz, I. R., Carpenter, D., & Docherty, J. P. (2001). The Expert Consensus Guideline Series. Pharmacotherapy of depressive disorders in older patients. *Postgraduate Medicine*, 1−86.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Arlington, VA: American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Bergman, E. J., & Haley, W. E. (2009). Depressive symptoms, social network, and bereavement service utilization and preferences among spouses of former hospice patients. *Journal of Palliative Medicine*, *12*, 170−176.

Boelen, P. A., & van den Bout, J. (2005). Complicated grief, depression, and anxiety as distinct post loss syndromes: A confirmatory factor analysis study. *The American Journal of Psychiatry.*, *162*(11), 2175−2177. Available from https://doi.org/10.1176/appi.ajp.162.11.2175.

Bonanno, G. A., & Boerner, K. (2007). The stage theory of grief. *JAMA.*, *297*(24), 2693. Available from https://doi.org/10.1001/jama.297.24.2693-a, author reply-4.

Bonanno, G. A., & Field, N. P. (2001). Examining the delayed grief hypothesis across 5 years of bereavement. *American Behavioral Scientist*, *44*(5), 798−816.

Bonanno, G. A., & Kaltman, S. (2001). The varieties of grief experience. *Clinical Psychology Review*, *21*(5), 705−734.

Bonnewyn, A., Shah, A., & Demyttenaere, K. (2009). Suicidality and suicide in older people. *Reviews in Clinical Gerontology.*, *19*(4), 271−294.

Bui, E. (2018). *Clinical handbook of bereavement and grief reactions*. Springer Publishing.

Caserta, M. S., & Lund, D. A. (1992). Bereaved older adults who seek early professional help. *Death Study.*, 16-17-30.

Centers for Disease Control and Prevention. (2017). *Fatal injury reports, national and regional, 1999−2017*.

Clayton, P. J. (1990). Bereavement and depression. *The Journal of Clinical Psychiatry*, *51*, 34−38.

Clayton, P. J., Halikes, J. A., & Maurice, W. L. (1971). The bereavement of the widowed. *Diseases of the Nervous System*, *32*, 597−604, Clayton 1971 ISSN: 0012-3714.

Cozza, S. J., Shear, M. K., Reynolds, C. F., Fisher, J. E., Zhou, J., Maercker, A., ... Lebowitz, B. (2019). Optimizing the clinical utility of four proposed criteria for a persistent and impairing grief disorder by emphasizing core, rather than associated symptoms. *Psychological Medicine*, 1−8.

Currier, J. M., Neimeyer, R. A., & Berman, J. S. (2008). The effectiveness of psychotherapeutic interventions for bereaved persons: A comprehensive quantitative review. *Psychological Bulletin*, *134*(5), 648.

Engle, G. L. (1961). Is grief a disease? A challenge for medical research. *Psychosomatic Medicine*, *23*, 18–22.

Fagundes, C. P., Murdock, K. W., LeRoy, A., Baameur, F., Thayer, J. F., & Heijnen, C. (2018). Spousal bereavement is associated with more pronounced ex vivo cytokine production and lower heart rate variability: Mechanisms underlying cardiovascular risk? *Psychoneuroendocrinology*, *93*, 65–71.

Freud, S. (1959). Mourning and melancholia. In E. Jones (Ed.), *Sigmund freud: Collected papers* (vol. 4, pp. 152–170). New York: Basic Books. (original work published 1917).

Germain, A., Caroff, K., Buysse, D. J., & Shear, M. K. (2005). Sleep quality in complicated grief. *Journal of Traumatic Stress.*, *18*(4), 343–346. Available from https://doi.org/10.1002/jts.20035.

Ghesquiere, A., Shear, M. K., & Duan, N. (2013). Outcomes of bereavement care among widowed older adults with complicated grief and depression. *Journal of Primary Care & Community Health*, *4*(4), 256–264. Available from https://doi.org/10.1177/2150131913481231.

Graff, S., Fenger-Grøn, M., Christensen, B., et al. (2016). Long-term risk of atrial fibrillation after the death of a partner. *Open Heart*, *3*, e000367. Available from https://doi.org/10.1136/openhrt-2015-000367.

Hall, C. A., Reynolds, C. F., III, Butters, M., Zisook, S., Simon, N., Corey-Bloom, J., … Shear, M. K. (2014). Cognitive functioning in complicated grief. *Journal of Psychiatric Research*, *58*, 20–25.

Hamilton, I. (2016). Understanding grief and bereavement. *British Journal of General Practice*, *66*(651), 523. Available from https://doi.org/10.3399/bjgp16X687325.

Hardison, H. G., Neimeyer, R. A., & Lichstein, K. L. (2005). Insomnia and complicated grief symptoms in bereaved college students. *Behavioral Sleep Medicine*, *3*(2), 99–111. Available from https://doi.org/10.1207/s15402010bsm0302_4.

Hensely, P. L. (2006). Treatment of bereavement-related depression and traumatic grief. *Journal of Affective Disorders.*, *92*(1), 117–124, 2006 May Epub 2006 Feb 3.

Heron, M. (2019). *Deaths: Leading causes for 2017*. National Vital Statistics Reports; vol 68 no 6. Hyattsville, MD.

Hibberd, R., Elwood, L. S., & Galovski, T. E. (2010). Risk and protective factors for posttraumatic stress disorder, prolonged grief, and depression in survivors of the violent death of a loved one. *Journal of Loss and Trauma*, *15*(5), 426–447. Available from https://doi.org/10.1080/15325024.2010.507660.

Jacobs, S. C., Nelson, J. C., & Zisook, S. (1987). Treating depression of bereavement with antidepressants: A pilot study. *Psychiatric Clinics of North America*, *10*, 501–510.

Jordan, J. R. (2001). Is suicide bereavement different? A reassessment of the literature. *Suicide & Life-Threatening Behavior*, *31*, 91–102.

Jordan, J. R. (2008). Bereavement after suicide. *Psychiatric Annals.*, *38*, 679–685.

Jordan, J. R., & McMenamy, J. (2004). Interventions for suicide survivors: A review of the literature. *Suicide and Life-Threatening Behavior*, *34*(4), 337–349.

Kennedy, S. H., Lam, R. W., Parikh, S. V., Canadian Network for Mood and Anxiety Treatments., et al. (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. *Journal of Affective Disorders.*, *117*(Suppl. 1), S1–S2.

Kersting, A., Brähler, E., Glaesmer, H., & Wagner, B. (2011). Prevalence of complicated grief in a representative population-based sample. *Journal of Affective Disorders*, *131*, 339–343. Available from https://doi.org/10.1016/j.jad, 2010.11.032.

Kok, R. M., & Reynolds, C. F. (2017). Management of depression in older adults: A review. *JAMA*, *317*(20), 2114–2122.

Kristensen, P., Weisæth, L., & Heir, T. (2012). Bereavement and mental health after sudden and violent losses: A review. *Psychiatry: Interpersonal & Biological Processes*, *75*(1), 76–97.

Kübler-Ross, E., Wessler, S., & Avioli, L. V. (1972). On death and dying. *JAMA*, *221*(2), 174–179.

Lannen, P. K., Wolfe, J., Prigerson, H. G., Onelov, E., & Kreicbergs, U. C. (2008). Unresolved grief in a national sample of bereaved parents: Impaired mental and physical health 4 to 9 years later. *Journal of Clinical Oncology.*, *26*(36), 5870–5876. Available from https://doi.org/10.1200/JCO.2007.14.6738.

Latham, A. E., & Prigerson, H. G. (2004). Suicidality and bereavement: Complicated grief as psychiatric disorder presenting greatest risk for suicidality. *Suicide and Life-Threatening Behavior*, *34*(4), 350–362. Available from https://doi.org/10.1521/suli.34.4.350.53737.

Lindemann, E. (1944). The symptomatology and management of acute grief. *American Journal of Psychiatry*, *101*, 141–148.

McMenamy, J. M., Jordan, J. R., & Mitchell, A. M. (2008). What do suicide survivors tell us they need? Results of a pilot study. *Suicide and Life-Threatening Behavior*, *38*(4), 375–389.

Meert, K. L., Donaldson, A. E., Newth, C. J., Harrison, R., Berger, J., Zimmerman, J., et al. (2010). Complicated grief and associated risk factors among parents following a child's death in the pediatric intensive care unit. *Archives of Pediatrics and Adolescent Medicine.*, *164*(11), 1045–1051.

Miller, M. D., Frank, E., Cornes, C., Imber, S. D., et al. (1994). Applying interpersonal psychotherapy to bereavement-related depression following loss of spouse in later life. *Journal of Psychotherapy Practice and Research*, *3*, 149–162.

Mitchell, A. M., Kim, Y., Prigerson, H. G., & Mortimer-Stephens, M. (2004). Complicated grief in survivors of suicide. *Crisis.*, *25*(1), 12–18.

Mitchell, A. M., & Terhorst, L. (2017). PTSD symptoms in survivors bereaved by the suicide of a significant other. *Journal of the American Psychiatric Nurses Association*, *23*(1), 61–65. Available from https://doi.org/10.1177/1078390316673716.

Ott, C. H. (2003). The impact of complicated grief on mental and physical health at various points in the bereavement process. *Death Studies.*, *27*(3), 249–272. Available from https://doi.org/10.1080/07481180302887.

Ott, C. H., Lueger, R. J., Kelber, S. T., et al. (2007). Spousal bereavement in older adults: Common, resilient, and chronic grief with defining characteristics. *The Journal of Nervous and Mental Disease*, *195*, 332–341.

Pasternak, R. E., Reynolds, C. F., Schlernitzauer, M., Hoch, C. C., Buysse, D. J., Houck, P. R., & Perel, J. M. (1991). Acute open-trial nortriptyline therapy of bereavement-related depression in late life. *The Journal of Clinical Psychiatry*, *52*(7), 307–310.

Pérez, H. C. S., Ikram, M. A., Direk, N., & Tiemeier, H. (2018). Prolonged grief and cognitive decline: A prospective population-based study in middle-aged and older persons. *The American Journal of Geriatric Psychiatry*, *26*(4), 451–460.

Prasad, A., Lerman, A., & Rihal, C. S. (2008). Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. *American Heart Journal*, *155*(3)), 408–417.

Prigerson, H. G., Bierhals, A. J., Kasl, S. V., Reynolds, C. F., 3rd, Shear, M. K., Day, N., et al. (1997). Traumatic grief as a risk factor for mental and physical morbidity. *The American Journal of Psychiatry.*, *154*(5), 616–623.

Prigerson, H. G., & Jacobs, S. C. (2001). Perspectives on care at the close of life. Caring for bereaved patients: "all the doctors just suddenly go." *JAMA*, *286*, 1369.

Prigerson, H. G., & Maciejewski, P. K. (2017). Rebuilding consensus on valid criteria for disordered grief. *JAMA Psychiatry*, *74*, 435–436.

Prigerson, H. G., Maciejewski, P. K., Reynolds, C. F., III, Bierhals, A. J., Newsom, J. T., Fasiczka, A., … Miller, M. (1995). The inventory of complicated grief: A scale to measure maladaptive symptoms of loss. *Psychiatry Research*, *59*(1-2), 65–79.

Reynolds, C. F., Cozza, S. J., & Shear, M. K. (2017). Clinically relevant diagnostic criteria for a persistent impairing grief disorder: Putting patients first. *JAMA Psychiatry*, *74*, 433–434.

Reynolds, C. F., III, Frank, E., Perel, J. M., et al. (1999). Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: A randomized controlled trial in patients older than 59 years. *JAMA.*, *281*, 39–45.

Robbins-Welty, G., Stahl, S., Zhang, J., Anderson, S., Schenker, Y., Shear, M. K., … Reynolds, C. F. (2018). Medical comorbidity in complicated grief: Results from the HEAL collaborative trial. *Journal of Psychiatric Research.*, *96*, 94–99. Available from https://doi.org/10.1016/j.jpsychires.2017.09.017, Epub 2017 Sep 20.

Rosnick, C. B., Small, B. J., & Burton, A. M. (2010). The effect of spousal bereavement on cognitive functioning in a sample of older adults. *Neuropsychology, Development, and Cognition*, *17*, 257–269.

Scogin, F., Welsh, D., Hanson, A., Stump, J., & Coates, A. (2005). Evidence-based psychotherapies for depression in older adults. *Clinical Psychology: Science and Practice.*, *12*, 222–237.

Shear, K., Frank, E., & Houck, P. R. (2005). Treatment of complicated grief: A randomized controlled trial. *JAMA*, *293*, 2601–2608.

Shear, K., Muldberg, S., & Periyakoil, V. (2017). Supporting patients who are bereaved. *BMJ*, *358*. Available from https://doi.org/10.1136/bmj.j2854, j2854.

Shear, K., & Mulhare, E. (2008). Complicated grief. *Psychiatric Annals.*, *38*(10), 662.

Shear, M. K. (2018). *Grief and bereavement in adults: Management*. UpToDate. <https://www.uptodate.com/contents/grief-and-bereavement-in-adults-clinical-features>.

Shear, M. K., Reynolds, C. F., 3rd, Simon, N. M., Zisook, S., Wang, Y., Mauro, C., … Skritskaya, N. (2016). Optimizing treatment of complicated grief: A randomized clinical trial. *JAMA Psychiatry*, *73*(7), 685–694. Available from https://doi.org/10.1001/jamapsychiatry.2016.0892.

Shear, M. K., & Shair, H. (2005). Attachment, loss, and complicated grief. *Developmental Psychobiology*, *47*(3), 252–267. Available from https://doi.org/10.1002/da.20780.

Shear, M. K., Simon, N., Wall, M., Zisook, S., Neimeyer, R., Duan, N., … Keshaviah, A. (2011). Complicated grief and related bereavement issues for DSM-5. *Depression and Anxiety*, *28*, 103–117.

Shear, M. K., Wang, Y., Skritskaya, N., Duan, N., Mauro, C., & Ghesquiere, A. (2014). Treatment of complicated grief in elderly persons: A randomized clinical trial. *JAMA Psychiatry*, *71*(11), 1287–1295.

Shuchter, S. R., & Zisook, S. (1986). Treatment of spousal bereavement: A multidimensional approach. *Psychiatric Annals*, *16*(5), 295–305.

Shuchter, S. R., & Zisook, S. (1993). The course of normal grief. In M. Stroebe, W. Stroebe, & R. Hansson (Eds.), *Handbook of bereavement: Theory, research, and intervention* (pp. 23–43). Cambridge: Cambridge University Press. Available from https://doi.org/10.1017/CBO9780511664076.003.

Silver, R. C., & Wortman, C. B. (2007). The stage theory of grief. *JAMA.*, *297*(24), 2692. Available from https://doi.org/10.1001/jama.297.24.2692-a, author reply 3-4.

Simon, N. M., Shear, K. M., Thompson, E. H., Zalta, A. K., Perlman, C., Reynolds, C. F., et al. (2007). The prevalence and correlates of psychiatric comorbidity in individuals with complicated grief. *Comprehensive Psychiatry*, *48*(5), 395–399. Available from https://doi.org/10.1016/j.comppsych.2007.05.002.

Sorenson, C., Bolick, B., Wright, K., & Hamilton, R. (2016). Understanding compassion fatigue in healthcare providers: A review of current literature. *Journal of Nursing Scholarship*, *48*(5), 456–465.

Stroebe, M., & Schut, H. (2010). The dual process model of coping with bereavement: A decade on. *OMEGA—Journal of Death and Dying*, *61*(4), 273–289.

Stroebe, M., Schut, H., & Stroebe, W. (2007). Health outcomes of bereavement. *Lancet*, *370*, 1960.

Stroebe, M., van Son, M., Stroebe, W., Kleber, R., Schut, H., & van den Bout, J. (2000). On the classification and diagnosis of pathological grief. *Clinical Psychology Review*, *20*(1), 57–75.

Stroebe, M. S., Hansson, R. O., Schut, H., et al. (Eds.), (2008). *Handbook of bereavement research and practice: Advances in theory and intervention*. Washington, DC: American Psychological Association.

Supiano, K. P., & Luptak, M. (2014). Complicated grief in older adults: A randomized controlled trial of complicated grief group therapy. *Gerontologist*, *54*, 840–856.

Tal Young, I., Iglewicz, A., Glorioso, D., Lanouette, N., Seay, K., Ilapakurti, M., & Zisook, S. (2012). Suicide bereavement and complicated grief. *Dialogues in Clinical Neuroscience*, *14*(2), 177–186.

Ward, L., Mathias, J. L., & Hitchings, S. E. (2007). Relationships between bereavement and cognitive functioning in older adults. *Gerontology*, *53*, 362–372.

Wetherell, J. L. (2012). Complicated grief therapy as a new treatment approach. *Dialogues in Clinical Neuroscience*, *14*(2), 159–166.

Wittouck, C., Van Autreve, S., De Jaegere, E., Portzky, G., & van Heeringen, K. (2011). The prevention and treatment of complicated grief: A meta-analysis. *Clinical Psychology Review*, *31*(1), 69–78.

World Health Organization. (2018). *International statistical classification of diseases and related health problems (11th Revision)*. <https://icd.who.int/browse11/l-m/en>.

Xavier, F. M., Ferraz, M. P., Trentini, C. M., Freitas, N. K., & Moriguchi, E. H. (2002). Bereavement-related cognitive impairment in an oldest-old community-dwelling Brazilian sample. *Journal of Clinical and Experimental Neuropsychology*, *24*(3), 294–301.

Zisook, S., Chentsova-Dutton, Y., & Shuchter, S. R. (1998). PTSD following bereavement. *Annals of Clinical Psychiatry*, *10*(4), 157–163.

Zisook, S., Corruble, E., Duan, N., Iglewicz, A., Karam, E. G., Lanuoette, N., … Katherine Shear, M. (2012). The bereavement exclusion and DSM-5. *Depression and Anxiety*, *29*(5), 425–443.

Zisook, S., Iglewicz, A., Avanzino, J., Maglione, J., Glorioso, D., Zetumer, S., … Shear, M. K. (2014). Bereavement: Course, consequences, and care. *Current Psychiatry Reports*, *16*, 482.

Zisook, S., Pies, R., & Iglewicz, A. (2013). Grief, depression, and the DSM-5. *Journal of Psychiatric Practice*, *19*, 386.

Zisook, S., Reynolds, C. F., III, Pies, R., Simon, N., Lebowitz, B., Madowitz, J., … Shear, M. K. (2010). Bereavement, complicated grief and DSM Part 1: Depression. *The Journal of Clinical Psychiatry*, *71*(7), 955.

Zisook, S., & Shear, K. (2009). Grief and bereavement: What psychiatrists need to know. *World Psychiatry*, *8*, 67.

Zisook, S., Shear, M. K., Reynolds, C. F., Simon, N. M., Mauro, C., Skritskaya, N. A., … Wetherell, J. L. (2018). Treatment of complicated grief in survivors of suicide loss: A HEAL Report. *The Journal of Clinical Psychiatry*, *79*(2), 17m11592.

Zisook, S., Shuchter, S. R., & Lyons, L. E. (1987). Predictors of psychological reactions during the early stages of widowhood. *Psychiatric Clinics of North America*, *10*(3), 355–368.

Zisook, S., Shuchter, S. R., Pedrelli, P., et al. (2001). Bupropion sustained release for bereavement: Results of an open trial. *The Journal of Clinical Psychiatry*, *62*, 227–230.

Zisook, S., Simon, N. M., Reynolds, C. F., 3rd, Pies, R., Lebowitz, B., Young, I. T., … Shear, M. K. (2010). Bereavement, complicated grief, and DSM, part 2: Complicated grief. *The Journal of Clinical Psychiatry*, *71*(8), 1097–1098.

Further reading

Conejero, I., Olié, E., Courtet, P., & Calati, R. (2018). Suicide in older adults: Current perspectives. *Clinical Interventions in Aging*, *13*, 691–699. Available from https://doi.org/10.2147/CIA.S130670.

Davidson, J. R. (2010). Major depressive disorder treatment guidelines in America and Europe. *The Journal of Clinical Psychiatry*, *71*, e04.

Gort, G. (1984). Pathological grief: Causes, recognition and treatment. *Canadian Family Physician*, *30*, 914–924.

Mojtabai, R. (2011). Bereavement-related depressive episodes: Characteristics, 3-year course, and implications for the DSM-5. *Archives of General Psychiatry*, *68*, 920–928.

O'Connor, M. F., & Arizmendi, B. J. (2014). Neuropsychological correlates of complicated grief in older spousally bereaved adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *69*, 12–18.

Reynolds, C. F., Stack, J., & Houle, J. (2011). *Healing Emotions After Loss (HEAL): Diagnosis and treatment of complicated grief*. Pittsburgh: University of Pittsburgh School of Medicine.

Travers, B., Ali, N., & Kolkiewicz, L. (2012). Bereavement in primary care mental health. In G. Ivbijaro (Ed.), *Companion to primary care mental health*. Oxford: Radcliffe Publishing.

U.S. Census Bureau. (2011). *Number, timing, and duration of marriages and divorces, 2009*. <https://www.census.gov/prod/2011pubs/p70-125.pdf>.

Chapter 19

Neuropsychology with older adults

Nathan Hantke[1,2] **and Nicholas T. Bott**[3,4]

[1]Department of Neurology, Oregon Health and Science University, Portland, OR, United States, [2]Mental Health and Neuroscience Division, VA Portland Health Care System, Portland, OR, United States, [3]Clinical Excellence Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States, [4]Department of Psychology, PGSP-Stanford Consortium, Palo Alto University, Palo Alto, CA, United States

Introduction

The process of aging is accompanied by many structural and cognitive changes. There is increasing evidence that late-life onset of depression and anxiety is associated with cognitive deficits greater than what is seen in normal aging and an increased risk for future cognitive decline (Beaudreau & O'Hara, 2008; Koenig, Bhalla, & Butters, 2014). This chapter will first provide a review of the cognitive changes commonly experienced by older adults. Second, this chapter will discuss the role of neuropsychology in the assessment of cognitive changes reflective of neurodegenerative disorders. Finally, this chapter will review research on the association between mental health symptoms and cognitive functioning in older adults, with an emphasis on late-life depression and anxiety.

Cognitive changes associated with aging

While there is variance among individuals, the cognitive changes associated with aging tend to be fairly uniform and ubiquitous (Salthouse, 2010). Attention, working memory, processing speed, and learning and memory are all particularly disrupted by the aging process and will be the focus of the next section (Drag & Bieliauskas, 2010). For conceptual reasons and continuity, the following section is organized by gross anatomy and cognitive domain. It is acknowledged that classifying cognitive abilities strictly by neuroanatomical correlates is an oversimplification and misleadingly implies a one-to-one ratio of cognitive domain and brain anatomy. Instead, cognitive functioning is undoubtedly the result of a dynamic relationship between brain regions and abilities, acting in synchrony to perform complex tasks.

Aging and frontal lobe functions

A leading theory in understanding age-related cognitive changes is the frontal aging hypothesis, which proposes that declines in the efficiency of the frontal lobes can account for the majority of the cognitive changes seen in older adults (West, 1996). The anterior region of the frontal lobes, the prefrontal cortex (PFC), is particularly vulnerable to the aging process, decreasing at an average rate of 5% every 10 years in older adults (Raz & Rodrigue, 2006). The PFC is integral in attention, working memory, executive functions, and a variety of other cognitive abilities (Rajah & D'Esposito, 2005). These functions are vital in performing both basic and complex tasks, and deficits in frontal functioning can cause large-scale disruption across other cognitive domains.

The ability to pay attention, a frontal lobe−mediated function, is often disrupted in aging and difficulty with attention is a common complaint by older adults. Specifically, older adults often experience difficulties in maintaining selective attention and inhibiting previously presented but no longer relevant information (Hartman & Hasher, 1991; Nielson, Langenecker, & Garavan, 2002). For example, older adults are more likely to provide incorrect, yet semantically related words during a memory recall task, as they have more difficulty inhibiting associated words within their neural networks (Kensinger, 2009). Similarly, the ability to switch back and forth between different tasks declines with age (Drag & Bieliauskas, 2010). This inability to engage and disengage attention is often described by older adults as difficulty multitasking or maintaining divided attention.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00019-3

Working memory is a dorsolateral PFC-mediated process that frequently declines with age. Functioning as the brain's short-term store, it allows the brain to briefly hold and perform mental operations. Requiring not only basic attention but also the ability to manipulate information, working memory is a cognitively and resource-demanding process. As expected given its dependence on the frontal lobe, working memory is susceptible to age-related decline, especially as the difficulty of a task increases. For example, performance on the cognitively demanding n-back task, which requires holding information in working memory while attending to current stimuli, declines with age at a greater rate than simpler tasks (Dobbs & Rule, 1989). Given the decreased cognitive efficiency seen in older adults and the significant cognitive resources required to shift, attend, filter, and inhibit incoming information, older adult working memory is naturally pushed harder than that of a younger adult to complete the same tasks.

Processing speed is an additional ability negatively affected by age. Older adults show decreases in processing speed on both a motor and cognitive level (Andrada-Serpa et al., 1989; Kensinger, 2009). However, reaction time especially decreases when cognitive resources are taxed. For example, making the decision to brake at a yellow light or continue through an intersection takes exponentially more processing time than simply stopping at a red light (Kensinger, 2009). Similarly, selectively attending or holding information in working memory significantly decreases processing speed and possibly influences the age-related declines seen in other domains (Park et al., 2003). Slowed processing speed also plays a significant global role in age-related cognitive difficulties. The processing-speed theory of aging proposes that a decrease in the speed of information processing causes most age-related cognitive impairments (Salthouse, 1996). The theory posits that older adults are unable to keep up with the pace of incoming information and have difficulty integrating simultaneously experienced information. Critical operations such as encoding, rehearsal, and retrieval of information are degraded or less accurate because older adults are unable to efficiently process stimuli or activate networks (Salthouse, 1996). The brain loses its ability to process large amounts of information in a timely manner, creating a "waterfall effect" in all other cognitive domains (Salthouse, 1996).

Executive functioning is a higher-order cognitive construct, contributing to goal-directed behavior, planning, self-regulation, and the ability to efficiently organize and retrieve information (Drag & Bieliauskas, 2010). Executive functioning relies heavily on the PFC and begins to sharply decline after the age of 60 in conjunction with the deterioration of the integrity of the region (Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Treitz, Heyder, & Daum, 2007). This decrease in the ability to implement efficient cognitive strategies may have a significant impact on all cognitive domains. Recent research suggests executive dysfunction predicts decline in an individual's ability to perform instrumental activities of daily living and future cognitive decline (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000).

Aging and memory

The hippocampus, which is important in the formation of new memories, is another brain region that appears to be preferentially impacted by age, decreasing in size at a rate of 1.7% each year in adults over the age of 55 (Walhovd et al., 2005; Winocur, Moscovitch, & Bontempi, 2010). Concordantly, older adults often report problem with long-term memory (LTM). One broad category within LTM is declarative (i.e., explicit) memory, which is the ability to recall facts and events (Brickman & Stern, 2009). Declarative memory can be further divided into semantic, episodic, and source memory. Semantic memory refers to the retention of general facts and knowledge. This type of memory tends to be the most stable memory system across the life span. Compared to episodic memory, semantic knowledge is "crystallized" and tends to increase gradually across the entire life span, showing only minimal decline in late-life (Brickman & Stern, 2009; Hedden & Gabrieli, 2004).

Episodic memory refers to the explicit retention and retrieval of personal events. Going beyond semantic memory, episodic memory incorporates the "who, what, where, when" of a specific memory (Brickman & Stern, 2009). While differentiated from semantic memory, the two systems constantly interact, as episodic information binds together to create semantic networks. A significant difference between the two is the sharp age-related decline of episodic memory. Because episodic memory relies heavily on regions of the brain frequently affected by the aging process, the medial temporal lobes, and PFC, older adults often demonstrate difficulty in learning and remembering specific details (Brickman & Stern, 2009). Instead, older adults often rely on cues and recognition instead of explicit recall. Reflective of this, older adults tend to do better on items that have a greater associative and recognition component as compared to free recall (Albert & Knoefel, 1994). Older adults depend on familiarity for memory recall and struggle with explicitly remembering information, often only recalling the gist of a conversation (Craik, 2006).

Similarly, older adults often report a decline in source memory (i.e., recalling the context in which information was learned). Older adults are significantly worse than younger adults at remembering who provided specific information in a conversation as well as details about the individual with whom they are conversing

(Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991). This inability to effectively recall information has been hypothesized to be caused by ineffective encoding and recall due to compromised frontal and hippocampal integrity (Duzel, Schutze, Yonelinas, & Heinze, 2011; Glisky, Rubin, & Davidson, 2001; Persson et al., 2006).

Summary

In summary, age-related changes in cognitive functioning are not uniform across cognitive domains. Attention, working memory, executive functioning, and episodic memory often demonstrate the sharpest declines (Pressman et al., 2016). This being said, the interactive nature of the brain makes it very difficult to parse out the age-related decline of one cognitive domain from another. Most likely, age-related cognitive decline is reflective of the anatomical changes associated with aging and each brain structure's integrated role within cognitive functioning.

Role of neuropsychology in differential diagnosis of pathological cognitive decline

The field of neuropsychology is based on the assumption that cognitive functioning can be measured via standardized tests. Performances on these measures are ascribed as broadly measuring a cognitive ability (e.g., verbal memory) or symptom (e.g., behavioral disinhibition). The quantification of these abilities allows for a patient's performance to be compared to demographically matched peers and provides a psychometrically derived method of monitoring cognitive status. Further, neuropsychological findings may assist differential diagnosis, as different disorders are often present with different patterns of cognitive strengths and deficits (Lezak, Howieson, Bigler, & Tranel, 2012). An example of a neuropsychological battery constructed to measure cognition in older adults is provided in Table 19.1.

Popular cognitive screening measures, such as the Montreal Cognitive Assessment (Nasreddine et al, 2005), play an important role in medical clinics by providing a snapshot of global cognition. For situations that necessitate a more thorough evaluation of cognition, a relatively brief cognitive measure comprised of domain-specific subtests may be appropriate. The Dementia Rating Scale-2 (Jurica, Leitten, & Mattis, 2001) and the Cognistat, formally known as the Neurobehavioral Cognitive Status Exam (Kiernan, Mueller, Langston, & Van Dyke, 1987), are two commonly used

TABLE 19.1 Sample battery of neuropsychological tests for assessing memory disorders in older adults.

Cognitive domain	Example test	Test description
Premorbid cognitive functioning	Wechsler Test of Adult Reading (WTAR)	Patient is asked to read aloud irregularly spelled words, assessing word familiarity, and by proxy, baseline intellectual function
Attention and working memory	Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span	Patient is asked to repeat and mentally manipulate verbally presented numbers
Processing speed	WAIS-IV coding	Timed number-to-symbol substitution task
Visuospatial skills	Rey-Osterrieth Complex Figure Test	Patient is asked to copy a complex design to assess visuospatial construction and planning ability
	Clock drawing	Patient is asked to draw a clock and follow verbal commands to assess for construction ability and executive functioning
Auditory learning and memory	California Verbal Learning Test Second Edition	Auditory, multitrial list learning, and memory task
	Wechsler Memory Scale (WMS-IV) Logical Memory	Auditory, story learning, and memory task
Visuospatial learning and memory	Brief Visuospatial Memory Test—Revised	Multitrial visuospatial figure learning and memory task
Language	Boston Naming Test	Measures confrontation naming ability via black and white drawings of objects
Executive functioning	Stroop Test	Measures cognitive control by having patient inhibit incongruent, overlearned responses (read the word "red" that is printed in green ink)
	Trail Making Test	Paper and pencil task that requires visual attention, psychomotor speed, and mental flexibility
Mood	Geriatric Depression Scale	30-Item self-report depression questionnaire

brief exams that take approximately 30 minutes to administer and provide a global measure of dementia severity via cut-offs. While lacking the depth and nuance afforded by a full neuropsychological battery, these 30-minute measures may provide a viable alternative for older adults unable to tolerate a long evaluation.

Neuropsychological testing can play a vital role in the differential diagnosis of cognitive aging, mild cognitive impairment (MCI), and dementia, including differential diagnosis of specific dementia syndromes. This section will outline the contribution of neuropsychological evaluation in the establishment of sensitive measures of cognition among cognitively normal (CN) or "preclinical" older adults at risk of developing Alzheimer's disease (AD) and the role of neuropsychological data in the refinement of MCI thresholds. Because AD is the most common form of dementia and is characterized primarily by circumscribed cognitive deficits, the neuropsychological profile of AD will serve as a reference point from which other dementia syndromes can be distinguished. The neuropsychological profile of AD will be compared with those of vascular dementia (VaD), Lewy body dementias (LBD), and frontotemporal dementias (FTD).

Research has recently recognized the potential disease entity of limbic-predominant age-related TDP-43 encephalopathy (LATE), an amnestic dementia syndrome found within the "oldest-old" that mimics AD in many ways with amygdala, hippocampus, and middle frontal gyrus involvement, proposed in that order (Nelson et al., 2019). Episodic memory is believed to be specifically impacted, with relatively preserved verbal fluency along with most other cognitive abilities until later in the disease process (Nelson et al., 2019). Given the new recognition of the entity, further research is necessary before firm statements can be made on correlated neuropsychological performance and LATE will not be thoroughly reviewed in this chapter; curious readers may wish to review the position paper by Nelson et al. (2019).

Tracking of preclinical cognitive change

Historically, neuropsychological evaluation has served to localize cognitive and socio-emotional impairments associated with known brain insult or pathology. As the sensitivity of biomarkers has increased, so too neuropsychological measures have evolved to identify dysfunction within specific syndromes and to discriminate between distinct neurodegenerative disorders. The role of neuropsychological data in the evaluation of AD provides a case in point. Neuropsychological data have been used extensively to characterize cognitive deficits associated with AD pathology and progression.

The public health threat posed by AD has continued to drive research into the development of a disease-modifying agent. The lack of success of virtually all drug trials targeting AD pathology has resulted in the establishment of "preclinical" or "at-risk" groups of older adults based upon factors such as family history of AD, genotype (Apolipoprotein E or *APOE* status), and amyloid imaging. Neuropsychological data are increasingly being incorporated into routine evaluation of preclinical or at-risk older adults as a form of preventative screening. Whereas the previous focus of such evaluation was the detection of MCI, preventative screening aims to collect longitudinal cognitive data of adults in midlife prior to the onset or proliferation of pathology (Levy, Tsoy, & Gable, 2016). This model uses a patient's own performance as a baseline of their cognitive function that can be followed longitudinally at defined time intervals. Changes in scores within the same individual over different time points can be compared and evaluated, even among CN patients. More significant changes within a CN patient across time points could signal the start of a pathological process, despite intact cognition. Such data may serve to initiate drug interventions targeting AD pathology at an earlier point in the pathological process, thereby enhancing the drug's therapeutic effects.

Differential diagnosis between dementia and mental health disorders in older adults can be particularly difficult, given the frequent comorbidity and overlap in cognitive deficits. Careful consideration of the clinical course and onset of symptoms is often a primary factor in determining etiology. For example, dementia often has an insidious onset while depression-related cognitive difficulties tend to cooccur with depressive episodes (O'Hara, Coman, & Butters, 2009). Also, during cognitive testing, individuals with depression may show fluctuating cognitive status depending on mood and effort, while individuals with dementia tend to be consistently impaired. The specific cognitive deficits associated with subtypes of dementia and the cognitive deficits associated with anxiety and depression are described in the following sections to help further characterize these differences.

Mild cognitive impairment

As discussed above, aging is associated with a variety of cognitive changes. Importantly, the amount of individual variability in cognitive performance increases with age. An average or normal performance on a cognitive task in a 75-year-old may be considered abnormal or impaired in a 55-year-old (Rogalski et al., 2013). Nevertheless, a subset of individuals demonstrates abnormal or impaired cognitive performance relative to their peers but does not meet criteria

for a diagnosis of dementia. The term MCI was coined by Peterson et al. to describe this subset of individuals (Petersen et al., 1999). The Petersen criteria were applied initially to the domain of memory and included: (1) presence of an objective memory deficit (≥1.5 standard deviations below average) compared to age-matched peers and (2) subjective memory complaint. These individuals were otherwise cognitively and functionally intact. The construct of MCI originally proposed by Petersen has since evolved to include nonmemory domains. The expanded criteria include: (1) presence of subjective or informant-reported impairment on cognitive tasks, (2) presence of an objective cognitive deficit (≥1.5 standard deviations below average) compared to age-matched peers, and/or (3) evidence of longitudinal decline on objective cognitive tasks (Winblad et al., 2004). These individuals are otherwise functionally intact, but neuropsychological testing with longitudinal monitoring of cognition is recommended in practice guidelines (Peterson et al., 2018). The addition of nonmemory domains yielded four distinct subtypes of MCI. Fig. 19.1 depicts a clinical decision tree using the Petersen/Windblad MCI criteria.

Critiques of the MCI construct have included overreliance upon subjective complaints (Edmonds et al., 2014; Lenehan, Klekociuk, & Summers, 2012) and single neuropsychological tests (Brooks, Iverson, Holdnack, & Feldman, 2008) and the variance in frequency of those classified as having MCI with only minor alterations in criteria (Jak et al., 2009). More recently, data-driven approaches to the definition of MCI have been proposed in an effort to increase the sensitivity of the construct (Edmonds et al., 2016). In particular, Jak and Bondi (Bondi et al., 2008) have operationalized impairment as: (1) task performance greater than one standard deviation below normative scores on two tests within a single cognitive domain or (2) task performance greater than one standard deviation below normative scores in at least three cognitive domains (Bondi et al., 2014). Fig. 19.2 depicts a clinical decision tree using the Jak/Bondi MCI

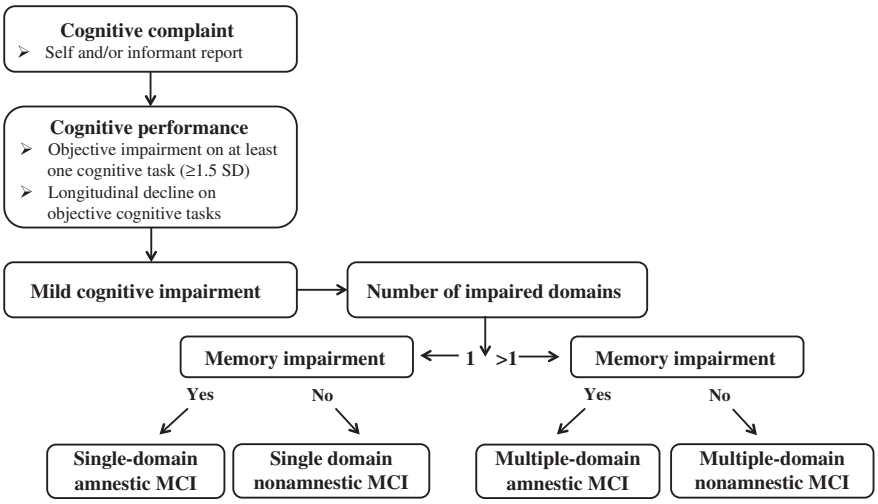


FIGURE 19.1 Petersen/Windblad mild cognitive impairment criteria.

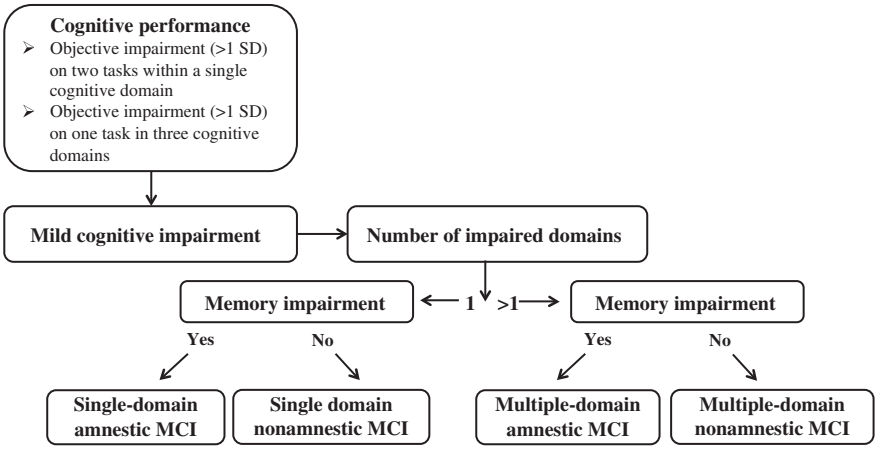


FIGURE 19.2 Jak/Bondi mild cognitive impairment criteria.

criteria. Application of the Jak/Bondi MCI criteria has yielded increased sensitivity by means of reduced false-negative classification of individuals (Bondi et al., 2014; Edmonds et al., 2016) and increased specificity by means of reduced false-positive rates compared to the Petersen/Winblad criteria (Edmonds et al., 2015).

Alzheimer's disease

AD is the most prevalent dementia syndrome with an estimated 40 million older adults worldwide and 5.5 million older adults in the United States. As life expectancy has increased, so too has the number of older adults suffering with AD, and the estimated number of cases of AD is expected to double every 20 years (Prince et al., 2013). The public health challenges associated with aging populations worldwide have triggered an increase in clinical research focused on the detection of biological markers and cognitive deficits associated with AD. Accurate detection of initial and progressive cognitive changes associated with AD offers hope for therapeutic lifestyle interventions (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014) and potential drug therapies.

AD is an age-related neurodegenerative disorder. AD pathology (amyloidogenic plaques and neurofibrillary tangles) typically begins within limbic regions of the brain associated with episodic memory (e.g., entorhinal cortex, hippocampus) and spreads to the association cortices within the parietal, temporal and frontal lobes. As a result, the earliest symptoms of AD involve memory difficulties, whether verbal or visual (Kawas et al., 2003; Rabin et al., 2009). In addition, AD-related cerebral amyloid angiopathy may manifest in increased white matter hyperintensities on neuroimaging, indicating vascular microbleeds attributable to AD-related pathology. As neuronal atrophy and synapse loss progress, the extent and severity of symptoms increase. As a clinical syndrome, AD is characterized by focal amnesia with attendant cognitive impairment in visuospatial abilities, attention, executive function, abstract reasoning, as well as language and semantic abilities (Weintraub, Wicklund, & Salmon, 2012).

Episodic memory deficits typically herald an underlying AD dementia syndrome, and neuropsychological study has substantiated the early deficits observed in episodic memory within AD (Salmon, 2000). Specifically, AD patients demonstrate rapid forgetting of newly learned information and are impaired on measures of free recall, cued recall, and recognition memory, demonstrating a pattern of performance consistent with impaired consolidation—as opposed to retrieval—of new information. These impairments reliably differentiate AD patients from healthy older adults (Delis et al., 1991) and are often measured by the patients' ability to learn and recall a short list of words (e.g., 9−15 words) over repeated trials. Additionally, AD patients more frequently make intrusion errors, whereby previously learned information is recalled when attempting to recall newly learned information (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Jacobs, Salmon, Troster, & Butters, 1990).

Along with episodic memory, declines in executive function are often noticeable in the early stages of AD (Perry & Hodges, 1999). In particular, mental manipulation of information targeted by tasks of set-shifting, self-monitoring, and sequencing have been shown to differentiate very mildly demented AD patients from CN older adults (Lefleche & Albert, 1995). In contrast, executive abilities targeted by cue-directed attention or verbal problem solving were not affected. Deficits in mental manipulation may also be captured on tests of working memory (Weintraub, et al., 2012). When combined with measures of delayed memory recall, executive function performance has been shown to predict the progression to AD (Albert, 1996).

Semantic memory deficits are also observable. Patients with AD exhibit impairment on verbal fluency, semantic fluency, and confrontation naming tasks (Hodges & Patterson, 1995; Nebes, 1989). Similar to episodic memory consolidation impairments exhibited by AD patients, impairment in this domain represents a true loss of semantic memory, as opposed to a retrieval deficit of otherwise intact semantic memory (Salmon & Bondi, 2009). On testing, this means patients with AD will likely miss semantic memory test items, regardless of the task design. In other words, if they are unable to name a picture of a pineapple on a confrontation naming task, they will also be unable to generate pineapple within the semantic category of "fruit," or properly assign pineapple to the correct semantic category.

Early stage AD patients usually demonstrate intact focused or sustained attention (Cherry, Buckwalter, & Henderson, 2002). As the disease progresses, however, deficits in sustained attention can be observed on tasks that require set-shifting and dual-processing (Perry & Hodges, 1999). Visuospatial deficits associated with AD are also less prominent in the early stage of the syndrome. Impairments in this domain are most reliably captured through the evaluation of visuoconstructional tasks such as clock drawing and complex figure copy (Cronin-Golomb & Amick, 2001). However, recent advances in the acquisition of data on visuoconstructional tasks such as clock drawing suggest that subtle variations in graphomotor organization may provide greater diagnostic sensitivity to cognitive domains typically affected in AD (e.g., learning, memory, and executive function) (Lamar et al., 2016).

Vascular dementia

VaD describes the progressive decline in cognitive functioning as a result of white matter disease (e.g., ischemic injury, infarcts). White matter disease can result in a fluctuating or stepwise decline in cognitive functioning, but VaD can also occur more abruptly as is the case when dementia is present in close proximity to a stroke (Wetzel & Kramer, 2008). Hodges and Graham (2001) outline three broad categories of VaD: multiinfarct dementia occurring as a result of multiple large cortical infarctions, dementia due to an infarct at a critical cerebrovascular location (e.g., posterior branch of the medial cerebral artery), and subcortical ischemic VaD (e.g., diffuse white matter pathology, lacunar strokes, leukoaraiosis) resulting from small vessel disease.

Executive dysfunction is more pronounced in patients with VaD than in patients with AD, with the latter demonstrating greater impairment on episodic memory, as patients with AD are more likely to demonstrate rapid forgetting while patients with VaD are more likely to have difficulty accessing learned information (Reed et al., 2007). As such, patients with VaD may be more likely to remember information when provided cues or prompts. Measures of processing speed—particularly reaction time—have also been shown to discriminate between patients with small vessel disease and age- and gender-matched controls, with reaction time correlating with performance on tasks of executive function and working memory (Jouvent, Reyes, De Guio, & Chabriat, 2015). Fronto-subcortical circuit dysfunction as a result of subcortical white matter pathology may represent the underlying functional neuroanatomy responsible for processing speed and executive function deficits in this population. VaD patients with white matter pathology have been shown to demonstrate greater executive dysfunction and visuoconstructional impairment, with relative sparing of memory and language (Mathias & Burke, 2009; Price, Jefferson, Merino, Heilman, & Libon, 2005).

Differential diagnosis between late-life depression-related cognitive deficits and VaD can be especially difficult, given their commonality in slowed processing speed, deficits in executive functioning, and possibly related etiology (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). A thorough evaluation of the patient's history for vascular events, proximal cognitive decline, and severity of depression can all be helpful in determining etiology.

Lewy Body dementias

LBD are named for the α-synuclein neuronal inclusions—known as Lewy bodies—found in the brain at autopsy and are a common form of non-Alzheimer's dementia, occurring in up to 20% of all older adults with dementia (McKeith et al., 1996), and up to 80% of individuals diagnosed with Parkinson's disease (PD) (Emre et al., 2007). In addition to the presence of Lewy bodies, patients with LBD often have cooccurring AD pathology (Ince & Perry, 2005), leading to a dementia syndrome that is similar to that of AD and difficult to differentiate until autopsy (Merdes et al., 2003). On neuropsychological testing, the presence of mixed pathology can obscure the cognitive profile, making it difficult to distinguish a "pure" AD from a mixed AD and dementia with Lewy bodies (DLB) presentation.

The term LBD includes diagnoses of DLB and Parkinson's disease dementia (PDD). Temporal sequencing of specific symptoms differentiates DLB from PDD. In DLB, a diagnosis of dementia is present before or concurrently with parkinsonian symptoms or within 1 year of onset of parkinsonian symptoms. PDD is characterized by a diagnosis of dementia that occurs 1 year or more after the development of PD. The most significant challenge associated with DLB is its early diagnosis and differentiation from AD. With respect to PDD, it is the early identification of cognitive deficits in PD patients (Walker, Possin, Boeve, & Aarsland, 2015). The neuropsychological profile of MCI in PD is varied. Executive dysfunction can feature more prominently (Bott et al., 2014), although attention, episodic memory, and visuospatial impairments may also be present.

The initial onset of cognitive decline in DLB and AD is often episodic memory impairment in the absence of other significant neurological symptoms. The presence of Parkinsonian features such as masked facies, rigidity, or bradykinesia, the recurrence of visual hallucinations, and fluctuating cognition occur more frequently in DLB patients (Salmon & Bondi, 2009). In addition, 74% of early stage pathologically confirmed DLB patients exhibited visuospatial or constructional impairment, compared with 45% of those with AD (Tiraboschi et al., 2006). A pattern of neuropsychological performance consisting of greater executive dysfunction, fluctuating attention and visuospatial impairment compared to AD patients, and greater memory impairment in AD patients compared to DLB patients has been documented among autopsy-confirmed patient groups (Ferman et al., 2006; Kraybill et al., 2005; Stavitsky et al., 2006), and the differences between these patterns have been shown to effectively distinguish early-stage DLB and AD patients (Tiraboschi, et al., 2006) (Table 19.2).

TABLE 19.2 Differentiation of dementia with Lewy bodies and Parkinson's disease dementia.

	Dementia with Lewy bodies (DLB)	Parkinson's disease dementia (PDD)
Core features	*Two required for probable, one for possible DLB* • Spontaneous parkinsonism • Fluctuating cognition • Recurrent visual hallucinations	*Required for probable or possible PDD* • Diagnosis of PD according to Queen Square Brain Bank Criteria • Dementia developing after established diagnosis of PD, with multidomain cognitive impairment and functional impairment in daily life
Central features	*Required for probable or possible diagnosis* • Progressive dementia with functional impairment in daily life	*Typical profile of cognitive deficits required for probable diagnosis* • Typical cognitive profile: impairment in at least two of the following domains: (1) attention; (2) executive function; (3) visuospatial function; (4) free recall, which usually improves with cueing
Suggestive features	*Suggestive feature plus one core feature describes probable DLB; suggestive features without core features describe possible DLB* • Decreased dopamine transporter uptake in the basal ganglia • Significant sensitivity to antipsychotics • Rapid eye movement sleep behavior disorder	
Supportive features	*Absence of supportive features does not exclude diagnosis* • Autonomic dysfunction • Depression • Falls and syncope • Generalized low uptake on single-photon emission CT perfusion or positron emission tomography (PET metabolism with reduced occipital activity • Nonvisual hallucinations • Relative preservation of medial temporal lobe structures • Slow-wave activity on electroencephalogram with temporal lobe transient sharp waves • Systematized delusions • Temporary unexplained loss of consciousness	*Absence of supportive features does not exclude diagnosis* • Anxious or depressed mood • Apathy • Delusions • Hallucinations • Prominent daytime sleepiness
Temporal sequence	Dementia develops prior to or within 1 year of spontaneous parkinsonism	Dementia develops at least 1 year after an established diagnosis of PD

Frontotemporal dementia

First described by Arnold Pick in 1892, FTD represents a diverse group of clinical syndromes marked by the progressive, focal neurodegeneration of the frontal and anterior temporal lobes termed frontotemporal lobar dementia. FTD is the second most common form of dementia for individuals 65 years and younger and is the third most common dementia for adults 65 years and older (Brunnstrom, Gustafson, Passant, & Englund, 2009). There are three clinical subtypes of FTD, including behavioral variant FTD (bvFTD) and two variants of primary progressive aphasia (PPA): semantic variant primary progressive aphasia (svPPA) and nonfluent variant primary progressive aphasia (nfvPPA).

Behavioral variant frontotemporal dementia

BvFTD is characterized by initial changes in personality (e.g., disinhibition, loss of social mores, apathy, stereotyped behaviors, hyperorality) along with progressive decline in social and cognitive functioning. The behavioral variant is characterized by focal and prominent bilateral frontal atrophy, which contribute to the underlying dysfunction of the salience network, which is responsible for socio-emotional awareness, motivation, and reward processing. As a result, patients with bvFTD typically lack insight into their behavior change, and report from family members or significant others is often necessary to establish a time course of symptomology and disease progression (Bott, Radke, Stephens, & Kramer, 2014). Despite some success (Kertesz, 2006), it can be difficult to distinguish AD from bvFTD based on behavioral presentation alone.

Extensive comparison of the neuropsychological profiles of patients with bvFTD and AD has been conducted (Kramer et al., 2003; Rascovsky et al., 2002), and the most recent clinical criteria for the diagnosis of bvFTD include early executive dysfunction with relative sparing of visuospatial abilities and episodic memory (Rascovsky et al., 2011). Several studies investigating performance on executive function, episodic memory, and visuospatial functioning in patients with bvFTD have found support for more significant executive dysfunction with more mild deficits in episodic memory and visuospatial abilities (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000; Mendez et al., 1996; Thomas-Anterion, Jacquin, & Laurent, 2000). Salmon, Hansen, Thal, & Galasko (2007) found that autopsy-confirmed frontotemporal lobar dementia patients performed worse on letter fluency relative to semantic fluency tests, with AD patients demonstrating the reverse pattern (semantic fluency worse than letter fluency). This dissociation may represent differences in the underlying neuroanatomical contributions of the frontal and temporal roles impacted in FTD and AD. On the other hand, studies have also found substantial overlap between bvFTD and AD on neuropsychological measures, both initially and at longitudinal follow-up. Recently, Ramanan et al. (2016) found that bvFTD and AD patients were indistinguishable at baseline on measures of executive function and memory. Moreover, annual longitudinal follow-up over the course of 4 years revealed comparable trajectories of decline on these measures. Longitudinal measurement of disinhibition via performance errors discriminated between the two groups. Given the conflicting results that continue to be reported, more sensitive measures need to be developed that more specifically target the areas affected early on in bvFTD such as ventromedial prefrontal cortex.

Primary progressive aphasia

PPA subtypes are present with significant disturbance and decline of language functioning. Declines in semantic knowledge are observed in svPPA, with agrammatism and motor−speech difficulties observed in nfvPPA (Gorno-Tempini et al., 2011). SvPPA is characterized by bilateral anterior temporal lobe atrophy, associated with language deficits, compulsions, and dysfunctions in emotional processing (Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005). nfvPPA is accompanied by left inferior frontal and insular atrophy, associated with initial expressive speech and syntax difficulties. Logopenic variant primary progressive aphasia (lvPPA) represents a third PPA variant and is characterized by reduced verbal output with intermittent disruptions in fluency and relatively spared grammar and oral motor speech. Focal neurodegeneration is found in the left temporoparietal junction. AD pathology is found on autopsy in these patients disproportionately distributed in language-related cortical areas (Mesulam, 2008).

Given the prominent language dysfunction present in PPA syndromes, it is not surprising that anomia and verbal and semantic fluency performance is impaired in these patients. In contrast with AD patients, anomia and verbal fluency deficits in PPA can occur without associated semantic loss, which when present in AD are a result of more fundamental dysfunction in semantic processing (Weintraub, et al., 2012). Similarly, frank language dysfunction such as paraphasias, agrammatism, or phonological sequencing errors, which are present early on in PPA, are not usually seen in patients with AD until further along in the disease course. The pattern of performance found on neuropsychological assessment in PPA patients has been differentiated from both bvFTD and AD patients. Characteristically, PPA patients have greater sparing of episodic memory and reasoning compared to bvFTD and AD patients (Wicklund, Johnson, & Weintraub, 2004). More recently, Butts et al. (2015) found that svPPA patients exhibited a pattern of performance on comprehensive neuropsychological evaluation restricted to temporal lobe function, whereas nfvPPA patients showed impairment on frontal lobe−mediated tasks.

The discipline of neuropsychology has continued to progress in its ability to identify fundamental cognitive processes associated with AD, with increasing research being devoted to the accurate identification of subtle cognitive changes in individuals as risk for the development of AD, even in the absence of clinical features. Similarly, comparison of the patterns of performance found across distinct age-related neurodegenerative syndromes has allowed for increased ability for neuropsychology to discriminate between dementia syndromes. As progress in the development of more sensitive cognitive measures accelerates, and the ease with which cognitive data can be collected through advances in technology, neuropsychological interpretation of cognitive disorders affecting older adults will continue to progress.

Cognition and mental health in older adults

Depression and anxiety are among the most common neuropsychiatric symptoms in community-dwelling older adults and also in those experiencing cognitive impairment (Geda et al., 2004). A recent US representative sample found nearly one in seven older adults have met criteria for Major Depressive Disorder in their lifetime, with anxiety

displaying similar rates across the life span (Bryant, Jackson, & Ames, 2008; Laborde-Lahoz et al., 2015). Further, many older adults do not meet criteria for a DSM-5 mental health disorder, yet still suffer from depressive symptoms that interfere with daily life. An epidemiological study found 31% of adults over the age of 65 experience subsyndromal levels of depression, and reports on the prevalence of subsyndromal anxiety in older adults range from 15% to 52%, with one-third of individuals with anxiety developing symptoms for the first time in older adulthood (Bryant, et al., 2008).

Recent research suggests anxiety and depression are both cross-sectionally correlated with worse cognitive functioning in older adults and are highly prevalent in dementia (Potter & Steffens, 2007). The presence of depression and anxiety symptoms is associated with increased risk of future cognitive decline, nearly doubling the risk that an older adult will convert from MCI to dementia over time (Palmer et al., 2007). However, depression and anxiety do not impact cognitive abilities in an identical fashion and often present different than the above-described dementias (Bierman, Comijs, Jonker, & Beekman, 2005). The following section presents the overlapping and unique cognitive deficits associated with late-life depression and anxiety and possible explanatory models.

Late-life depression and cognitive performance

Cognitive problems are very common in older adults with depression, as 20%−50% of individuals with late-life depression demonstrate cognitive difficulties greater than their peers (Butters et al., 2004; Sheline et al., 2006). While individuals with depression may show globally lower cognitive scores as compared to older adults with no depressive symptoms, several cognitive domains appear to be selectively impaired greater than others. Specifically, episodic memory, nonverbal intelligence, processing speed, and executive functioning are frequently impaired in older adults reporting depression (Boone, 1995; Butters, et al., 2004). Interestingly, the cognitive difficulties that are often linked to depression may be more or less prevalent depending on the age of onset and types of clinical symptoms reported by an individual. There is evidence that depression with the first onset in late-life is more likely to be associated with executive dysfunction, while recurrent and chronic depression with a younger age of onset is more often associated with memory difficulties (Rapp et al., 2005). Also, difficulties with executive functioning and processing speed show a strong relation to increasing symptom severity in those with depression, particularly in individuals who report apathy (Boone, 1995; Feil, Razani, Boone, & Lesser, 2003). Consistent with this finding, an imaging study of depressed older adults performing a cognitive control task showed decreased PFC activation, a region also believed to play a role in apathy (Dumas & Newhouse, 2015; Levy & Dubois, 2006).

The slowed processing speed often seen in individuals with depression may be of particular importance, as 40% of individuals with depression demonstrate impairment in this domain (Butters, et al., 2004). Research suggests a unique relationship between late-life depression and slowed processing speed that cannot be attributed to other factors common in aging, such as cooccurring medical problems or vascular concerns (Butters, et al., 2004; Sheline, et al., 2006). As processing speed is a basic component of all cognitive functioning, Butters et al. (2004) suggest it may be the driving force behind the majority of cognitive deficits in depression. Consistent with this hypothesis, the authors reported findings that suggest impairment in processing speed account for the majority of variance seen across depression-related cognitive deficits (Butters, et al., 2004). There is evidence that slowed processing speed is a permanent deficit among older adults with late-life depression, as only a subset of older adults shows improved cognition after successful treatment of depression (Butters et al., 2000; Doraiswamy et al., 2003; Nebes et al., 2003). Such findings suggest this deficit may be a trait of late-life depression and not symptom dependent. There is also evidence that executive functioning is impaired in depression, even after controlling for processing speed (Dybedal, Tanum, Sundet, Gaarden, & Bjolseth, 2013).

Late-life depression and cognitive decline

In addition to cognitive difficulties in cross-sectional studies, depression is linked to increased risk for future cognitive decline. It is likely that the severity of depressive symptoms is important in understanding which individuals will be at higher risk for developing dementia in the future. A recent study by Kaup et al. (2016) tracked a sample of nearly 2500 older adults, assessing depressive symptoms and cognitive status over the course of a decade. Their findings showed that individuals with a high-level depression of increasing severity over time are at a greater risk for developing dementia (Kaup et al., 2016). Also, prior research suggests the rate of dementia increases by 13% with every inpatient hospitalization related to depression, again suggesting that greater symptom severity increases dementia risk (Kessing & Andersen, 2004). Multiple other longitudinal studies of depression and cognition in older

adults report similar findings, suggesting a fairly robust relationship in at least a subset of older adults reporting depression. One study found greater depressive symptom severity is associated with increased risk for cognitive decline at 5-year follow-up and three times greater likelihood of developing MCI or dementia in older women (Spira, Rebok, Stone, Kramer, & Yaffe, 2012). In another sample of older women who were CN at baseline, higher levels of depression were associated with future cognitive impairment across multiple cognitive domains (Rosenberg, Mielke, Xue, & Carlson, 2010). Further, studies have found an association between late-onset depression and AD, with reports as high as a 50% increased likelihood of developing dementia for those individuals reporting depression as compared to those who do not (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006).

Cognitive models linking late-life depression and cognition

One primary proposed model for understanding the relationship between late-life depression and cognitive deficits is known as the vascular depression hypothesis. The hypothesis posits that frontal−subcortical−limbic dysfunction, caused by cerebrovascular disease burden, causes both difficulty in mood regulation and the cognitive deficits commonly associated with late-life depression (Aizenstein et al., 2016; Massman, Delis, Butters, Dupont, & Gillin, 1992). Specifically, cerebrovascular disease disrupts subcortical circuits, producing executive dysfunction, slowed processing speed, and several symptoms of depression (Alexopoulos, et al., 2002). Prior neuroimaging studies have provided strong evidence for this relationship between vascular-related white matter lesions, depression, and cognitive problems, including VaD (Taylor, Aizenstein, & Alexopoulos, 2013). Late-life depression is frequently associated with greater cerebrovascular disease burden in neuroimaging studies (Coffey, Figiel, Djang, Saunders, & Weiner, 1989), and evidence of white matter lesions on MRI is a proposed criteria for a diagnosis of vascular depression (Krishnan, Hays, & Blazer, 1997). Individuals with vascular-driven depression often have poor response to treatment with antidepressants, as do individuals with executive dysfunction, which may suggest a commonality between these two factors (Alexopoulos et al., 2005; Groves, Douglas, & Porter, 2018).

Late-life anxiety and cognitive performance

The study of anxiety and its impact on cognitive performance have received increasing attention over the last decade and gained an appreciation as an important factor in understanding aging and cognition. Extant research generally supports the view that older adults with symptoms of anxiety have worse global cognitive functioning as compared to asymptomatic peers (Beaudreau & O'Hara, 2008). The relationship between cognition and anxiety is often thought to be negatively correlated, in that older adults reporting elevated levels of anxiety have poorer cognitive functioning as compared to older adults reporting fewer anxiety symptoms (Sinoff & Werner, 2003). However, there is evidence that anxiety symptom severity may have a U-shaped relationship with cognitive functioning, in that mild anxiety is beneficial to cognitive performance while elevated levels are detrimental (Bierman, et al., 2005). Similar to depression, elevated symptoms of anxiety are sometimes associated with cognitive deficits in specific domains, including attention, processing speed, memory, and cognitive control.

Attention and processing speed are two cognitive abilities that are frequently shown to be worse in individuals with anxiety (Beaudreau & O'Hara, 2009; Wetherell, Reynolds, Gatz, & Pedersen, 2002). There is evidence that higher levels of anxiety disrupt attention, but primarily in the context of tasks that are more effortful or are more complex (Wetherell, et al., 2002). In addition, older adults reporting greater severity of anxiety symptoms perform worse on tasks of divided attention than those reporting minimal anxiety (Hogan, 2003). While anxiety symptoms are often associated with poor attention in cross-sectional studies, there is little evidence that anxiety predicts worsening attention over time, as several longitudinal studies have reported null findings (Gulpers et al., 2016).

There is also research suggesting anxiety has a negative influence on an individual's ability to learn and remember information. Older adult samples show worse learning and memory for verbal information in individuals reporting greater generalized anxiety symptoms (Mantella et al., 2007). There is evidence that individuals with greater symptoms of anxiety employ less efficient learning strategies, which compromises the initial learning of information and results in poor memory performance (Yochim, Mueller, & Segal, 2013). Thus, it may be possible that learning and memory deficits in individuals with anxiety may be partially accounted for by deficits in cognitive control and executive functioning.

Late-life anxiety and cognitive control

Cognitive control has received increasing attention as an important cognitive process in understanding anxiety. The construct of cognitive control refers to the processes which are integral for an individual to maintain and switch goals (Miller, 2000). Aspects of attention, working memory, and inhibitory abilities are all vital components of cognitive control, allowing individuals to shift their attention, adapt to their circumstances, and employ mental flexibility. Cognitive control may be disrupted transdiagnostically in individuals with psychiatric disorders, and there is growing evidence that cognitive control deficits may largely account for the socio-occupational difficulties commonly seen in individuals with mood disorders (McTeague, Goodkind, & Etkin, 2016).

One common tool to assess cognitive control is the Stroop Task. This task requires individuals to inhibition an overlearned, more automatic response, and instead provides an incongruent answer—do not read a color word (e.g., red) and instead name the color of the printed ink. In older adults, inhibitory ability appears to be lower in those with more severe anxiety symptoms (Beaudreau & O'Hara, 2008). These findings were not due to depressive symptoms, suggesting anxiety uniquely impacts inhibitory abilities. Another cognitive control ability, set-shifting (e.g., alternate between numbers and letters sequentially), is worse in individuals with higher levels of anxiety (Yochim, et al., 2013). Consistent with these findings, Butters et al. (2011) found poorer cognitive control abilities in older adults with generalized anxiety disorder (GAD) compared to older nonpsychiatric controls. Cognitive control is likely important in the process of controlling worry, a prominent symptom of anxiety, which suggests an important relationship between cognitive control and anxiety (Hallion, Ruscio, & Jha, 2014). Interestingly, there is evidence that the presence of worry in and of itself is detrimental to cognitive control abilities, even when individuals are not actively engaged in attempts to control worry (Hallion, et al., 2014).

Anxiety and cognitive decline

There is increasing empirical evidence that anxiety is associated with future cognitive decline. A recent meta-analysis by Gulpers et al. (2016) found that anxiety symptoms predict incidence of cognitive impairment and dementia, particularly in those over the age of 80. Several studies report the onset of anxiety precedes cognitive decline in older adults and that greater anxiety symptoms in cognitively intact older adults place individuals at an increased risk for future cognitive decline and a diagnosis of dementia (Burton, Campbell, Jordan, Strauss, & Mallen, 2013; Gallacher et al., 2009; Potvin, Forget, Grenier, Préville, & Hudon, 2011; Sinoff & Werner, 2003). In a recent study, Petkus and colleagues (2016) found similar findings, showing that baseline levels of anxiety were associated with a diagnosis of dementia over a 28-year timespan. Further, individuals who reported high anxiety at any time during the follow-up had a 48% increased risk for dementia than those who did not report high levels of anxiety.

Cooccurring anxiety and depression

Disentangling the relationship between cognition and mental health symptoms is complicated in individuals with cooccurring disorders. Mantella et al. (2007) compared cognitive performance in older adults with major depressive disorder (MDD), GAD, and those without a psychiatric diagnosis with the goal of examining the unique and common impact of depression and anxiety on cognition. While the GAD and MDD groups both showed deficits in memory recall following a delay, only the GAD group demonstrated significantly worse immediate memory. While anxiety and depression may have varying cognitive profiles, there is evidence that cooccurring anxiety and depressive symptoms in older adults have a dose effect on cognition, hastening cognitive and functional decline as compared to those with MDD alone (DeLuca et al., 2005).

Cognitive models linking late-life anxiety and cognition

There are several proposed models that attempt to explain the link between elevated anxiety and cognitive deficits. One of the most commonly cited theories is Eysenck's Processing Efficiency Theory and subsequent expansion with the Attentional Control Theory (Eysenck, Derakshan, Santos, & Calvo, 2007). Eysenck and colleagues propose that individuals with high levels of anxiety are preoccupied with monitoring external and internal threat, which depletes cognitive resources important for attention and quickly processing information (Eysenck et al., 2007). As processing speed and attention are basic components of cognitive processing, anxiety may result in both top-down (goal-directed behavior)

and bottom-up (stimulus-response behavior) processing deficiencies, as well as difficulty in more complex tasks that require focused attention or shifting between tasks (Eysenck, et al., 2007).

Marchant and Howard (2015) propose a modification to the Processing Efficiency Theory, merging Eysenck's theory with the concept of cognitive reserve. Cognitive reserve, typically couched in aging and dementia, describes a constellation of factors that are thought to bestow relative protection against cognitive decline (Stern, 2002). Marchant and Howard introduce the concept of Cognitive Debt, defined as thoughts and behaviors that deplete cognitive resources and increase an individual's vulnerability for dementia (Marchant & Howard, 2015). The authors posit that anxiety taxes cognitive reserve and usurps mental resources, which decreases an individual's ability to compensate for age-related cognitive decline or neurodegenerative-related loss of cognitive function. Further, the authors propose that repetitive negative thinking (e.g., worry and rumination) particularly disrupts cognitive functioning, creating difficulties with cognitive control and selective attention by diverting cognitive resources (Marchant & Howard, 2015).

Multiple studies report findings that can be interrupted as consistent with either model, suggesting anxiety symptom severity is likely one part of the mosaic representing the complicated, multifactorial process of cognitive functioning in older adults. Also, the directionality of the relationship between anxiety and cognitive difficulties is still uncertain. It may be that anxiety competes for attentional resources, disrupting cognitive efficiency. It may also be that individuals with anxiety are less able to inhibit anxiety-related thoughts and symptoms due to cognitive dysfunction, resulting in repetitive negative thinking. This is compatible with recent research indicating attention and working memory abilities are important in effective emotion regulation in older adults (Hantke et al., 2016).

Conclusion

Dementia and its subtypes are by definition characterized by cognitive deficits greater than expected in healthy aging. Depression and anxiety symptoms are also often associated with cognitive difficulties beyond normal aging. While these neurodegenerative diseases and mental health disorders often demonstrate differing cognitive profiles, clinical courses, and pathologies, these disorders are often cooccurring and there is increasing evidence for the involvement of common brain regions. Further, recent research suggests mental health problems may be associated with a higher risk for future cognitive decline and incidence of dementia. There is growing evidence that the interaction between cognition and late-life psychiatric symptoms represents a reciprocal relationship, and future research exploring the possibility of late-life psychiatric phenotypes and related cognitive profiles may provide insight into both mental health and cognitive decline in older adults (O'Hara, 2012).

References

Aizenstein, H. J., Baskys, A., Boldrini, M., Butters, M. A., Diniz, B. S., Jaiswal, M. K., ... Tene, O. (2016). Vascular depression consensus report—A critical update. *BMC Medicine*, *14*(1), 161, 2016 Nov 3.

Albert, M. L., & Knoefel, J. E. (1994). *Clinical neurology of aging* (2nd ed.). New York, NY: Oxford University Press.

Albert, M. S. (1996). Cognitive and neurobiologic markers of early Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(24), 13547−13551.

Alexopoulos, G. S., Kiosses, D. N., Heo, M., Murphy, C. F., Shanmugham, B., & Gunning-Dixon, F. (2005). Executive dysfunction and the course of geriatric depression. *Biological Psychiatry*, *58*(3), 204−210. Available from https://doi.org/10.1016/j.biopsych.2005.04.024, S0006-3223(05)00484-1 [pii].

Alexopoulos, G. S., Kiosses, D. N., Klimstra, S., Kalayam, B., & Bruce, M. L. (2002). Clinical presentation of the "depression-executive dysfunction syndrome" of late life. *The American Journal of Geriatric Psychiatry*, *10*(1), 98−106.

Andrada-Serpa, M. J., Tosswill, J., Schor, D., Linhares, D., Dobbin, J., & Pereira, M. S. (1989). Seroepidemiologic survey for antibodies to human retroviruses in human and non-human primates in Brazil. *International Journal of Cancer*, *44*(3), 389−393.

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *The American Journal of Geriatric Psychiatry*, *16*(10), 790−803.

Beaudreau, S. A., & O'Hara, R. (2009). The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging*, *24*(2), 507−512. Available from https://doi.org/10.1037/a0016035, 2009-08094-022 [pii].

Bierman, E. J., Comijs, H. C., Jonker, C., & Beekman, A. T. (2005). Effects of anxiety versus depression on cognition in later life. *The American Journal of Geriatric Psychiatry*, *13*(8), 686−693. Available from https://doi.org/10.1176/appi.ajgp.13.8.686.

Bondi, M. W., Edmonds, E. C., Jak, A. J., Clark, L. R., Delano-Wood, L., McDonald, C. R., ... Salmon, D. P. (2014). Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *Journal of Alzheimer's Disease*, *42*(1), 275−289. Available from https://doi.org/10.3233/JAD-140276.

Bondi, M. W., Jak, A. J., Delano-Wood, L., Jacobson, M. W., Delis, D. C., & Salmon, D. P. (2008). Neuropsychological contributions to the early identification of Alzheimer's disease. *Neuropsychology Review*, *18*(1), 73−90. Available from https://doi.org/10.1007/s11065-008-9054-1.

Boone, D. E. (1995). A cross-sectional analysis of WAIS-R aging patterns with psychiatric inpatients: Support for Horn's hypothesis that fluid cognitive abilities decline. *Perceptual and Motor Skills*, *81*(2), 371−379. Available from https://doi.org/10.2466/pms.1995.81.2.371.

Bott, N. T., Johnson, E. T., Schuff, N., Galifianakis, N., Subas, T., Pollock, J., ... Possin, K. L. (2014). Sensitive measures of executive dysfunction in non-demented Parkinson's disease. *Parkinsonism and Related Disorders*, *20*(12), 1430−1433. Available from https://doi.org/10.1016/j.parkreldis.2014.10.007.

Bott, N. T., Radke, A., Stephens, M. L., & Kramer, J. H. (2014). Frontotemporal dementia: Diagnosis, deficits and management. *Neurodegenerative Disease Management.*, *4*(6), 439−454. Available from https://doi.org/10.2217/nmt.14.34.

Brickman, A. M., & Stern, Y. (Eds.), (2009). *Aging and memory in humans*. Burlington, MA: Academic Press.

Brooks, B. L., Iverson, G. L., Holdnack, J. A., & Feldman, H. H. (2008). Potential for misclassification of mild cognitive impairment: A study of memory scores on the Wechsler Memory Scale-III in healthy older adults. *Journal of the International Neuropsychological Society*, *14*(3), 463−478. Available from https://doi.org/10.1017/S1355617708080521.

Brunnstrom, H., Gustafson, L., Passant, U., & Englund, E. (2009). Prevalence of dementia subtypes: A 30-year retrospective survey of neuropathological reports. *Archives of Gerontology and Geriatrics*, *49*(1), 146−149. Available from https://doi.org/10.1016/j.archger.2008.06.005.

Bryant, C., Jackson, H., & Ames, D. (2008). The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *Journal of Affective Disorders*, *109*(3), 233−250. Available from https://doi.org/10.1016/j.jad.2007.11.008, S0165-0327(07)00398-9 [pii].

Burton, C., Campbell, P., Jordan, K., Strauss, V., & Mallen, C. (2013). The association of anxiety and depression with future dementia diagnosis: A case-control study in primary care. *Family Practice.*, *30*(1), 25−30. Available from https://doi.org/10.1093/fampra/cms044.

Butters, M. A., Becker, J. T., Nebes, R. D., Zmuda, M. D., Mulsant, B. H., Pollock, B. G., & Reynolds, C. F., 3rd (2000). Changes in cognitive functioning following treatment of late-life depression. *The American Journal of Psychiatry*, *157*(12), 1949−1954.

Butters, M. A., Bhalla, R. K., Andreescu, C., Wetherell, J. L., Mantella, R., Begley, A. E., & Lenze, E. J. (2011). Changes in neuropsychological functioning following treatment for late-life generalised anxiety disorder. *British Journal of Psychiatry*, *199*(3), 211−218. Available from https://doi.org/10.1192/bjp.bp.110.090217.

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H., ... Becker, J. T. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry*, *61*(6), 587−595.

Butters, N., Granholm, E., Salmon, D., Grant, I., & Wolfe, J. (1987). Episodic and semantic memory: A comparison of amnesic and demented patients. *Journal of Clinical and Experimental Neuropsychology*, *9*(5), 479−497.

Butts, A. M., Machulda, M. M., Duffy, J. R., Strand, E. A., Whitwell, J. L., & Josephs, K. A. (2015). Neuropsychological profiles differ among the three variants of primary progressive aphasia. *Journal of the International Neuropsychological Society*, *21*(6), 429−435. Available from https://doi.org/10.1017/S1355617715000399.

Cahn-Weiner, D. A., Malloy, P. F., Boyle, P. A., Marran, M., & Salloway, S. (2000). Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *The Clinical Neuropsychologist*, *14*(2), 187−195. Available from https://doi.org/10.1076/1385-4046(200005)14:2;1-Z;FT187.

Cherry, B. J., Buckwalter, J. G., & Henderson, V. W. (2002). Better preservation of memory span relative to supraspan immediate recall in Alzheimer's disease. *Neuropsychologia*, *40*(7), 846−852.

Coffey, C. E., Figiel, G. S., Djang, W. T., Saunders, W. B., & Weiner, R. D. (1989). White matter hyperintensity on magnetic resonance imaging: Clinical and neuroanatomic correlates in the depressed elderly. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *1*(2), 135−144.

Craik, F. I. (2006). Brain-behavior relations across the lifespan: A commentary. *Neuroscience & Biobehavioral Reviews*, *30*(6), 885−892. Available from https://doi.org/10.1016/j.neubiorev.2006.06.010, S0149-7634(06)00055-8 [pii].

Cronin-Golomb, A., & Amick, M. (2001). Spatial abilities in aging, Alzheimer's disease, and Parkinson's disease. In (2 ed.F. Boller, & S. Cappa (Eds.), *Handbook on the neuropsychology of aging and dementia.* (Vol. 6Amsterdam: Elsevier.

Delis, D., Massman, P., Butters, N., Salmon, D., Cermak, L., & Kramer, J. (1991). Profiles of demented and amnesic patients on the California Verbal Learning Test: Implications for the assessment of memory disorders. *Psychological Assessment*, *3*, 19−26.

DeLuca, A. K., Lenze, E. J., Mulsant, B. H., Butters, M. A., Karp, J. F., Dew, M. A., ... Reynolds, C. F., 3rd (2005). Comorbid anxiety disorder in late life depression: Association with memory decline over four years. *International Journal of Geriatric Psychiatry*, *20*(9), 848−854. Available from https://doi.org/10.1002/gps.1366.

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F., 3rd (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *British Journal of Psychiatry*, *202*(5), 329−335. Available from https://doi.org/10.1192/bjp.bp.112.118307, 202/5/329 [pii].

Dobbs, A. R., & Rule, B. G. (1989). Adult age differences in working memory. *Psychology and Aging*, *4*(4), 500−503.

Doraiswamy, P. M., Krishnan, K. R., Oxman, T., Jenkyn, L. R., Coffey, D. J., Burt, T., & Clary, C. M. (2003). Does antidepressant therapy improve cognition in elderly depressed patients? *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(12), M1137−M1144.

Drag, L. L., & Bieliauskas, L. A. (2010). Contemporary review 2009: Cognitive aging. *Journal of Geriatric Psychiatry and Neurology*, *23*(2), 75−93. Available from https://doi.org/10.1177/0891988709358590.

Dumas, J. A., & Newhouse, P. A. (2015). Impaired working memory in geriatric depression: An FMRI study. *The American Journal of Geriatric Psychiatry*, *23*(4), 433−436. Available from https://doi.org/10.1016/j.jagp.2014.09.011, S1064-7481(14)00281-4 [pii].

Duzel, E., Schutze, H., Yonelinas, A. P., & Heinze, H. J. (2011). Functional phenotyping of successful aging in long-term memory: Preserved performance in the absence of neural compensation. *Hippocampus*, *21*(8), 803−814. Available from https://doi.org/10.1002/hipo.20834.

Dybedal, G. S., Tanum, L., Sundet, K., Gaarden, T. L., & Bjolseth, T. M. (2013). Neuropsychological functioning in late-life depression. *Frontiers in Psychology*, *4*, 381. Available from https://doi.org/10.3389/fpsyg.2013.00381.

Edmonds, E. C., Delano-Wood, L., Clark, L. R., Jak, A. J., Nation, D. A., McDonald, C. R., ... Neuroimaging, I. (2015). Susceptibility of the conventional criteria for mild cognitive impairment to false-positive diagnostic errors. *Alzheimer's & Dementia*, *11*(4), 415–424. Available from https://doi.org/10.1016/j.jalz.2014.03.005.

Edmonds, E. C., Delano-Wood, L., Galasko, D. R., Salmon, D. P., Bondi, M. W., & Alzheimer's Disease Neuroimaging, I. (2014). Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *Journal of the International Neuropsychological Society*, *20*(8), 836–847. Available from https://doi.org/10.1017/S135561771400068X.

Edmonds, E. C., Delano-Wood, L., Jak, A. J., Galasko, D. R., Salmon, D. P., Bondi, M. W., & Alzheimer's Disease Neuroimaging, I. (2016). "Missed" mild cognitive impairment: High false-negative error rate based on conventional diagnostic criteria. *Journal of Alzheimer's Disease*, *52*(2), 685–691. Available from https://doi.org/10.3233/JAD-150986.

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology*, *22*(5), 626–637. Available from https://doi.org/10.1037/0894-4105.22.5.626, 2008-11707-008 [pii].

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., ... Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*, *22*(12), 1689–1707. Available from https://doi.org/10.1002/mds.21507, quiz 1837.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion*, *7*(2), 336–353. Available from https://doi.org/10.1037/1528-3542.7.2.336.

Feil, D., Razani, J., Boone, K., & Lesser, I. (2003). Apathy and cognitive performance in older adults with depression. *International Journal of Geriatric Psychiatry*, *18*(6), 479–485.

Ferman, T. J., Smith, G. E., Boeve, B. F., Graff-Radford, N. R., Lucas, J. A., Knopman, D. S., ... Dickson, D. W. (2006). Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. *The Clinical Neuropsychologist*, *20*(4), 623–636. Available from https://doi.org/10.1080/13854040500376831.

Gallacher, J., Bayer, A., Fish, M., Pickering, J., Pedro, S., Dunstan, F., ... Ben-Shlomo, Y. (2009). Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. *Psychosomatic Medicine*, *71*(6), 659–666. Available from https://doi.org/10.1097/PSY.0b013e3181a6177c.

Geda, Y. E., Smith, G. E., Knopman, D. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., ... Petersen, R. C. (2004). De novo genesis of neuropsychiatric symptoms in mild cognitive impairment (MCI). *International Psychogeriatrics*, *16*(1), 51–60.

Glisky, E. L., Rubin, S. R., & Davidson, P. S. (2001). Source memory in older adults: An encoding or retrieval problem? *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *27*(5), 1131–1146.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., ... Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006–1014. Available from https://doi.org/10.1212/WNL.0b013e31821103e6.

Groves, S. J., Douglas, K. M., & Porter, R. J. (2018). A systematic review of cognitive predictors of treatment outcome in major depression. *Frontiers in Psychiatry*, *28*(9), 1–20. Available from https://doi.org/10.3389/fpsyt.2018.00382.

Gulpers, B., Ramakers, I., Hamel, R., Kohler, S., Oude Voshaar, R., & Verhey, F. (2016). Anxiety as a predictor for cognitive decline and dementia: A systematic review and meta-analysis. *The American Journal of Geriatric Psychiatry*, *24*(10), 823–842. Available from https://doi.org/10.1016/j.jagp.2016.05.015.

Hallion, L. S., Ruscio, A. M., & Jha, A. P. (2014). Fractionating the role of executive control in control over worry: A preliminary investigation. *Behaviour Research and Therapy*, *54*, 1–6. Available from https://doi.org/10.1016/j.brat.2013.12.002.

Hantke, N. C., Gyurak, A., Van Moorleghem, K., Waring, J. D., Adamson, M. M., O'Hara, R., & Beaudreau, S. A. (2016). Disentangling cognition and emotion in older adults: The role of cognitive control and mental health in emotional conflict adaptation. *International Journal of Geriatric Psychiatry*, *32*, 840–848. Available from https://doi.org/10.1002/gps.4535.

Hartman, M., & Hasher, L. (1991). Aging and suppression: Memory for previously relevant information. *Psychology and Aging*, *6*(4), 587–594.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience*, *5*(2), 87–96. Available from https://doi.org/10.1038/nrn1323, nrn1323 [pii].

Hodges, J., & Graham, N. (2001). Vascular dementias. In J. Hodges (Ed.), *Early-onset dementia: A multidisciplinary approach* (pp. 319–337). Oxford: Oxford Univ. Press.

Hodges, J., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*, *33*(4), 441–459.

Hogan, M. J. (2003). Divided attention in older but not younger adults is impaired by anxiety. *Experimental Aging Research*, *29*(2), 111–136.

Ince, P., & Perry, E. (2005). Pathology of dementia with Lewy bodies. In A. Burns, J. O'Brien, & D. Ames (Eds.), *Dementia.* (3 ed., pp. 615–633). London: Hodder Arnold.

Jacobs, D., Salmon, D. P., Troster, A. I., & Butters, N. (1990). Intrusion errors in the figural memory of patients with Alzheimer's and Huntington's disease. *Archives of Clinical Neuropsychology*, *5*(1), 49–57.

Jak, A. J., Bondi, M. W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D. P., & Delis, D. C. (2009). Quantification of five neuropsychological approaches to defining mild cognitive impairment. *The American Journal of Geriatric Psychiatry*, *17*(5), 368–375. Available from https://doi.org/10.1097/JGP.0b013e31819431d5.

Jouvent, E., Reyes, S., De Guio, F., & Chabriat, H. (2015). Reaction time is a marker of early cognitive and behavioral alterations in pure cerebral small vessel disease. *Journal of Alzheimer's Disease*, *47*(2), 413–419. Available from https://doi.org/10.3233/JAD-150083.

Jurica, P. J., Leitten, C. L., & Mattis, S. (2001). *Dementia Rating Scale-2*. Odessa, FL: Psychological Assessment Resources.

Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., … Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, *73*(5), 525–531.

Kawas, C. H., Corrada, M. M., Brookmeyer, R., Morrison, A., Resnick, S. M., Zonderman, A. B., & Arenberg, D. (2003). Visual memory predicts Alzheimer's disease more than a decade before diagnosis. *Neurology*, *60*(7), 1089–1093.

Kensinger, E. A. (Ed.), (2009). *Cognition in aging and age-related disease.*. Burlington, MA: Academic Press.

Kertesz, A. (2006). Progress in clinical neurosciences: Frontotemporal dementia-pick's disease. *Canadian Journal of Neurological Sciences*, *33*(2), 141–148.

Kessing, L. V., & Andersen, P. K. (2004). Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(12), 1662–1666. Available from https://doi.org/10.1136/jnnp.2003.031773.

Kiernan, R. J., Mueller, J., Langston, J. W., & Van Dyke, C. (1987). The neurobehavioral cognitive status examination: A brief but differentiated approach to cognitive assessment. *Annals of Internal Medicine*, *107*, 481–485.

Koenig, A. M., Bhalla, R. K., & Butters, M. A. (2014). Cognitive functioning and late-life depression. *Journal of the International Neuropsychological Society*, *20*(5), 461–467. Available from https://doi.org/10.1017/s1355617714000198.

Kramer, J. H., Jurik, J., Sha, S. J., Rankin, K. P., Rosen, H. J., Johnson, J. K., & Miller, B. L. (2003). Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cognitive and Behavioral Neurology*, *16*(4), 211–218.

Kraybill, M. L., Larson, E. B., Tsuang, D. W., Teri, L., McCormick, W. C., Bowen, J. D., … Cherrier, M. M. (2005). Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology*, *64*(12), 2069–2073. Available from https://doi.org/10.1212/01.WNL.0000165987.89198.65.

Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *The American Journal of Psychiatry*, *154*(4), 497–501. Available from https://doi.org/10.1176/ajp.154.4.497.

Laborde-Lahoz, P., El-Gabalawy, R., Kinley, J., Kirwin, P. D., Sareen, J., & Pietrzak, R. H. (2015). Subsyndromal depression among older adults in the USA: Prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. *International Journal of Geriatric Psychiatry*, *30*(7), 677–685. Available from https://doi.org/10.1002/gps.4204.

Lamar, M., Ajilore, O., Leow, A., Charlton, R., Cohen, J., GadElkarim, J., … Kumar, A. (2016). Cognitive and connectome properties detectable through individual differences in graphomotor organization. *Neuropsychologia*, *85*, 301–309. Available from https://doi.org/10.1016/j.neuropsychologia.2016.03.034.

Lefleche, G., & Albert, M. (1995). Executive function deficits in early AD involve concurrent manipulation of information (e.g., set-shifting, sequencing) rather than cued-directed attention or problem solving. *Neuropsychology*, *9*, 313–320.

Lenehan, M. E., Klekociuk, S. Z., & Summers, M. J. (2012). Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): Is it time to abandon subjective memory complaint as an MCI diagnostic criterion? *International Psychogeriatrics*, *24*(9), 1505–1514. Available from https://doi.org/10.1017/S1041610212000695.

Levy, B., Tsoy, E., & Gable, S. (2016). Developing cognitive markers of Alzheimer's disease for primary care: Implications for behavioral and global prevention. *Journal of Alzheimer's Disease*, *54*(4), 1259–1272. Available from https://doi.org/10.3233/JAD-160309.

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*, *16*(7), 916–928. Available from https://doi.org/10.1093/cercor/bhj043, bhj043 [pii].

Lezak, D. L., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment.* (5th ed.). Oxford; New York: Oxford University Press.

Mantella, R. C., Butters, M. A., Dew, M. A., Mulsant, B. H., Begley, A. E., Tracey, B., … Lenze, E. J. (2007). Cognitive impairment in late-life generalized anxiety disorder. *The American Journal of Geriatric Psychiatry*, *15*(8), 673–679.

Marchant, N. L., & Howard, R. J. (2015). Cognitive debt and Alzheimer's disease. *Journal of Alzheimer's Disease*, *44*(3), 755–770. Available from https://doi.org/10.3233/jad-141515.

Massman, P. J., Delis, D. C., Butters, N., Dupont, R. M., & Gillin, J. C. (1992). The subcortical dysfunction hypothesis of memory deficits in depression: Neuropsychological validation in a subgroup of patients. *Journal of Clinical and Experimental Neuropsychology*, *14*(5), 687–706. Available from https://doi.org/10.1080/01688639208402856.

Mathias, J. L., & Burke, J. (2009). Cognitive functioning in Alzheimer's and vascular dementia: A meta-analysis. *Neuropsychology*, *23*(4), 411–423. Available from https://doi.org/10.1037/a0015384.

Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, *55*(11), 1613–1620.

McKeith, I. G., Galasko, D., Kosaka, K., Perry, E. K., Dickson, D. W., Hansen, L. A., … Perry, R. H. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology*, *47*(5), 1113–1124.

McTeague, L. M., Goodkind, M. S., & Etkin, A. (2016). Transdiagnostic impairment of cognitive control in mental illness. *Journal of Psychiatric Research*, *83*, 37–46.

Mendez, M. F., Cherrier, M., Perryman, K. M., Pachana, N., Miller, B. L., & Cummings, J. L. (1996). Frontotemporal dementia versus Alzheimer's disease: Differential cognitive features. *Neurology*, *47*(5), 1189–1194.

Merdes, A. R., Hansen, L. A., Jeste, D. V., Galasko, D., Hofstetter, C. R., Ho, G. J., ... Corey-Bloom, J. (2003). Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. *Neurology*, *60*(10), 1586–1590.

Mesulam, M. (2008). Primary progressive aphasia pathology. *Annals of Neurology*, *63*(1), 124–125. Available from https://doi.org/10.1002/ana.20940.

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience*, *1*(1), 59–65. Available from https://doi.org/10.1038/35036228.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow, H. (2005). Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699.

Nebes, R. D. (1989). Semantic memory in Alzheimer's disease. *Psychological Bulletin*, *106*(3), 377–394.

Nebes, R. D., Pollock, B. G., Houck, P. R., Butters, M. A., Mulsant, B. H., Zmuda, M. D., & Reynolds, C. F., 3rd (2003). Persistence of cognitive impairment in geriatric patients following antidepressant treatment: A randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of Psychiatric Research*, *37*(2), 99–108. Available from https://doi.org/S0022395602000857, [pii].

Nelson, P. T., Dickson, D. W., Trojanowski, J. Q., Jack, C. R., Boyle, P. A., Afranakis, K., & Schneider, J. A. (2019). Limbic-predominant age-related TDP-34 encephalopathy (LATE): Consensus, working group report. *Brain*, *142*(6), 1503–1527.

Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychology and Aging*, *17*(1), 56–71.

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. Available from https://doi.org/10.1016/S1474-4422(14)70136-X.

O'Hara, R. (2012). The reciprocal relationship of neurocognitive and neuropsychiatric function in late life. *The American Journal of Geriatric Psychiatry*, *20*(12), 1001–1005. Available from https://doi.org/10.1097/JGP.0b013e318275d60f, S1064-7481(12)62011-9 [pii].

O'Hara, R., Coman, E., & Butters, M. A. (2009). *Clinical neuropsychology (2nd Ed)*. Washington, DC: American Psychological Association.

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry*, *63*(5), 530–538. Available from https://doi.org/10.1001/archpsyc.63.5.530, 63/5/530 [pii].

Palmer, K., Berger, A. K., Monastero, R., Winblad, B., Backman, L., & Fratiglioni, L. (2007). Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology*, *68*(19), 1596–1602. Available from https://doi.org/10.1212/01.wnl.0000260968.92345.3f, 68/19/1596 [pii].

Park, D. C., Welsh, R. C., Marshuetz, C., Gutchess, A. H., Mikels, J., Polk, T. A., ... Taylor, S. F. (2003). Working memory for complex scenes: Age differences in frontal and hippocampal activations. *Journal of Cognitive Neuroscience*, *15*(8), 1122–1134. Available from https://doi.org/10.1162/089892903322598094.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain*, *122*(Pt 3), 383–404.

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L. G., Ingvar, M., & Buckner, R. L. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral Cortex*, *16*(7), 907–915. Available from https://doi.org/10.1093/cercor/bhj036, bhj036 [pii].

Peterson, R. C., Lopez, O., Armstrong, M. J., Getchius, T. S. D., Ganguli, M., Glass, D., et al. (2018). Practice guidelines update summary: Mild cognitive impairment. *Neurology*, *90*(3), 126–135.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology*, *56*(3), 303–308.

Petkus, A. J., Reynolds, C. A., Wetherell, J. L., Kremen, W. S., Pedersen, N. L., & Gatz, M. (2016). Anxiety is associated with increased risk of dementia in older Swedish twins. *Alzheimers Dement*, *12*(4), 399–406. Available from https://doi.org/10.1016/j.jalz.2015.09.008.

Potter, G. G., & Steffens, D. C. (2007). Contribution of depression to cognitive impairment and dementia in older adults. *Neurologist*, *13*(3), 105–117. Available from https://doi.org/10.1097/01.nrl.0000252947.15389.a9, 00127893-200705000-00001 [pii].

Potvin, O., Forget, H., Grenier, S., Préville, M., & Hudon, C. (2011). Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. *Journal of the American Geriatrics Society*, *59*(8), 1421–1428. Available from https://doi.org/10.1111/j.1532-5415.2011.03521.x.

Pressman, P. S., Noniyeva, Y., Bott, N., Dutt, S., Sturm, V., Miller, B. L., & Kramer, J. H. (2016). Comparing volume loss in neuroanatomical regions of emotion versus regions of cognition in healthy aging. *PLoS One*, *11*(8), e0158187. Available from https://doi.org/10.1371/journal.pone.0158187, PONE-D-16-00832 [pii].

Price, C. C., Jefferson, A. L., Merino, J. G., Heilman, K. M., & Libon, D. J. (2005). Subcortical vascular dementia: Integrating neuropsychological and neuroradiologic data. *Neurology*, *65*(3), 376–382. Available from https://doi.org/10.1212/01.wnl.0000168877.06011.15.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and meta-analysis. *Alzheimer's & Dementia*, *9*(1), 63–75. Available from https://doi.org/10.1016/j.jalz.2012.11.007, e62.

Rabin, L. A., Pare, N., Saykin, A. J., Brown, M. J., Wishart, H. A., Flashman, L. A., & Santulli, R. B. (2009). Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *16*(3), 357–376. Available from https://doi.org/10.1080/13825580902825220.

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: A review of PET and fMRI studies on working and episodic memory. *Brain*, *128*(Pt 9), 1964–1983. Available from https://doi.org/10.1093/brain/awh608, awh608 [pii].

Ramanan, S., Bertoux, M., Flanagan, E., Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2016). Longitudinal executive function and episodic memory profiles in behavioral-variant frontotemporal dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *23*, 34−43. Available from https://doi.org/10.1017/S1355617716000837.

Rankin, K. P., Baldwin, E., Pace-Savitsky, C., Kramer, J. H., & Miller, B. L. (2005). Self awareness and personality change in dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(5), 632−639. Available from https://doi.org/10.1136/jnnp.2004.042879.

Rapp, M. A., Dahlman, K., Sano, M., Grossman, H. T., Haroutunian, V., & Gorman, J. M. (2005). Neuropsychological differences between late-onset and recurrent geriatric major depression. *The American Journal of Psychiatry*, *162*(4), 691−698. Available from https://doi.org/10.1176/appi.ajp.162.4.691, 162/4/691 [pii].

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., ... Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(Pt 9), 2456−2477. Available from https://doi.org/10.1093/brain/awr179.

Rascovsky, K., Salmon, D. P., Ho, G. J., Galasko, D., Peavy, G. M., Hansen, L. A., & Thal, L. J. (2002). Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology*, *58*(12), 1801−1808.

Rascovsky, K., Salmon, D. P., Hansen, L. A., Thal, L. J., & Galasko, D. (2007). Disparate letter and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. *Neuropsychology*, *21*(1), 20−30. Available from https://doi.org/10.1037/0894-4105.21.1.20.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews*, *30*(6), 730−748. Available from https://doi.org/10.1016/j.neubiorev.2006.07.001.

Reed, B. R., Mungas, D. M., Kramer, J. H., Ellis, W., Vinters, H. V., Zarow, C., ... Chui, H. C. (2007). Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*, *130*(Pt 3), 731−739. Available from https://doi.org/10.1093/brain/awl385.

Rogalski, E. J., Gefen, T., Shi, J., Samimi, M., Bigio, E., Weintraub, S., ... Mesulam, M. M. (2013). Youthful memory capacity in old brains: Anatomic and genetic clues from the Northwestern SuperAging Project. *Journal of Cognitive Neuroscience*, *25*(1), 29−36. Available from https://doi.org/10.1162/jocn_a_00300.

Rosenberg, P. B., Mielke, M. M., Xue, Q. L., & Carlson, M. C. (2010). Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *The American Journal of Geriatric Psychiatry*, *18*(3), 204−211. Available from https://doi.org/10.1097/JGP.0b013e3181c53487.

Salmon, D. P. (2000). Disorders of memory in Alzheimer's disease. In (2 ed.L. S. Cermak (Ed.), *Handbook of neuropsychology: Memory and its disorders* (Vol. 2Amsterdam: Elsevier.

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual Review of Psychology*, *60*, 257−282. Available from https://doi.org/10.1146/annurev.psych.57.102904.190024.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403−428.

Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society*, *16*(5), 754−760. Available from https://doi.org/10.1017/s1355617710000706.

Schacter, D. L., Kaszniak, A. W., Kihlstrom, J. F., & Valdiserri, M. (1991). The relation between source memory and aging. *Psychology and Aging*, *6*(4), 559−568.

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., ... Doraiswamy, P. M. (2006). Cognitive function in late life depression: Relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, *60*(1), 58−65. Available from https://doi.org/10.1016/j.biopsych.2005.09.019, S0006-3223(05)01320-X [pii].

Sinoff, G., & Werner, P. (2003). Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. *International Journal of Geriatric Psychiatry*, *18*(10), 951−959. Available from https://doi.org/10.1002/gps.1004.

Spira, A. P., Rebok, G. W., Stone, K. L., Kramer, J. H., & Yaffe, K. (2012). Depressive symptoms in oldest-old women: Risk of mild cognitive impairment and dementia. *The American Journal of Geriatric Psychiatry*, *20*(12), 1006−1015. Available from https://doi.org/10.1097/JGP.0b013e318235b611.

Stavitsky, K., Brickman, A. M., Scarmeas, N., Torgan, R. L., Tang, M. X., Albert, M., ... Stern, Y. (2006). The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer disease. *Archives of Neurology*, *63*(10), 1450−1456. Available from https://doi.org/10.1001/archneur.63.10.1450.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448−460.

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963−974. Available from https://doi.org/10.1038/mp.2013.20, mp201320 [pii].

Thomas-Anterion, C., Jacquin, K., & Laurent, B. (2000). Differential mechanisms of impairment of remote memory in Alzheimer's and frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, *11*(2), 100−106. Available from https://doi.org/10.1159/000017221.

Tiraboschi, P., Salmon, D. P., Hansen, L. A., Hofstetter, R. C., Thal, L. J., & Corey-Bloom, J. (2006). What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain*, *129*(Pt 3), 729−735. Available from https://doi.org/10.1093/brain/awh725.

Treitz, F. H., Heyder, K., & Daum, I. (2007). Differential course of executive control changes during normal aging. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *14*(4), 370−393. Available from https://doi.org/10.1080/13825580600678442, 779748552 [pii].

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Fischl, B., Salat, D., ... Dale, A. M. (2005). Cortical volume and speed-of-processing are complementary in prediction of performance intelligence. *Neuropsychologia*, *43*(5), 704–713. Available from https://doi.org/10.1016/j.neuropsychologia.2004.08.006, S0028-3932(04)00224-6 [pii].

Walker, Z., Possin, K. L., Boeve, B. F., & Aarsland, D. (2015). Lewy body dementias. *Lancet*, *386*(10004), 1683–1697. Available from https://doi.org/10.1016/S0140-6736(15)00462-6.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a006171. Available from https://doi.org/10.1101/cshperspect.a006171.

Wetherell, J. L., Reynolds, C. A., Gatz, M., & Pedersen, N. L. (2002). Anxiety, cognitive performance, and cognitive decline in normal aging. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *57*(3), P246–P255.

West, R. L. (1996). An application of Prefrontal Cortex Function Theory in cognitive aging. *Psychological Bulletin*, *120*(2), 272–292.

Wetzel, M., & Kramer, J. (2008). The neuropsychology of vascular dementia. In G. Goldenberg, & B. Miller (Eds.), *Handbook of Clinical Neurology.* (pp. 567–583). New York: Elsevier.

Wicklund, A. H., Johnson, N., & Weintraub, S. (2004). Preservation of reasoning in primary progressive aphasia: Further differentiation from Alzheimer's disease and the behavioral presentation of frontotemporal dementia. *Journal of Clinical and Experimental Neuropsychology*, *26*(3), 347–355. Available from https://doi.org/10.1080/13803390490510077.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., ... Petersen, R. C. (2004). Mild cognitive impairment—Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. Available from https://doi.org/10.1111/j.1365-2796.2004.01380.x.

Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal-neocortical interactions. *Neuropsychologia*, *48*(8), 2339–2356. Available from https://doi.org/10.1016/j.neuropsychologia.2010.04.016, S0028-3932(10)00162-4 [pii].

Yochim, B. P., Mueller, A. E., & Segal, D. L. (2013). Late life anxiety is associated with decreased memory and executive functioning in community dwelling older adults. *Journal of Anxiety Disorders*, *27*(6), 567–575. Available from https://doi.org/10.1016/j.janxdis.2012.10.010.

Further reading

Beaudreau, S. A., Rideaux, T., O'Hara, R., & Arean, P. (2015). Does cognition predict treatment response and remission in psychotherapy for late-life depression? *The American Journal of Geriatric Psychiatry*, *23*(2), 215–219. Available from https://doi.org/10.1016/j.jagp.2014.09.003.

This page intentionally left blank

Chapter 20

Integrative precision-medicine approach to cognitive assessment in older adults

Sharon Naparstek[1,2], Omer Linkovski[1,2,3] and Limor Gertner[4]

[1]Department of Psychiatry and Behavioral Sciences and Wu Tsai Neurosciences Institute, Stanford University School of Medicine, Stanford, CA, United States, [2]Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), Veterans Affairs Palo Alto Healthcare System, Palo Alto, CA, United States, [3]Department of Medical Neurobiology (Physiology), Faculty of Medicine, The Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University, Jerusalem, Israel, [4]Neuropsychiatric Clinic, Soroka University Medical Center, Beer-Sheva, Israel

Introduction

Brain−behavior interactions are imperative across a wide range of medical practices and are commonly probed by neuropsychological assessments. These assessments are carried out in order to support diagnosis of congenital or acquired neurological conditions or to assist in treatment planning or tracking (Lezak, Howieson, & Loring, 2012). Recent advancements include standardization of tools and norms (Elkana, Tal, Oren, Soffer, & Ash, 2019), the development of computer-based tests (Naparstek, El-Said, et al., 2019), and incorporation of test performance with neuroimaging tools for clinical prediction (Jack et al., 2019; Licher et al., 2019). However, current practices are challenged by cultural biases, time-consuming procedures, and relying on commercial testing tools. These factors may limit assessments' quality and prevalence in clinical and research settings, widening health disparities and hindering scientific advancement (Naparstek, Linkovski, & O'Hara, 2019). In the era of precision medicine, optimizing neuropsychological assessments is a necessity. The current chapter will suggest how and why a precision medicine approach should be applied in the field of neuropsychological assessment, and how applying this framework will increase sensitivity and specificity of existing diagnoses and improve treatment selection and outcome. By using an illustrative case study, we describe current discrepancies and suggest ways to implement and embrace the following changes: (1) explore behavior using a dimensional cross-diagnostic approach integrating different information levels (e.g., biology, cognition and behavior); (2) study brain atrophy and brain connectivity as potent markers of brain−behavior interactions; (3) adopt an open-science approach by creating open databases with neuroanatomical and behavioral records of different patient populations; and (4) incorporate technology in the assessment by using computerized tests and ecological momentary assessment (EMA) tools to complement the traditional tests and measures. Combining novel neurocognitive indexes with advanced genomics and state-of-the-art neuroimaging will allow creating individual profiles spanning the brain−behavior interaction. These profiles would guide personalized diagnostic and prognostic treatment strategies.

Case description

Mr. P. is a 60-year-old male referred to neuropsychological evaluation by his physician, following slight, although progressive, deterioration in his language abilities. In his intake, Mr. P. and his wife described that over the past 2 years Mr. P. has been experiencing difficulties in his verbal abilities, that he defined as: *"a difficulty to express what I want and need,"* alongside a loss of interest in daily activities and loss of energy. His physician diagnosed him with mild depression and prescribed a serotonin-specific reuptake inhibitor (SSRI). While energy levels improved to some extent, spoken language abilities continued to deteriorate, leading to frustration and withdrawal. A differential diagnosis of a progressive neurological disease was raised, leading the physician to refer Mr. P. to a computerized tomography (CT) scan that revealed no evidence of brain atrophy, vascular abnormalities, or signs of stroke. In the neuropsychological assessment, Mr. P. was highly motivated and cooperative. His memory and attention abilities were preserved,

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00020-X

and auditory comprehension was intact. However, when asked to describe his condition and engage in conversational speech, there were pronounced difficulties in word retrieval as well as verbal paraphasia. His performance in verbal tests was inconsistent, with some abilities highly impaired and others within the average range. Overall, his mood was euthymic but shifted when Mr. P. encountered difficulties. Since language deficits were inconsistent across the assessment, with discrepancies between spontaneous speech and test performance, and between different tests, the clinician sought to extend the evaluation and referred Mr. P. to an extensive neurological evaluation along with speech therapy. Given that the etiology of Mr. P.'s depressive symptoms remained unclear, the clinician also recommended that Mr. P. engages in cognitive behavioral therapy to help cope with his condition and improve resilience.

Such a scenario is not uncommon in our field. This delicate interplay between cognitive deficiencies inside and outside the office, and between cognitive and emotional factors, cannot be fully understood with traditional neuropsychological tools. Patients might complain about behavioral or emotional symptoms that do not necessarily appear as cognitive deficiencies, and vice versa (McDonald, Flashman, & Saykin, 2002). Such discrepancies question the validity of our neuropsychological tools and call for a joint effort to improve existing tools and develop new ways to learn about our examinees' everyday difficulties and experiences. In recent years, mental health providers and researchers addressed similar issues—inadequacy of existing diagnostic tools and diagnoses bearing low specificity and low sensitivity, leading to high variability among patients suffering from the same mental illness and to high comorbidity between different conditions. For example, under current DSM-5 criteria, one can be diagnosed as suffering from posttraumatic stress disorder in as many as 636,120 ways (Galatzer-Levy & Bryant, 2013). Adhering to this critique, a global effort has set out to optimize diagnosis and care in mental health practice. This effort and similar ones across medicine are referred to as "precision medicine" (Mirnezami, Nicholson, & Darzi, 2012). In this chapter, we explain how a precision medicine perspective can benefit clinical neuropsychology and outline tangible steps toward implementing such a framework in our field.

Beyond-symptoms approach

In his assessment, Mr. P. exhibited language deficits and mood lability. These symptoms are evident in multiple disorders and might be caused by multiple etiologies. Studying overt symptoms is our way to create a snapshot of the individual's condition and is highly informative. However, combining symptoms with transdiagnostic objective measures, such as genetic information and neural structure and function, may assist in creating a more comprehensive picture of one's condition by defining specific subtypes (Karalunas et al., 2014; Licher et al., 2019) improving clinical prediction (Jack et al., 2019; Maron-Katz et al., 2019) and defining vulnerability and resilience factors (Rutherford, Taylor, Brown, Sneed, & Roose, 2016). One such framework is the Research Domain Criteria (RDoC), launched by the US National Institute of Mental Health almost 10 years ago. Under this framework, researchers are encouraged to study mental health by examining transdiagnostic markers that are supported by cognitive and neural science and can be assessed by objective tools (Insel et al., 2010; Insel & Cuthbert, 2015). Although defined as a research framework, studies inspired by RDoC are achieving the desired added value. For example, subtyping of children with attention deficit hyperactivity disorder by their behavior (i.e., temperament) and validating these groups by objective measures (i.e., physiological response and neural connectivity) yielded superior clinical prediction compared to clinical symptoms alone (Karalunas et al., 2014). A recent call to include aging-related criteria in RDoC for the study of late-life depression (LLD) demonstrates the transition from a symptom to a transdiagnostic-based perspective and its clinical utility (Rutherford et al., 2016). Whereas 30 years ago, research focused on identification of general neuropsychological and neural symptoms, recent studies focus on unique biomarker/behavior interactions that might uncover heterogeneity of LLD and thus enable to improve early diagnosis and develop targeted interventions.

For Mr. P., an RDoC-guided assessment would have enabled a detailed examination of the reciprocal interactions between the emotional, cognitive, and biological aging processes that might have been overlooked in the existing assessment. Combining biological markers (e.g., genetic biomarkers, measures of gait and movement) with the cognitive and emotional measures may have assisted in defining and refining the diagnosis and in identifying Mr. P.'s risk (e.g., brain atrophy, fatigue, social isolation), as well as resilience (e.g., "normative" process of neuroinflammation, engagement in physical and social activity) factors. These, in turn, might lead to specific actions and therapeutic interventions.

Brain atrophy and connectivity

Clinical neurology and neuropsychology are rooted deep within the study of lesion localization. Verbal expression and comprehension, memory abilities, and executive functions were all defined following patients with focal lesions, which

led to changes in these abilities. Accordingly, studying the effects of aging over the brain has traditionally focused on describing the changes in brain volume, as an underlying mechanism of cognitive deterioration (Siman-Tov et al., 2017). Age-related reduction of gray matter (GM) and a decrease of brain volume were found in multiple cortical (i.e., frontal, occipital, and parietal) and subcortical (i.e., hippocampus, striatum, thalamus, and cerebellum) regions (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012; Raz et al., 2005). The decrease in GM volume follows a linear trend and correlates with cognitive deterioration in executive functions, attention, and memory, and perhaps mediates some psychiatric symptoms as well (Fjell & Walhovd, 2010). For example, a common pattern of cortical GM atrophy in the occipital and parietal lobes was described in a transdiagnostic sample of patients suffering from visual hallucinations (including patients with Parkinson's disease, Alzheimer's disease, dementia with Lewy bodies, and schizophrenia) (Carter & Ffytche, 2015; Ibarretxe-Bilbao et al., 2008). Finally, subtyping patients with dementia based on GM atrophy yielded distinct subtypes with unique cognitive and clinical profiles. These novel subtypes can improve our understanding of the heterogeneity of this disease (Ranasinghe et al., 2016).

These traditional approaches, of studying brain atrophy and lesion localization as an underlying mechanism of normative and pathological aging, were challenged by inconsistencies between brain/symptom mapping. Examples include similar symptoms that are caused from lesions in different locations; lesions leading to unpredicted symptoms; and symptoms occurring with no obvious lesions. These inconsistencies, alongside the understanding that most cognitive tasks necessitate integration of distinct brain operations (Siman-Tov et al., 2017) and that the interconnections of the human brain might serve as a preliminary stage for understanding its function (Sporns, Tononi, & Kötter, 2005), shifted the focus of attention from brain structure toward brain connectivity. Connectivity relates to one of two classes: (1) structural/anatomical connectivity, referring to the presence of an axonal connection between two brain regions and (2) functional connectivity, referring to the temporal correlation, or coherence, of spatially remote neurophysiological events. Alterations in both structural and functional connectivity have been shown to consistently occur in different neuropsychiatric disorders (Konrad & Eickhoff, 2010; Tamminga et al., 2014). Accordingly, reduction in axonal connectivity and changes in axon diffusion were suggested to explain many aging-related phenomena (Leuchter et al., 1994). One example is the suggestion that the decrease in processing speed, a fundamental mechanism underlying cognitive decline, results from a decrease in the connectivity between different brain areas, leading to slow and inefficient transfer of information across the brain (Catani & Ffytche, 2005; Fjell & Walhovd, 2010; Madden, Bennett, & Song, 2009; Rueda et al., 2004).

Two recent scientific approaches incorporating the study of brain networks to deepen our understanding of aging and neuropsychological disorders are lesion network mapping (Fox, 2018) and network degeneration (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). In lesion network mapping, different lesions leading to similar disorders are studied. Once the different lesions are mapped onto the brain, the functional (or anatomical) connectivity of that region to the rest of the brain is computed, using existing brain atlases. These maps can then be compared between lesions (people) and the shared functional (or anatomical) networks can be extracted and used for patient stratification, prognosis, or guiding therapy (Boes et al., 2015; Fox, 2018). The network degeneration hypothesis suggests that neurodegenerative diseases are related to dysfunction of neural networks (Buckner et al., 2005; Palop, Chin, & Mucke, 2006). This hypothesis warrants mapping and comparing different regions of cortical atrophy rather than locations of lesions. One such study found that in five distinct neurodegenerative diseases (Alzheimer's disease, behavioral variant frontotemporal dementia, semantic dementia, progressive nonfluent aphasia, and corticobasal syndrome), robust large-scale networks were affected in a specific manner, suggesting that neurodegeneration does not occur in an arbitrary pattern and can thus be monitored (Seeley et al., 2009). Importantly, by providing objective biomarkers, connectivity measures have the potential of defining unique biotypes of disorders, which may aid patient stratification and in predicting therapeutic outcomes (Arns et al., 2016; Barch, 2017; Williams, 2016). Connectivity measures are obtained mostly by employing MRI-based techniques, which are costly and not practical for clinical use. However, reducing costs and improving technology (Boto et al., 2018), as well as improving connectivity measures of existing tools (i.e., EEG connectivity; Li et al., 2013), may increase clinical availability and utility of these measures.

In Mr. P.'s case, a preliminary CT scan showed no signs of brain lesion or atrophy. One possibility is that Mr. P. suffers from more diffused microlesions in specific white matter tracts that cannot be detected in a standard CT scan and necessitate a specific MRI scan. Alternatively, it is possible that the scan was carried out too early to detect such changes and thus needs to be repeated. If future brain imaging will reveal a lesion or atrophy, mapping these onto existing connectivity maps might assist in gaining better understanding of the nature of his disease, expected patterns of deficits, or unique interaction between cognitive and emotional deficits that might not be exhibited in early stages of the disease.

An open-science approach

In recent years, there is a growing critique on the massive amount of false-positive results in many scientific fields, including psychology (Munafò et al., 2017). An open science collaboration initiative examining the reproducibility of published psychological studies, failed to find similar effects for most of the studies, despite strongly controlling for any possible difference between the original and replication study (Open Science Collaboration, 2015). Such critique has inspired different efforts to improve transparency and reproducibility of scientific studies. In neuroscience, the Organization of Human Brain Mapping created the Committee on Best Practices in Data Analysis and Sharing to compile a report on: "... the best practices for open science in neuroimaging" (Nichols et al., 2017). This report focuses on open science and specifically on data sharing as a tool to optimize research practice and improve generalizability. Implementing a similar methodology in the field of neuropsychological evaluation is necessary. Relevant data might include deidentified medical records of the examinee's brain lesion (including brain imaging), raw and normed scores on validated tests, and emerging tests and tasks. Importantly, personal data that are shared need to be handled in compliance with medical confidentiality rules and regulations (i.e., protected health information). Accumulating large data sets will enable us to analyze results in a data-driven, cross-diagnostic approach that will assist in the search for common and diverse factors between different conditions and improve treatment selection and outcome. Open access to tests and their results will enable us to revalidate and update existing test norms (Naparstek, El-Said, et al., 2019), to include relevant factors such as cultural background and socioeconomic status.

In the example above, Mr. P.'s performance was compared to age- and education-matched norms. This comparison did not consider other relevant aspects of his cognitive abilities such as cultural differences or socioeconomic status, which are known to affect cognitive and emotional functions through frontal and limbic circuits (Noble, Houston, Kan, & Sowell, 2012). Comparing performance to a more carefully matched sample might have yielded a more accurate profile of his cognitive abilities.

Incorporating technology in the assessment

Use of computerized testing

Unlocking the potential of open science cannot be achieved using pencil-and-paper tests alone. The call for computerized, automated assessments was presented more than 30 years ago and more recently by both the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology (Bauer et al., 2012). However, intensive efforts to create such systems have failed due to the inability of computers to make the fine-grained levels of interpretation, thus leading to the conclusion that "... contextual information (i.e., clinical history) was critical to neuropsychological interpretation" (Adams, Kvale, & Keegan, 1984). Nowadays, it is clear that the modern neuropsychologist needs to have the ability to assess cognition, both in the clinic and in the laboratory, in a brief, yet comprehensive standardized way. In the clinic, such assessments are used for specific, targeted questions, such as evaluating cognitive changes pre- and post-neurological interventions. Example includes shunting in idiopathic normal pressure hydrocephalus (Thomas et al., 2005) or electrocorticography monitoring in epilepsy patients (Sanai, Mirzadeh, & Berger, 2008). Alternatively, such assessments are useful when repeated overtime to track age- or disease-related decline (e.g., Ewers et al., 2012). From an open-science perspective, the use of computerized tests simplifies the process of data sharing, making tasks, tools, and performance easily accessible. In the laboratory, the need for standardized brief assessments is highly relevant when conducting multicenter studies and collecting mass amounts of data, for example, in the search for biomarkers for dementia (Naparstek, Linkovski, et al., 2019). This understanding has led to the development of computerized tests (i.e., Naparstek, El-Said, et al., 2019) and test batteries such as the NIH toolbox (Gershon et al., 2013). However, currently, these batteries are implemented mostly in research settings and still necessitate some basic computer/Internet skills (Casaletto & Heaton, 2017). It has also been suggested that clinicians resist embracing these advanced technologies, thus hindering their incorporation into clinical settings (Parsey & Schmitter-Edgecombe, 2013). Aside from providing a brief, standardized procedure, computerized tests have the potential of obtaining additional information on the examinees' cognitive/behavioral abilities. For example, the stop signal task measure for response inhibition efficiency (i.e., stop-signal response time, SSRT) can predict one's propensity towards repeated checking (Linkovski, Kalanthroff, Henik & Anholt, 2013); and likelihood of relapse in gamblers (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008). Computerized tests also enable assessment of detection or processing speed deficits that are highly relevant in the diagnosis of dementia (Larner, 2014). Moreover, the objective nature of such measures simplifies their re-administration, which may eventually inform clinicians on illness trajectory.

In Mr. P.'s assessment, the use of computerized measures, combined with other traditional tools, might have assisted in two ways: (1) obtaining information about processing speed, which might have assisted in diagnosis and (2) repeating a computerized test after beginning the therapeutic intervention would enable to track Mr. P.'s cognitive abilities and assess advancement in therapy, in an affordable rapid way, to guide treatment customization.

Ecological Momentary Assessments

EMAs are a set of methods using repeated collection of real-time data on subjects' behavior and experience in their natural environments (Shiffman, Stone, & Hufford, 2008). Such data can be collected using low- or high-tech tools ranging from notebook diaries to smartphone apps. In these methods, data are collected: (1) in the individual's real-world environment and not in the clinician's office, making it generalizable to the individual's real-life experience; (2) "here-and-now" relating to the current situation, reducing memory bias; and (3) several times a day or a week, creating a more comprehensive picture of how behavior, cognition, and emotion change overtime. Using EMA, individuals might be asked to retrospectively assess their state once-a-day using a diary or report their current state on random or fixed daily intervals (i.e., via a smartphone). Older adults can benefit greatly from the inclusion of EMA to traditional assessments. The tightly connected physiological-cognitive-emotional states, as well as the cognitive deficits that might affect patient self-reports, make EMA highly relevant in this population (Cain, Depp, & Jeste, 2009). In their review of the literature, Cain et al. (2009) described different applications of EMA in aging population, including tracking of physical abilities, assessment of activities of daily living, and evaluation of affective state. Most studies employed paper-and-pencil diaries, thus avoiding any technological barriers, and reported overall high compliance. Whereas studies differed in their rationale, those that used EMA as an outcome measure for therapeutic interventions found subtle changes that were not detected by global, in-clinic measures such as standard self-reports (Furlan, Kallan, Ten Have, Lucki, & Katz, 2004). Importantly, EMA can also be used to assess cognitive well-being/functioning. In their study of older adults with HIV, Moore and colleagues included EMA of memory and concentration alongside affective, social, and physiological well-being and found these reports to highly correlate with laboratory-based measures of these abilities (Moore et al., 2017).

Given the discrepancy between Mr. P.'s description of his cognitive/emotional deficits and his performance during the neuropsychological assessment, combining EMA measures might have assisted the clinician in resolving this apparent contradiction. Tracking these fluctuations overtime, in a nonbiased and ecologically valid manner, might assist in defining therapeutic targets.

Conclusion

In 1985, after extensive research, Ralph Reitan published the Halstead–Reitan Neuropsychological Battery while calling for a new era in the field of neuropsychological evaluation: from art to science (Reed & Reed, 1997). We believe that today, 35 years later, Reitan's call should be reiterated by calling our scientific field to move one step further, from an approximate science to a precise one. From a science that describes only certain, general aspects of cognition; to a science that integrates biology, cognition and behavior to create a comprehensive and unique profile, improving diagnosis and treatment. Such a shift toward precise neuropsychology holds a great promise for our examinees and for clinical neuropsychology as a profession.

References

Adams, K. M., Kvale, V. I., & Keegan, J. F. (1984). Relative accuracy of three automated systems for neuropsychological interpretation. *Journal of Clinical and Experimental Neuropsychology*, *6*(4), 413–431.

Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D. M., Etkin, A., … Gordon, E. (2016). EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *127*(1), 509–519. Available from https://doi.org/10.1016/j.clinph.2015.05.032, S1388-2457(15)00673-2 [pii].

Barch, D. M. (2017). Resting-state functional connectivity in the human connectome project: Current status and relevance to understanding psychopathology. *Harvard Review of Psychiatry*, *25*(5), 209–217. Available from https://doi.org/10.1097/HRP.0000000000000166.

Bauer, R. M., Iverson, G. L., Cernich, A. N., Binder, L. M., Ruff, R. M., & Naugle, R. I. (2012). Computerized neuropsychological assessment devices: Joint position paper of the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. *The Clinical Neuropsychologist*, *26*(2), 177–196.

Boes, A. D., Prasad, S., Liu, H., Liu, Q., Pascual-Leone, A., Caviness, V. S., Jr, & Fox, M. D. (2015). Network localization of neurological symptoms from focal brain lesions. *Brain*, *138*(10), 3061–3075.

Boto, E., Holmes, N., Leggett, J., Roberts, G., Shah, V., Meyer, S. S., … Bestmann, S. (2018). Moving magnetoencephalography towards real-world applications with a wearable system. *Nature*, *555*, 657–661.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., … Mintun, M. A. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: Evidence for a relationship between default activity, amyloid, and memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(34), 7709–7717. Available from https://doi.org/10.1523/JNEUROSCI.2177-05.2005, [pii].

Cain, A. E., Depp, C. A., & Jeste, D. V. (2009). Ecological momentary assessment in aging research: A critical review. *Journal of Psychiatric Research*, *43*(11), 987–996.

Carter, R., & Ffytche, D. H. (2015). On visual hallucinations and cortical networks: A trans-diagnostic review. *Journal of Neurology*, *262*(7), 1780–1790.

Casaletto, K. B., & Heaton, R. K. (2017). Neuropsychological assessment: Past and future. *Journal of the International Neuropsychological Society*, *23*(9–10), 778–790.

Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain*, *128*(10), 2224–2239.

Elkana, O., Tal, N., Oren, N., Soffer, S., & Ash, E. L. (2019). Is the cutoff of the MoCA too high? Longitudinal data from highly educated older adults. *Journal of Geriatric Psychiatry and Neurology*, 1–6.

Ewers, M., Walsh, C., Trojanowski, J. Q., Shaw, L. M., Petersen, R. C., Jack, C. R., Jr, … North American Alzheimer's Disease Neuroimaging Initiative (ADNI). (2012). Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiology of Aging*, *33*(7), 1203–1214. Available from https://doi.org/10.1016/j.neurobiolaging.2010.10.019.

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, *21*(3), 187–222.

Fox, M. D. (2018). Mapping symptoms to brain networks with the human connectome. *New England Journal of Medicine*, *379*(23), 2237–2245.

Furlan, P. M., Kallan, M. J., Ten Have, T., Lucki, I., & Katz, I. (2004). SSRIs do not cause affective blunting in healthy elderly volunteers. *The American Journal of Geriatric Psychiatry*, *12*(3), 323–330.

Galatzer-Levy, I. R., & Bryant, R. A. (2013). 636,120 ways to have posttraumatic stress disorder. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *8*(6), 651–662. Available from https://doi.org/10.1177/1745691613504115.

Gershon, R. C., Wagster, M. V., Hendrie, H. C., Fox, N. A., Cook, K. F., & Nowinski, C. J. (2013). NIH toolbox for assessment of neurological and behavioral function. *Neurology*, *80*(11 Suppl 3), S2–S6. Available from https://doi.org/10.1212/WNL.0b013e3182872e5f.

Goudriaan, A., Oosterlaan, J., De Beurs, E., & Van Den Brink, W. (2008). The role of self-reported impulsivity and reward sensitivity versus neurocognitive measures of disinhibition and decision-making in the prediction of relapse in pathological gamblers. *Psychological Medicine*, *38*(1), 41–50.

Hedman, A. M., van Haren, N. E., Schnack, H. G., Kahn, R. S., & Hulshoff Pol, H. E. (2012). Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Human Brain Mapping*, *33*(8), 1987–2002.

Ibarretxe-Bilbao, N., Ramirez-Ruiz, B., Tolosa, E., Martí, M. J., Valldeoriola, F., Bargallo, N., & Junque, C. (2008). Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia. *Journal of Neurology*, *255*(9), 1324–1331.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, *167*(7), 748–751.

Insel, T. R., & Cuthbert, B. N. (2015). Brain disorders? Precisely. *Science (New York, N.Y.)*, *348*(6234), 499–500. Available from https://doi.org/10.1126/science.aab2358.

Jack, C. R., Wiste, H. J., Therneau, T. M., Weigand, S. D., Knopman, D. S., Mielke, M. M., … Schwarz, C. G. (2019). Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *The Journal of the American Medical Association*, *321*(23), 2316–2325.

Karalunas, S. L., Fair, D., Musser, E. D., Aykes, K., Iyer, S. P., & Nigg, J. T. (2014). Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: Toward biologically based nosologic criteria. *JAMA Psychiatry*, *71*(9), 1015–1024.

Konrad, K., & Eickhoff, S. B. (2010). Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Human Brain Mapping*, *31*(6), 904–916.

Larner, A. J. (2014). *Dementia in clinical practice: A neurological perspective: Pragmatic studies in the cognitive function clinic*. Springer.

Leuchter, A. F., Dunkin, J. J., Lufkin, R. B., Anzai, Y., Cook, I. A., & Newton, T. F. (1994). Effect of white matter disease on functional connections in the aging brain. *Journal of Neurology, Neurosurgery, and Psychiatry*, *57*(11), 1347–1354. Available from https://doi.org/10.1136/jnnp.57.11.1347.

Lezak, M., Howieson, D., & Loring, D. (2012). *Neuropsychological assessment* (5th edn). Oxford, New York: Oxford university press, ISBN, 10, 9780195395525.

Li, C., Chen, L., Tu, P., Wang, S., Chen, M., Su, T., & Hsieh, J. (2013). Impaired prefronto-thalamic functional connectivity as a key feature of treatment-resistant depression: A combined MEG, PET and rTMS study. *PLoS One*, *8*(8), e70089.

Licher, S., Leening, M. J., Yilmaz, P., Wolters, F. J., Heeringa, J., Bindels, P. J., … Steyerberg, E. W. (2019). Development and validation of a dementia risk prediction model in the general population: An analysis of three longitudinal studies. *American Journal of Psychiatry*, *176*(7), 543–551.

Linkovski, O., Kalanthroff, E., Henik, A., & Anholt, G. (2013). Did I turn off the stove? Good inhibitory control can protect from influences of repeated checking. *Journal of Behavior Therapy and Experimental Psychiatry*, *44*, 30–36.

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. *Neuropsychology Review*, *19*(4), 415–435.

Maron-Katz, A., Zhang, Y., Wu, W., Toll, R. T., Naparstek, S., De Los Angeles, C., … Etkin, A. (2019). Individual patterns of abnormality in resting-state functional connectivity reveal two data-driven PTSD subgroups. *American Journal of Psychiatry*.

McDonald, B. C., Flashman, L. A., & Saykin, A. J. (2002). Executive dysfunction following traumatic brain injury: Neural substrates and treatment strategies. *NeuroRehabilitation*, *17*(4), 333–344.

Mirnezami, R., Nicholson, J., & Darzi, A. (2012). Preparing for precision medicine. *New England Journal of Medicine*, *366*(6), 489–491.

Moore, R. C., Kaufmann, C. N., Rooney, A. S., Moore, D. J., Eyler, L. T., Granholm, E., … Scott, J. (2017). Feasibility and acceptability of ecological momentary assessment of daily functioning among older adults with HIV. *The American Journal of Geriatric Psychiatry*, *25*(8), 829–840.

Munafò, M. R., Nosek, B. A., Bishop, D. V., Button, K. S., Chambers, C. D., Du Sert, N. P., … Ioannidis, J. P. (2017). A manifesto for reproducible science. *Nature Human Behaviour*, *1*(1), 1–9.

Naparstek, S., El-Said, D., Eisenberg, M. L., Jordan, J. T., O'Hara, R., & Etkin, A. (2019). Development of VM-REACT: Verbal memory RecAll computerized test. *Journal of Psychiatric Research*, *114*, 170–177.

Naparstek, S., Linkovski, O., & O'Hara, R. (2019). The future of dementia biomarkers needs better neuropsychology. *American Journal of Psychiatry*, *176*, 1050.

Nichols, T. E., Das, S., Eickhoff, S. B., Evans, A. C., Glatard, T., Hanke, M., … Poline, J. (2017). Best practices in data analysis and sharing in neuroimaging using MRI. *Nature Neuroscience*, *20*(3), 299.

Noble, K. G., Houston, S. M., Kan, E., & Sowell, E. R. (2012). Neural correlates of socioeconomic status in the developing human brain. *Developmental Science*, *15*(4), 516–527.

Open Science Collaboration. (2015). Estimating the reproducibility of psychological science. *Science (New York, N.Y.)*, *349*(6251), aac4716. Available from https://doi.org/10.1126/science.aac4716.

Palop, J. J., Chin, J., & Mucke, L. (2006). A network dysfunction perspective on neurodegenerative diseases. *Nature*, *443*(7113), 768–773.

Parsey, C. M., & Schmitter-Edgecombe, M. (2013). Applications of technology in neuropsychological assessment. *The Clinical Neuropsychologist*, *27*(8), 1328–1361.

Ranasinghe, K. G., Rankin, K. P., Pressman, P. S., Perry, D. C., Lobach, I. V., Seeley, W. W., … Shany-Ur, T. (2016). Distinct subtypes of behavioral variant frontotemporal dementia based on patterns of network degeneration. *JAMA Neurology*, *73*(9), 1078–1088.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689.

Reed, J. C., & Reed, H. B. C. (1997). The Halstead–Reitan neuropsychological battery. In G. Goldstein, & T. M. Incagnoli (Eds.), *Contemporary approaches to neuropsychological assessment. Critical issues in neuropsychology*. Boston, MA: Springer.

Rueda, M. R., Fan, J., McCandliss, B. D., Halparin, J. D., Gruber, D. B., Lercari, L. P., & Posner, M. I. (2004). Development of attentional networks in childhood. *Neuropsychologia*, *42*(8), 1029–1040.

Rutherford, B. R., Taylor, W. D., Brown, P. J., Sneed, J. R., & Roose, S. P. (2016). Biological aging and the future of geriatric psychiatry. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *72*(3), 343–352.

Sanai, N., Mirzadeh, Z., & Berger, M. S. (2008). Functional outcome after language mapping for glioma resection. *New England Journal of Medicine*, *358*(1), 18–27.

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, *62*(1), 42–52.

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*, 1–32.

Siman-Tov, T., Bosak, N., Sprecher, E., Paz, R., Eran, A., Aharon-Peretz, J., & Kahn, I. (2017). Early age-related functional connectivity decline in high-order cognitive networks. *Frontiers in Aging Neuroscience*, *8*, 330.

Sporns, O., Tononi, G., & Kötter, R. (2005). The human connectome: A structural description of the human brain. *PLoS Computational Biology*, *1*(4), e42.

Tamminga, C. A., Pearlson, G., Keshavan, M., Sweeney, J., Clementz, B., & Thaker, G. (2014). Bipolar and schizophrenia network for intermediate phenotypes: Outcomes across the psychosis continuum. *Schizophrenia Bulletin*, *40*(Suppl_2), S131–S137.

Thomas, G., McGirt, M. J., Woodworth, G., Heidler, J., Rigamonti, D., Hillis, A. E., & Williams, M. A. (2005). Baseline neuropsychological profile and cognitive response to cerebrospinal fluid shunting for idiopathic normal pressure hydrocephalus. *Dementia and Geriatric Cognitive Disorders*, *20*(2–3), 163–168. Available from https://doi.org/10.1159/000087092, [pii].

Williams, L. M. (2016). Precision psychiatry: A neural circuit taxonomy for depression and anxiety. *The Lancet Psychiatry*, *3*(5), 472–480.

This page intentionally left blank

Chapter 21

Functional assessment in geriatric mental health

Adriana Seelye[1,2,3,4], Sarah Brown[5], Katherine Dorociak[1], Jeffrey Kaye[3,4], Katherine Wild[3,4] and Snezana Urosevic[1,2]

[1]*Minneapolis VA Health Care System, Minneapolis, MN, United States,* [2]*Department of Psychiatry, University of Minnesota, Minneapolis, MN, United States,* [3]*Department of Neurology, Oregon Health & Science University, Portland, OR, United States,* [4]*Oregon Center for Aging & Technology, Portland, OR, United States,* [5]*Bio-Medical Library, University of Minnesota, Minneapolis, MN, United States*

Introduction

Understanding a person's ability to live independently and safely and maintain a high quality of life in older adulthood has important clinical and public health implications (Rockwood, 2007). Knowledge of functional status in older adulthood is critical to informing the diagnosis of neurocognitive and mental disorders that commonly affect older adults, facilitating decisions about need for transition to higher levels of care (e.g., in-home aid and assistance, assisted living, nursing home placement), and demonstrating effectiveness of treatments (e.g., medication, psychotherapy) in clinical trials or daily clinical practice (Koroukian et al., 2016; Loeb & Jonas, 2015; Naik, 2017; Rajan, Hebert, Scherr, Mendes de Leon, & Evans, 2013; Reed et al., 2016). If understanding daily functioning in older adults and developing interventions to optimize their functioning are important goals, then sensitive, clinically relevant, and reliable assessment tools for the aging population are required. Despite broad clinical and public health implications, the knowledge base about daily function in normative aging, neurodegenerative diseases, and mental health conditions during older adulthood is limited and lacks cohesion (Rockwood, 2007). This may be related to the conceptual and methodological challenges inherent in measuring daily functioning in aging populations in a standardized and meaningful way. Indeed, older adults' lives, environments, and activities are heterogeneous, complex, and continually evolving (Genoe, Liechty, & Marston, 2018). For example, there is a breadth of potential domains of functioning (e.g., social, self-care, financial) that are relevant in older adulthood and intra-individual variability in the ways people engage in and perform daily tasks (Austin, Klein, Mattek, & Kaye, 2017; Farias et al., 2013). Real-world functional activities are mediated by multiple types of cognitive abilities not often examined in laboratory settings such as context, prospective, and temporal order memory (Beaver & Schmitter-Edgecombe, 2017). Thus, development of functional assessment tools requires an appreciation of the need to balance individualized, ecologically relevant assessment with standardized assessment for reference standard purposes. To be useful, functional assessment tools need to discriminate between subtle levels of functioning, parse out cognitive and noncognitive contributions to functioning (Wilms, Riedel-Heller, & Angermeyer, 2007), and assess subtle yet meaningful changes in functioning (Koster, Knol, Uitdehaag, Scheltens, & Sikkes, 2015; Seelye, Mattek, Sharma, Riley, et al., 2017). Historically, crude measures of function with low evidence supporting sensitivity to change have been used as secondary outcome measures in clinical trials (Robert et al., 2010). In clinical practice, standardized assessment of function is the exception rather than the norm.

Classification and assessment of function in older adults

Functioning in older adults is typically classified in two ways: instrumental activities of daily living (IADLs) and basic activities of daily living (BADLs). IADLs are high-level, cognitively complex everyday tasks that are critical to independent living such as medication management, financial management, driving, use of everyday technology, meal preparation, housekeeping, laundry, and shopping (Gold, 2012; Jekel et al., 2015). BADLs are less cognitively demanding

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00021-1

tasks related to providing self-care such as grooming, bathing, toileting, ambulating, and eating. Social, occupational, hobbies, or leisure activities are aspects of functioning studied less often in aging and dementia populations as compared to other populations. Across aging populations, daily function is commonly measured in one of two ways: subjectively through self-or informant-rating scales and objectively through performance-based assessment of function in a clinic or lab setting. Each method has strengths and weaknesses that influence how they are used in research and clinical practice settings (Bingham, Kumar, Dawson, Mulsant, & Flint, 2018; Kallenberg et al., 2016; Wesson, Clemson, Brodaty, & Reppermund, 2016). Self- or informant-report scales are easy to administer and score, can usually be completed by a patient or informant with minimal instruction from a trained provider, and are typically the least expensive or burdensome option. However, self- and informant report are notoriously unreliable even with cognitively intact elderly individuals (Wild, Mattek, Austin, & Kaye, 2016). Furthermore, the psychometric properties of self- and informant-rating scales have often been questioned (Fieo, Austin, Starr, & Deary, 2011; Sikkes et al., 2012) and are prone to large ceiling effects due to inability to discriminate between normal and mildly impaired levels of function (Fieo et al., 2011). Performance-based assessment involves direct testing of function through performance of common daily tasks using simulated household objects (e.g., pillbox, bank statement) in a laboratory or clinic setting, but is only a brief snapshot of a person's capacity in a controlled and unfamiliar environment. Performance-based assessment of function assumes that performance on the exam reflects "typical" function, which may be inaccurate given that the tasks assessed and the stimuli used may be unfamiliar, and the clinical exam itself may be anxiety-provoking. Since simulated household objects and situations are used, these measures may not be representative of what a person actually does or is capable of doing in their own environment. A recent systematic review concluded that there is insufficient evidence on psychometric properties of performance-based IADL measures for older adults and additional evaluation is needed (Wesson et al., 2016). Furthermore, there is evidence to suggest that self-report and performance-based functional assessment are not perfectly correlated and may tap into different aspects of daily function, especially for different aging populations such as normal aging or mild cognitive impairment (MCI) (Schmitter-Edgecombe & Parsey, 2014).

Conceptual framework for cognitively mediated daily function in older adulthood

The cognitively mediated model of everyday functioning suggests that domains of everyday function that are sensitive to central nervous system age-related changes and/or abnormalities should be measured by identifying daily functional tasks that rely, to a large extent, on those cognitive abilities that are known to be affected in a given condition (Farias et al., 2008, 2013). Performing higher-order IADLs requires multiple constituent cognitive abilities working in concert, including memory, executive functions, cognitive efficiency, visuospatial abilities, and language abilities (Cahn-Weiner, Malloy, Boyle, Marran, & Salloway, 2000; Gold, 2012; Royall et al., 2007; Schmitter-Edgecombe & Parsey, 2014). As these cognitive processes are differentially affected by underlying neural processes of normative aging, neurodegenerative diseases of aging, and psychiatric conditions, the strongest cognitive predictors of functional status may differ slightly in normative aging and disorders of aging (Cahn-Weiner et al., 2000; Jekel et al., 2015; Schmitter-Edgecombe & Parsey, 2014).

Although several cognitive domains are involved in higher-order daily tasks, memory and executive functioning abilities are among the strongest predictors of IADLs across aging populations (Caixeta et al., 2017; Gold, 2012; Overdorp, Kessels, Claassen, & Oosterman, 2016; Pennarts, Schouws, & Bongers, 2014; Sajatovic, Forester, Gildengers, & Mulsant, 2013; Schmitter-Edgecombe & Parsey, 2014; Seelye, Mattek, Sharma, Witter, et al., 2017). Driving is one of the most complex IADLs and relies on intact executive functions more than any other cognitive domain. Specifically, the executive components of divided attention and set-shifting under timed conditions most frequently predict impaired performance on road tests in older adults (Asimakopulos et al., 2012; Dobbs & Shergill, 2013; Ott et al., 2013; Papandonatos, Ott, Davis, Barco, & Carr, 2015). Time to complete Trails B may be a more sensitive predictor of road test impairment than the number of errors in older adults without a diagnosis of cognitive impairment (Duncanson, Hollis, & O'Connor, 2018). In recent studies employing automated continuous driving sensors, poorer performance on executive tasks of navigation (i.e., maze drawing time) related to certain types of driving errors (e.g., lane maintenance errors, not looking far enough ahead) (Papandonatos et al., 2015). Executive dysfunction, more broadly, can also impact subtle aspects of driving (e.g., less time on the highway, driving fewer miles, less day-to-day fluctuations in driving habits) in older adulthood (Seelye, Mattek, Sharma, et al., 2017). In a subsequent analysis from Seelye et al. (2017), poorer divided attention, mental flexibility, and cognitive control under timed conditions (assessed with Trail Making Test Part B and Stroop tasks) were uniquely associated with less time driving on the highway and higher variability in week-to-week trips taken after controlling for age. More research is needed using reliable, sensitive

measures to understand the aspects of executive functioning that relate to driving fitness in real-world conditions, with no one neuropsychological test shown to be a sufficiently robust predictor of driving performance in older adult populations (Papandonatos et al., 2015).

Medication-taking is a similarly complex activity that older adults engage in regularly and that is vulnerable to age-related, neurodegenerative, and psychiatric cognitive decline (Depp et al., 2012; Insel, Morrow, Brewer, & Figueredo, 2006). Similar to driving, medication-taking is also highly dependent on executive functioning abilities. Executive functioning not only predicts medication adherence, but also more subtle aspects of medication management, including daytime variability in medication-taking time of day (Seelye et al., 2018). Better cognitive control (assessed with Stroop task) was uniquely associated with less variability in medication-taking time (lower interquartile range) in a sample of nondemented community-dwelling older adults, even after accounting for effects of age and a complex attention measure. In addition to executive functioning, memory is an important predictor of medication management abilities in healthy older adults (Seelye et al., 2018; Smith et al., 2017; Thiruchselvam et al., 2012). Traditionally episodic memory has been related to a decline in medication management, although noncontent memory (i.e., temporal order, source, and prospective memory) also has a unique impact on the ability to complete this task (Schmitter-Edgecombe, Woo, & Greeley, 2009; Zogg, Woods, Sauceda, Wiebe, & Simoni, 2012). Decline in episodic or content memory has been linked to the integrity of the medial temporal lobes (Guillozet, Weintraub, Mash, & Mesulam, 2003), while noncontent memory (i.e., temporal order, source, and prospective memory) involve separate cognitive processes mediated by the frontal lobe and its connections to subcortical regions (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003). Evidence suggests that memory and executive functions are most important to performance of IADLs in older adults, with subtle changes in IADLs acting as sensitive predictors of future cognitive decline (Seelye, Mattek, Sharma, Riley, et al., 2017).

In normative aging, changes in daily functioning are mediated by age-related changes in frontal-subcortical circuits and the integrity of white matter tracts, which impact cognitive functioning through reduced speed and efficiency of everyday activity performance (Adolfsdottir, Wollschlaeger, Wehling, & Lundervold, 2017; Braver & Barch, 2002; Wolf et al., 2014). Diseases of aging that affect neural and cognitive functioning, such as Alzheimer's disease (AD), have a significant negative impact on daily functioning that gradually worsens over time (Allard et al., 2014; Barbe et al., 2017; Benke et al., 2015; Farias et al., 2006; Gordon et al., 2016; Marson, 2015). The typical neuropathology of AD begins in the medial temporal cortical areas; as such, cognitive functions central to these areas such as episodic memory are affected early in the course of the disease. In AD and amnestic MCI (prodromal AD), daily functioning is affected differentially than in normative aging and nonamnestic MCI subtypes, likely based on distinct but not mutually exclusive underlying neuropathology (Bangen et al., 2010). For example, amnestic cognitive impairments in MCI manifest as errors of omission, inaccuracies, and missed steps compared to the reduced speed and inefficiency, with preserved accuracy, seen in normative aging (Schmitter-Edgecombe & Parsey, 2014; Seelye, Schmitter-Edgecombe, Cook, & Crandall, 2013). Following the cognitively mediated everyday functioning framework, functional assessment tools should be able to objectively capture these subtle differences in everyday functioning performance that differentiate various clinical syndromes.

Mood disorders, such as unipolar depression, are associated with cognitive deficits through neural system abnormalities that can also impact daily functioning and contribute to negative outcomes in older adulthood (Bhamani, Khan, Karim, & Mir, 2015; Bingham et al., 2018; DemİR Akça et al., 2014; Snyder, 2013). Serious mental illnesses, such as bipolar disorders (BD) and schizophrenia, are associated with a similar pattern of cognitive deficits as unipolar depression, although typically they are associated with more severe cognitive impairment. This in turn, translates into more significant functional impairment (Ascher-Svanum, Novick, Haro, Aguado, & Cui, 2013; Cholet et al., 2014; Diniz et al., 2017; Eissa, Hassan, Hwedi, & Khalil, 2013; Gildengers et al., 2007, 2012; Sajatovic et al., 2013; Smith, Muir, & Blackwood, 2006). Everyday functional impairment in BD and schizophrenia contributes to high rates of hospitalizations, disability, and other negative outcomes (Bartels, Forester, Miles, & Joyce, 2000; Sajatovic, Friedman, Sabharwal, & Bingham, 2004; Sajatovic et al., 2015; Wu et al., 2013). Although functional impairment in mood disorders is not expected to progressively worsen due to the underlying mood disorder itself as with a neurodegenerative disease, as people age into older adulthood, neural system abnormalities and cognitive deficits in mood disorders have the potential to interact with normative aging brain changes to accelerate or worsen the day-to-day functional consequences associated with either alone (Dhingra & Rabins, 1991; Gildengers et al., 2009).

Assessment of daily function in normative aging, mild cognitive impairment, and Alzheimer's disease

Neurodegenerative diseases such as AD have increased prevalence in older adulthood with age being the biggest risk factor. In 2016, over 5.4 million Americans were affected with AD, and due to the rapid aging of the US population,

the number of people affected in 2050 will nearly triple to a projected 13.8 million (Alzheimer's Association, 2017). Detection and monitoring of the earliest observable changes in the preclinical to MCI stages will be critical to intervene at the stages of disease when prevention and treatments may be most effective and to reduce the cost and consequences of functional decline, especially for older adults who live alone. For example, if patterns of subtle IADL decline are identified early for an older person living alone, remote family members and health care providers could be proactively alerted about the functional status and needs of independent-living older individuals before a crisis; compensatory strategies could be implemented early to help the person maintain independent functioning and optimize quality of life. Interventions could be used to optimize adjustment and safety, maintain social connections, and minimize mood symptoms, resulting in maintaining independent functioning in people with MCI and early AD. Still, a significant barrier to early detection and monitoring in this population is that early functional changes are insidious and slowly progressing, often going undetected until later in the disease process after neurobiological and cognitive changes have had an obvious and significant impact on functional abilities.

The current conceptual framework for AD is the presence of a prodromal phase of underlying disease pathology in the absence of overt clinical symptoms followed by an insidious onset of clinical symptoms and gradual decline of cognitive and functional abilities, with the entire process extending over 20 years (Jack et al., 2011; Reiman et al., 2011a,b; Sperling et al., 2011). Initial clinical symptoms include gradually worsening ability to remember new information, such as difficulty remembering recent conversations, details, or events, and asking for the same information. Declining cognitive functioning impacts performance of cognitively demanding daily tasks, such as medication-taking, financial management, and everyday technology use, leading to less efficient and effective performance often coupled with increased use of compensatory aids (Farias et al., 2006; Gold, 2012; Schmitter-Edgecombe & Parsey, 2014; Seelye et al., 2013; Seelye, Mattek, Sharma, Riley, et al., 2017; Seelye, Mattek, Sharma, Witter, et al., 2017). Later symptoms include impaired communication, disorientation, confusion, poor judgment, and behavioral and neuropsychiatric symptoms (Alves, Correia, Miguel, Alegria, & Bugalho, 2012).

Differences in the observed timing sequence of AD biomarker abnormalities may be a reflection of our measurement tools' sensitivity to detect slowly developing change rather than to the actual timing of these neurobiological changes (Edmonds et al., 2015). Historical inability to observe early functional changes may be due to the use of insensitive measures (i.e., IADL rating scales or screening measures), infrequent measurement and unsophisticated analytic techniques (i.e., using group mean scores from annual testing to measure change), or variations in the way functional decline is defined (Alves et al., 2012; Dorsey, Venuto, Venkataraman, Harris, & Kieburtz, 2015; Rockwood, 2007; Wesson et al., 2016). Available IADL assessments were not developed to measure early subtle changes in daily functioning, but rather more marked functional impairment occurring later in disease progression (Fieo et al., 2011), leading to large ceiling effects and inability to discriminate between normal and mildly impaired function. Item response theory and computerized adaptive testing methods have been applied to self- and informant IADL assessment tools to reduce ceiling effects and improve the tool's ability to measure early and subtle IADL decline in community-dwelling older adults (Fieo et al., 2011; Koster et al., 2015).

Fundamental features of IADL changes in early AD—insidious onset and gradual decline—are difficult to assess with available tools and methods. A fundamental limitation of available subjective and objective IADL measures is infrequent administration, which is the hallmark feature of the episodic clinic-based assessment paradigm used in clinical practice and research settings. Even if accurate, sensitive, reliable, and convenient functional assessment tools were available, one snapshot of a person's functional capacity in a highly controlled environment does not lend itself to tracking subtle fluctuations in functioning over time, which may emerge earlier than overall decline and be a more powerful indicator of future cognitive decline (Dodge, Mattek, Austin, Hayes, & Kaye, 2012; Kaye et al., 2014).

Despite their limitations, self- and informant-based IADL rating scales are widely used in aging and dementia research (Jekel et al., 2015). Measures commonly reported in the literature include the Functional Assessment Questionnaire (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), Lawton−Brody Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969), the Everyday Cognition (ECog) scale (Farias et al., 2008), and the Amsterdam IADL Questionnaire (Sikkes et al., 2012). While used less broadly, performance-based IADL assessment tools that have been reported in the literature include the Observed Tasks of Daily Living—Revised (Diehl et al., 2005), the Everyday Performance Test (Willis & Marsiske, 1997), the Naturalistic Action Task (Giovannetti et al., 2008), and the Independent Living Scales (Loeb, 1996). Performance-based measures have demonstrated slightly larger effect sizes in detecting group differences in daily functioning across the continuum of normative aging to dementia (Jekel et al., 2015). Some performance-based IADL measures for older adults assess or sample only a single domain of function, such as the Financial Capacity Instrument (Marson, 2000), which may be appropriate for certain settings but limits the range and type of potentially useful data that can be collected and investigated. Other IADL measures include more

domains of function but are longer, more challenging to complete, and may require training to administer (Sikkes et al., 2012). Regardless of self-report or performance-based assessment method, available measures do not assess an individual's actual IADL performance under typical real-world conditions.

In the aging and dementia literature, self/collateral reported IADL changes have been identified up to 10 years prior to dementia diagnosis (Peres et al., 2008; Verlinden et al., 2016) and are strong predictors of prospective conversion to MCI and AD (Edmonds et al., 2015; Gomar et al., 2011; Verlinden et al., 2016). Empirical evidence supports a continuum of everyday functioning from normative aging to MCI to dementia, with normative aging being associated with decreased efficiency but similar accuracy compared to younger adults, MCI being associated with decreased efficiency (slower) and accuracy (more error-prone, but with ability to compensate), and then to dementia when cognitive impairment significantly interferes with independence in everyday activities and assistance is required (Jekel et al., 2015; Schmitter-Edgecombe & Parsey, 2014; Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008).

With evidence that early changes in cognitively demanding daily activities emerge in the transition between normal cognition and the development of MCI but are difficult to assess with available clinic-based tools, researchers have recently turned toward developing methodologies to assess older adults' real-world daily functioning by incorporating technology (Kaye et al., 2011; Lyons et al., 2015). An innovative approach that is gaining traction in the field is to employ passive sensors in the home environment for high-frequency, continuous "in the background" assessment to capture changes in important daily activities that may signal new-onset cognitive decline (Seligman & Giovannetti, 2015; Zhang, Karunanithi, Bradford, & van Kasteren, 2014). This approach has the potential to establish person-specific patterns of daily functioning that are markers of transition from normal to abnormal aging. The goal is to identify early daily activity pattern changes, or "digital biomarkers," that occur in prodromal AD through computational modeling and data analytics (Lin et al., 2018; Lyons et al., 2015; Seelye, Mattek, Sharma, Witter, et al., 2017), and in turn, use this information to provide early interventions to prolong independent living (Peetoom, Lexis, Joore, Dirksen, & De Witte, 2015).

Unobtrusive continuous "in the background" monitoring of routine daily activities that occur in one's home environment that requires little to no extra effort is a novel alternate approach to conventional episodic daily function assessments. Frequent observation of individuals within their own environment will make it possible to obtain larger samples of data that may facilitate the detection of subtle yet meaningful change in behavior associated with cognitive decline earlier than conventional methods. There is a growing body of empirical evidence showing that aspects of older adults' routine computer use such as time spent on the computer per day, day-to-day variability in computer use, time to complete a weekly online task, time of day online tasks are completed, and mouse movement patterns are promising early markers of cognitively mediated functional decline in older adults that can be assessed continuously in a nontaxing way (Kaye et al., 2014; Seelye, Hagler, et al., 2015; Seelye, Mattek, et al., 2015; Seelye, Mattek, Sharma, Riley, et al., 2017). Studies have also used passive sensors to monitor older adults' routine medication-taking habits and have found that subtle aspects of medication-taking, such as the time of day a pillbox is first opened and variability in this metric over time, are sensitive markers of mild cognitive decline (Austin et al., 2017). Sensor-based monitoring of older adults' driving habits represents another promising direction for functional assessment that has been shown to be feasible, well-accepted, and sensitive to MCI (Seelye, Mattek, Sharma, Witter, et al., 2017). Evidence shows that executive functions such as divided attention and cognitive control under timed conditions are specific predictors of driving on road test and real-world contexts (Duncanson et al., 2018).

Functional assessment in older adult mental health

Functional impairment is a defining feature of all mental disorders across the life span, including in older adulthood. DSM-5 diagnostic criteria for major depressive disorder specifies that symptoms must have a clinically significant impact on an individual's functioning in social, occupational, or other important domains of functioning (American Psychiatric Association, 2013). Impairment in daily functioning is also a core feature of BD and schizophrenia diagnostic criteria. DSM-5 BD criteria specify that the mood symptoms must have a significant impact on an individual's functioning; similarly in schizophrenia, the symptoms must impair one's life and get in the way of her ability to work (or go to/participate in school), have positive relationships (or any relationships at all), and practice self-care.

Despite the need for accurate and reliable functional assessment measures across mental health populations, a recent systematic review of functional assessment instruments used in older adult populations with depression showed that there are very few measures with reported psychometric data (Bingham et al., 2018). In fact, only two measures were found to have formal validity data in older adults with depression. Only one is based on performance assessment called the Performance Assessment of Self-care Skills (Rodakowski et al., 2014). This review emphasized the importance of

validating IADL measures in each specific population as measures developed for individuals with more severe cognitive and functional impairments (e.g., schizophrenia) may not be as sensitive for subtler changes in functioning seen in depression, BD, or anxiety disorders. In mental health populations, there is also a bias in reporting of life events and reporting of functional impairment that is not always associated with observed task performance, highlighting the need for more objective and ecologically valid functional assessment tools (Bingham et al., 2018). Performance-based IADL measures such as the UCSD Performance-Based Skills Assessment (UPSA) (Becattini-Oliveira, Dutra, Spenciere de Oliveira Campos, de Araujo, & Charchat-Fichman, 2018; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001) are most frequently used in older adult schizophrenia research and less often used with other aging psychiatric populations, such as depression (Bingham et al., 2018). In contrast to aging and MCI populations, remote sensing and in-home activity monitoring technologies have not yet been applied to provide real-time, real-world functional assessment in aging psychiatric disorder populations.

Compared to the MCI and dementia literature, the literature on functional assessment in older adult psychopathology is sparse and limited with considerable variability across mental disorders. Considering evidence that cognitive impairment can precede depressive symptoms in older adults (Jajodia & Borders, 2011) and that depressive symptoms may have causal contributions to functional impairment (Gonzalez et al., 2008), longitudinal data are needed to establish directionality of the associations between depression and cognitively mediated functional impairment. Broadly in the aging and mental health literature, information on established cutoffs or golden standards for IADL assessment measures is very limited (Ascher-Svanum et al., 2013). In the schizophrenia literature, most studies have wide age ranges (e.g., from 15 to 80) (Scanlan & Still, 2013) with a mean age in middle adulthood (40s and 50s). Very few studies focus exclusively on older adults' age 65 + with schizophrenia or with clinically diagnosed depression. In general, research examining daily function in older adults above age 50 with mental disorders is severely lacking.

Assessment of daily function in older adult depression

In the depression literature, most studies looking at associations between depression and daily functioning use nonclinically depressed older adult community-dwelling samples. Thus, these findings should be interpreted with that *caveat* as it is not clear that the observed associations would translate to populations with clinical diagnoses of depression. In normative older adulthood, there is often a high cooccurrence of depression and cognitive impairment (Arve, Tilvis, Lehtonen, Valvanne, & Sairanen, 1999; Villarreal, Grajales, Lopez, Britton, & Panama Aging Research Initiative, 2015) that increases every 5 years after age 70. By age 85, 25% of older adults age 85 or older experience both depression and cognitive impairment (Arve et al., 1999). Community-dwelling older adults with depressive symptoms also have a higher rate of self-reported functional difficulties (Tomita & Burns, 2013). More severe depression in medically (nonpsychiatrically) hospitalized patients at discharge predicts worse functional dependence 6-month postdischarge (Chen, Huang, & Chen, 2014). There are higher rates of depression in older adults with cognitive and physical health conditions and these depressive symptoms in turn can affect functioning (Bingham et al., 2018) and quality of life (Stein & Barrett-Connor, 2002) independent of physical illness. Evidence suggests that, after accounting for effects of various demographic factors and physical illness (number of diseases), depression is still a significant predictor of self-reported daily functioning (Song, Meade, Akobundu, & Sahyoun, 2014). Depressive symptoms and self-reported IADL impairment have been shown to independently predict mortality, and mortality is increased for older adults with cooccurring depression and functional impairment (Mutambudzi, Chen, Markides, & Al Snih, 2016).

Brewster and colleagues (2017) used a self-report depression questionnaire to measure depressive symptoms in community-dwelling older adults without clinical depression and found that increased depressive symptoms were associated with worse performance on the Timed IADL Test (e.g., time taken and accuracy to perform several IADLs such as making change, reading food labels, and reading directions on prescription bottles) after controlling for age, sex, and education (Brewster, Peterson, Roker, Ellis, & Edwards, 2017). This relationship was fully mediated by cognitive test performance in the domains of executive functioning and memory, consistent with findings from the aging and MCI literature showing the importance of executive functioning and memory to supporting everyday function (Jekel et al., 2015). A study by Rog et al. (2014) with a sample of 199 cognitively intact older adults, 87 with MCI and 58 with dementia, found that in the whole sample, depression had a unique association with worse everyday function using the ECog, even after accounting for memory and executive function composite scores. Further, even after accounting for cognition and depression, apathy symptoms had a unique association with global and each domain of everyday function (Rog et al., 2014). The impact of depressive symptoms on daily function in older adults over and above cognition is likely dependent on mood symptoms severity (Classon, Fallman, Wressle, & Marcusson, 2016). A study by Thielke et al. (2014) explored associations between self-reported depressive symptoms and aspects of daily functioning such as time spent in and outside the home using in-home activity monitoring technologies. Low mood in their sample of community-dwelling older adults

without clinical depression was associated with going out of the house less and using the computer less (Thielke et al., 2014). Findings from this study suggest that in-home sensor technologies to unobtrusively monitor daily function may have potential for research and clinical care in older adults with depressive symptoms.

Assessment of daily function in older adult schizophrenia

Impairments in daily function have been demonstrated widely in the aging and schizophrenia literature with technology-based/computerized, performance-based, and self-report assessment of function (Czaja, Loewenstein, Lee, Fu, & Harvey, 2017; Czaja, Loewenstein, Sabbag, et al., 2017; Moore et al., 2013); however, studies of schizophrenia tend to be based on samples of participants with wide age ranges. The UPSA is a performance-based measure that is commonly used to assess functional capacity in studies of older adults with severe mental illness (Patterson et al., 2001). A recent systematic review found the UPSA to have good psychometric properties including in versions that have been culturally adapted (Becattini-Oliveira et al., 2018) and computerized, mobile, and brief versions of the UPSA have been developed (Moore et al., 2013, 2015). Neurocognitive functioning is a strong predictor of performance-based IADL and observer-rated real-life daily functioning across studies of adults with schizophrenia with a mean age in the 50s (Holshausen, Harvey, Elvevag, Foltz, & Bowie, 2014; Moore et al., 2015). In 232 patients with schizophrenia age 19−79 (mean age of 49), global cognition predicted all domains of functioning on the UPSA, except for management of household tasks, even after controlling for effects of age, education, gender, and negative symptoms. The largest effect was found on communication skills; surprisingly, severity of negative symptoms did not predict any of the functional domains (Kalache et al., 2015). Further, some studies have suggested a weak link between negative symptoms and daily function (Bowie & Harvey, 2005); others have found no significant relationship between positive or negative symptom severities and C-UPSA or UPSA performance (Moore et al., 2013), or a weak relationship with negative symptoms and no relationship between daily functioning and positive symptoms ($r = -0.26$ to -0.36) (Lysaker et al., 2011). Scanlan and Still (2013) used a comprehensive functional assessment approach (self-report, informant report, observation by occupational therapist) to assess function in participants with schizophrenia age 15−80 (mean age of 40). In this sample, the greatest functional impairment and greatest functional dependence were found for medication and money management. Seventy-one percent of participants were rated as dependent or partially dependent for medication management, while 56.3% were rated as dependent or partially dependent for money management (Scanlan & Still, 2013).

Assessment of daily function in older adult bipolar disorder

Similar to the depression literature, studies of older adults with bipolar disorder (OABD) have predominantly used self-report measures of IADL function that have limited ecological validity and are unable to capture subtle changes or fluctuations in function over time. Performance-based and/or technology-based IADL assessment tools, such as the UPSA, have been used less commonly in the OABD literature compared to the schizophrenia literature. A meta-analysis provided evidence for a strong association between cognitive ability and everyday functioning in BD, similar to that seen in schizophrenia (Depp et al., 2012). OABD have greater deficits in everyday functional tasks than healthy older adults (Henry, Minassian, & Perry, 2013) and are at elevated risk for dementia through underlying processes independent of AD neurodegenerative disease (Diniz et al., 2017), potentially through breakdown of executive functioning processes mediated by frontal-subcortical brain regions that leads to worsening functional impairment and diagnosis of dementia. Comes, Rosa, Reinares, Torrent, and Vieta (2017) examined functioning in 33 euthymic OABD and 30 healthy controls (mean age 69 and 66, all age > 55). OABD demonstrated worse psychosocial functioning, autonomy, occupational functioning, cognitive functioning, financial issues, and interpersonal relationships (Comes et al., 2017). Worse functioning in this study was associated with more severe symptoms of depression and mania and with a greater number of hospitalizations over lifetime. OABD perform worse on a performance-based IADL measure than healthy older adults after controlling for age, education, and cardiovascular burden (Gildengers et al., 2007, 2013). Cognitive function, specifically executive function, predicts IADL performance (Caixeta et al., 2017; Pennarts et al., 2014; Sajatovic et al., 2013). In these studies, there were group differences at baseline and across 2-year follow-up, but no difference in rate of change of cognitive impairment over time.

Conclusions

Measuring daily function is a key component of clinical research and practice with aging populations that presents with both unique challenges and opportunities. Large individual variability in the functional activities typically performed by older adults renders generating normative data for functional assessment measures more difficult compared to

standardized cognitive assessment tools. Functional assessment instruments that do not discriminate with fine precision across the normal to mildly impaired range of functional ability can lead to ceiling effects for people with subclinical cognitive impairment and mild mood disturbance, limiting their utility in research and clinical settings. Given that functional impairment is a core feature of neurodegenerative diseases and mental disorders and that a certain degree of age-related functional decline is also normative (e.g., slower completion of IADLs), assessment of daily function should be vitally important to inform differential diagnosis and treatment when older adults present with cognitive decline, functional decline, and/or a history of mental disorders. Still, available literature on functional assessment in older adult mental health populations is sparse and limited, with considerable variability across specific mental disorders. The literature on functional assessment in aging and dementia is more abundant, but is still hindered by limitations of available assessment tools and conventional assessment paradigms. Across aging populations, there is strong evidence that memory and executive functions are most important to performance of IADLs in older adults, especially for driving and medication adherence. Divided attention, cognitive control, noncontent memory (prospective, temporal order), and episodic memory are specific cognitive abilities that have been implicated in IADL performance in older adult populations. More research is needed to determine the specific aspects of executive and memory functions that uniquely contribute to real-world IADL performance in specific older adult populations, and how these IADLs are affected by normal and abnormal aging, in order to inform potential interventions to prolong independent living. Perhaps the most important and clinically relevant aspect of functioning to measure across aging populations (normative aging, neurocognitive disorders, and mood disorders) is subtle intra-individual variability in daily functioning, which may be a sensitive marker of underlying or emerging neurocognitive or affective symptoms and is not well captured by currently available assessment tools.

To address the gaps identified in the literature, continued development and refinement of functional assessment tools that can measure subtle changes in older adults' daily lives due to neurodegenerative disease *and* mental disorders with greater individualization and precision are critically needed. According to Robert and colleagues (2010), for a functional outcome measure to be successfully adopted into research and clinical practice settings, it needs to be practical, easy, and quick to administer, validated for the population of interest, assess multiple domains, be applicable to broad stages of functioning (normal to severely impaired), monitor subtle changes in functioning, and be sensitive to treatment effects. Considerations for assessment of daily function in older adults with mood disorders, such as depression and BD, include the impact of mood symptoms on daily functioning above and beyond cognitive contributions, the relationship between elevated functional impairment (Henry et al., 2013) and heightened risk for dementia (Diniz et al., 2017), and timing of the assessment to correspond with mood symptom presence and severity which may be episodic or fluctuating in nature.

Incorporating passive sensing and pervasive computing into the development of new functional assessment tools may address some of the challenges and hurdles that have prevented the field from moving forward. In-home monitoring, real-time data collection, and data analytics are all promising approaches that are now being applied to provide objective characterization of function and change or decline in functioning in normative aging, MCI, and dementia research. In-home monitoring of IADLs has not yet been applied to older adult mental health disorder populations and is warranted. Ultimately, no matter how useful or impactful it might be, successful integration of technology-based functional assessment in older adults' daily lives depends on their and their families' perceptions, attitudes, and ultimately, acceptance and adoption of these approaches (Boise et al., 2013; Claes, Devriendt, Tournoy, & Milisen, 2015). Future work is needed to explore attitudes and perceptions of older adults with normal cognition, MCI, and across mental health diagnoses toward computerized, mobile, and sensor-based monitoring of daily function including technical aspects, its potential usefulness, the availability of collected information, functional requirements of the system or device, privacy and confidentiality, and potential time- and cost-related benefits.

References

Adolfsdottir, S., Wollschlaeger, D., Wehling, E., & Lundervold, A. J. (2017). Inhibition and switching in healthy aging: A longitudinal study. *Journal of the International Neuropsychological Society*, *23*(1), 90−97. Available from https://doi.org/10.1017/S1355617716000898.

Allard, M., Husky, M., Catheline, G., Pelletier, A., Dilharreguy, B., Amieva, H., … Swendsen, J. (2014). Mobile technologies in the early detection of cognitive decline. *PLoS One*, *9*(12), e112197. Available from https://doi.org/10.1371/journal.pone.0112197.

Alves, L., Correia, A. S., Miguel, R., Alegria, P., & Bugalho, P. (2012). Alzheimer's disease: A clinical practice-oriented review. *Frontiers in Neurology*, *3*, 63. Available from https://doi.org/10.3389/fneur.2012.00063.

Alzheimer's Association. (2017). Alzheimer's *d*isease *f*acts and *f*igures.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Arve, S., Tilvis, R. S., Lehtonen, A., Valvanne, J., & Sairanen, S. (1999). Coexistence of lowered mood and cognitive impairment of elderly people in five birth cohorts. *Aging (Milano)*, *11*(2), 90–95.

Ascher-Svanum, H., Novick, D., Haro, J. M., Aguado, J., & Cui, Z. (2013). Empirically driven definitions of "good," "moderate," and "poor" levels of functioning in the treatment of schizophrenia. *Quality of Life Research*, *22*(8), 2085–2094. Available from https://doi.org/10.1007/s11136-012-0335-z.

Asimakopulos, J., Boychuck, Z., Sondergaard, D., Poulin, V., Menard, I., & Korner-Bitensky, N. (2012). Assessing executive function in relation to fitness to drive: A review of tools and their ability to predict safe driving. *Australian Occupational Therapy Journal*, *59*(6), 402–427. Available from https://doi.org/10.1111/j.1440-1630.2011.00963.x.

Austin, J., Klein, K., Mattek, N., & Kaye, J. (2017). Variability in medication taking is associated with cognitive performance in nondemented older adults. *Alzheimer's & Dementia*, *6*, 210–213. Available from https://doi.org/10.1016/j.dadm.2017.02.003.

Bangen, K. J., Jak, A. J., Schiehser, D. M., Delano-Wood, L., Tuminello, E., Han, S. D., ... Bondi, M. W. (2010). Complex activities of daily living vary by mild cognitive impairment subtype. *Journal of the International Neuropsychological Society*, *16*(4), 630–639. Available from https://doi.org/10.1017/S1355617710000330.

Barbe, C., Morrone, I., Wolak-Thierry, A., Drame, M., Jolly, D., Novella, J.-L., & Mahmoudi, R. (2017). Impact of functional alterations on quality of life in patients with Alzheimer's disease. *Aging and Mental Health*, *21*(5), 571–576. Available from https://doi.org/10.1080/13607863.2015.1132674.

Bartels, S. J., Forester, B., Miles, K. M., & Joyce, T. (2000). Mental health service use by elderly patients with bipolar disorder and unipolar major depression. *The American Journal of Geriatric Psychiatry*, *8*(2), 160–166.

Beaver, J., & Schmitter-Edgecombe, M. (2017). Multiple types of memory and everyday functional assessment in older adults. *Archives of Clinical Neuropsychology*, *32*(4), 413–426. Available from https://doi.org/10.1093/arclin/acx016.

Becattini-Oliveira, A. C., Dutra, D. F., Spenciere de Oliveira Campos, B., de Araujo, V. C., & Charchat-Fichman, H. (2018). A systematic review of a functional assessment Tool: UCSD performance-based skill assessment (UPSA). *Psychiatry Research*, *267*, 12–18. Available from https://doi.org/10.1016/j.psychres.2018.05.005.

Benke, T., Sanin, G., Lechner, A., Dal-Bianco, P., Ransmayr, G., Uranus, M., ... Group, P. S. (2015). Predictors of patient dependence in mild-to-moderate Alzheimer's disease. *Journal of Alzheimer's Disease*, *43*(2), 443–449. Available from https://doi.org/10.3233/JAD-140099.

Bhamani, M. A., Khan, M. M., Karim, M. S., & Mir, M. U. (2015). Depression and its association with functional status and physical activity in the elderly in Karachi, Pakistan. *Asian Journal of Psychiatry*, *14*, 46–51. Available from https://doi.org/10.1016/j.ajp.2014.12.004.

Bingham, K. S., Kumar, S., Dawson, D. R., Mulsant, B. H., & Flint, A. J. (2018). A systematic review of the measurement of function in late-life depression. *The American Journal of Geriatric Psychiatry*, *26*(1), 54–72. Available from https://doi.org/10.1016/j.jagp.2017.08.011.

Boise, L., Wild, K., Mattek, N., Ruhl, M., Dodge, H. H., & Kaye, J. (2013). Willingness of older adults to share data and privacy concerns after exposure to unobtrusive in-home monitoring. *Gerontechnology*, *11*(3), 428–435. Available from https://doi.org/10.4017/gt.2013.11.3.001.00.

Bowie, C. R., & Harvey, P. D. (2005). Cognition in schizophrenia: Impairments, determinants, and functional importance. *Psychiatric Clinics of North America*, *28*(3), 613–633, 626. Available from https://doi.org/10.1016/j.psc.2005.05.004.

Braver, T. S., & Barch, D. M. (2002). A theory of cognitive control, aging cognition, and neuromodulation. *Neuroscience & Biobehavioral Reviews*, *26*(7), 809–817.

Brewster, G. S., Peterson, L., Roker, R., Ellis, M. L., & Edwards, J. D. (2017). Depressive symptoms, cognition, and everyday function among community-residing older adults. *Journal of Aging and Health*, *29*(3), 367–388. Available from https://doi.org/10.1177/0898264316635587.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia*, *39*(6), 545–555.

Burgess, P. W., Scott, S. K., & Frith, C. D. (2003). The role of the rostral frontal cortex (area 10) in prospective memory: A lateral versus medial dissociation. *Neuropsychologia*, *41*(8), 906–918.

Cahn-Weiner, D. A., Malloy, P. F., Boyle, P. A., Marran, M., & Salloway, S. (2000). Prediction of functional status from neuropsychological tests in community-dwelling elderly individuals. *Clinical Neuropsychologist*, *14*(2), 187–195. Available from https://doi.org/10.1076/1385-4046(200005)14:2;1-Z;FT187.

Caixeta, L., Soares, V. L., Vieira, R. T., Soares, C. D., Caixeta, V., Ferreira, S. B., & Aversi-Ferreira, T. A. (2017). Executive function is selectively impaired in old age bipolar depression. *Frontiers in Psychology*, *8*, 194. Available from https://doi.org/10.3389/fpsyg.2017.00194.

Chen, C. M., Huang, G. H., & Chen, C. C. (2014). Older patients' depressive symptoms 6 months after prolonged hospitalization: Course and interrelationships with major associated factors. *Archives of Gerontology and Geriatrics*, *58*(3), 339–343. Available from https://doi.org/10.1016/j.archger.2013.12.007.

Cholet, J., Sauvaget, A., Vanelle, J. M., Hommet, C., Mondon, K., Mamet, J. P., & Camus, V. (2014). Using the brief assessment of cognition in schizophrenia (BACS) to assess cognitive impairment in older patients with schizophrenia and bipolar disorder. *Bipolar Disorders*, *16*(3), 326–336. Available from https://doi.org/10.1111/bdi.12171.

Claes, V., Devriendt, E., Tournoy, J., & Milisen, K. (2015). Attitudes and perceptions of adults of 60 years and older towards in-home monitoring of the activities of daily living with contactless sensors: An explorative study. *International Journal of Nursing Studies*, *52*(1), 134–148. Available from https://doi.org/10.1016/j.ijnurstu.2014.05.010.

Classon, E., Fallman, K., Wressle, E., & Marcusson, J. (2016). Relations between concurrent longitudinal changes in cognition, depressive symptoms, self-rated health and everyday function in normally aging octogenarians. *PLoS One*, *11*(8), e0160742. Available from https://doi.org/10.1371/journal.pone.0160742.

Comes, M., Rosa, A., Reinares, M., Torrent, C., & Vieta, E. (2017). Functional impairment in older adults with bipolar disorder. *The Journal of Nervous and Mental Disease*, *205*(6), 443−447. Available from https://doi.org/10.1097/NMD.0000000000000683.

Czaja, S. J., Loewenstein, D. A., Lee, C. C., Fu, S. H., & Harvey, P. D. (2017). Assessing functional performance using computer-based simulations of everyday activities. *Schizophrenia Research*, *183*, 130−136. Available from https://doi.org/10.1016/j.schres.2016.11.014.

Czaja, S. J., Loewenstein, D. A., Sabbag, S. A., Curiel, R. E., Crocco, E., & Harvey, P. D. (2017). A novel method for direct assessment of everyday competence among older adults. *Journal of Alzheimer's Disease*, *57*(4), 1229−1238. Available from https://doi.org/10.3233/JAD-161183.

Demİr Akça, A. S., Saraçlı, Ö., Emre, U., Atasoy, N., Güdül, S., Barut, B. Ö., ... Atasoy, H. T. (2014). Relationship of cognitive functions with daily living activities, depression, anxiety and clinical variables in hospitalized elderly patients. *Noropsikiyatri Arsivi*, *51*(3), 267−274. Available from https://doi.org/10.4274/npa.y7053.

Depp, C. A., Mausbach, B. T., Harmell, A. L., Savla, G. N., Bowie, C. R., Harvey, P. D., & Patterson, T. L. (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disorders*, *14*(3), 217−226. Available from https://doi.org/10.1111/j.1399-5618.2012.01011.x.

Dhingra, U., & Rabins, P. V. (1991). Mania in the elderly: A 5-7 year follow-up. *Journal of the American Geriatrics Society*, *39*(6), 581−583.

Diehl, M., Marsiske, M., Horgas, A. L., Rosenberg, A., Saczynski, J. S., & Willis, S. L. (2005). The revised observed tasks of daily living: A performance-based assessment of everyday problem solving in older adults. *Journal of Applied Gerontology*, *24*(3), 211−230. Available from https://doi.org/10.1177/0733464804273772.

Diniz, B. S., Teixeira, A. L., Cao, F., Gildengers, A., Soares, J. C., Butters, M. A., & Reynolds, C. F., 3rd (2017). History of bipolar disorder and the risk of dementia: A systematic review and meta-analysis. *The American Journal of Geriatric Psychiatry*, *25*(4), 357−362. Available from https://doi.org/10.1016/j.jagp.2016.11.014.

Dobbs, B. M., & Shergill, S. S. (2013). How effective is the trail making test (parts A and B) in identifying cognitively impaired drivers? *Age Ageing*, *42*(5), 577−581. Available from https://doi.org/10.1093/ageing/aft073.

Dodge, H. H., Mattek, N. C., Austin, D., Hayes, T. L., & Kaye, J. A. (2012). In-home walking speeds and variability trajectories associated with mild cognitive impairment. *Neurology*, *78*(24), 1946−1952. Available from https://doi.org/10.1212/WNL.0b013e318259e1de.

Dorsey, E. R., Venuto, C., Venkataraman, V., Harris, D. A., & Kieburtz, K. (2015). Novel methods and technologies for 21st-century clinical trials: A review. *JAMA Neurology*, *72*(5), 582−588. Available from https://doi.org/10.1001/jamaneurol.2014.4524.

Duncanson, H., Hollis, A. M., & O'Connor, M. G. (2018). Errors versus speed on the trail making test: Relevance to driving performance. *Accident Analysis & Prevention*, *113*, 125−130. Available from https://doi.org/10.1016/j.aap.2018.01.004.

Edmonds, E. C., Delano-Wood, L., Galasko, D. R., Salmon, D. P., Bondi, M. W., & Alzheimer's Disease Neuroimaging, I. (2015). Subtle cognitive decline and biomarker staging in preclinical Alzheimer's disease. *Journal of Alzheimer's Disease*, *47*(1), 231−242. Available from https://doi.org/10.3233/JAD-150128.

Eissa, A. M., Hassan, G. A. M., Hwedi, D., & Khalil, A. H. (2013). Cognitive profile in late-onset schizophrenia: A comparative study with early-onset schizophrenia. *Middle East Current Psychiatry*, *20*(1), 6−13. Available from https://doi.org/10.1097/01.XME.0000422841.09287.77.

Farias, S. T., Mungas, D., Reed, B. R., Cahn-Weiner, D., Jagust, W., Baynes, K., & Decarli, C. (2008). The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology*, *22*(4), 531−544. Available from https://doi.org/10.1037/0894-4105.22.4.531.

Farias, S. T., Mungas, D., Reed, B. R., Harvey, D., Cahn-Weiner, D., & Decarli, C. (2006). MCI is associated with deficits in everyday functioning. *Alzheimer Disease and Associated Disorders*, *20*(4), 217−223. Available from https://doi.org/10.1097/01.wad.0000213849.51495.d9.

Farias, S. T., Park, L. Q., Harvey, D. J., Simon, C., Reed, B. R., Carmichael, O., & Mungas, D. (2013). Everyday cognition in older adults: Associations with neuropsychological performance and structural brain imaging. *Journal of the International Neuropsychological Society*, *19*(4), 430−441. Available from https://doi.org/10.1017/S1355617712001609.

Fieo, R. A., Austin, E. J., Starr, J. M., & Deary, I. J. (2011). Calibrating ADL-IADL scales to improve measurement accuracy and to extend the disability construct into the preclinical range: A systematic review. *BMC Geriatrics*, *11*, 42. Available from https://doi.org/10.1186/1471-2318-11-42.

Genoe, M. R., Liechty, T., & Marston, H. R. (2018). Retirement transitions among baby boomers: Findings from an online qualitative study. *Canadian Journal on Aging*, *37*(4), 450−463. Available from https://doi.org/10.1017/S0714980818000314.

Gildengers, A. G., Butters, M. A., Chisholm, D., Anderson, S. J., Begley, A., Holm, M., ... Mulsant, B. H. (2012). Cognition in older adults with bipolar disorder versus major depressive disorder. *Bipolar Disorders*, *14*(2), 198−205. Available from https://doi.org/10.1111/j.1399-5618.2012.00995.x.

Gildengers, A. G., Butters, M. A., Chisholm, D., Rogers, J. C., Holm, M. B., Bhalla, R. K., ... Mulsant, B. H. (2007). Cognitive functioning and instrumental activities of daily living in late-life bipolar disorder. *The American Journal of Geriatric Psychiatry*, *15*(2), 174−179. Available from https://doi.org/10.1097/JGP.0b013e31802dd367.

Gildengers, A. G., Chisholm, D., Butters, M. A., Anderson, S. J., Begley, A., Holm, M., ... Mulsant, B. H. (2013). Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: Evidence for neuroprogression? *Psychological Medicine*, *43*(4), 801−811. Available from https://doi.org/10.1017/S0033291712001614.

Gildengers, A. G., Mulsant, B. H., Begley, A., Mazumdar, S., Hyams, A. V., Reynolds Iii, C. F., ... Butters, M. A. (2009). The longitudinal course of cognition in older adults with bipolar disorder. *Bipolar Disorders*, *11*(7), 744–752. Available from https://doi.org/10.1111/j.1399-5618.2009.00739.x.

Giovannetti, T., Bettcher, B. M., Brennan, L., Libon, D. J., Burke, M., Duey, K., ... Wambach, D. (2008). Characterization of everyday functioning in mild cognitive impairment: A direct assessment approach. *Dementia and Geriatric Cognitive Disorders*, *25*(4), 359–365. Available from https://doi.org/10.1159/000121005.

Gold, D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 11–34. Available from https://doi.org/10.1080/13803395.2011.614598.

Gomar, J. J., Bobes-Bascaran, M. T., Conejero-Goldberg, C., Davies, P., Goldberg, T. E., & Alzheimer's Disease Neuroimaging, I. (2011). Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Archives of General Psychiatry*, *68*(9), 961–969. Available from https://doi.org/10.1001/archgenpsychiatry.2011.96.

Gonzalez, J. S., Peyrot, M., McCarl, L. A., Collins, E. M., Serpa, L., Mimiaga, M. J., & Safren, S. A. (2008). Depression and diabetes treatment non-adherence: A meta-analysis. *Diabetes Care*, *31*(12), 2398–2403. Available from https://doi.org/10.2337/dc08-1341.

Gordon, M. F., Lenderking, W. R., Duhig, A., Chandler, J., Lundy, J. J., Miller, D. S., ... Patient-Reported Outcome Consortium's Cognition Working, G. (2016). Development of a patient-reported outcome instrument to assess complex activities of daily living and interpersonal functioning in persons with mild cognitive impairment: The qualitative research phase. *Alzheimer's & Dementia*, *12*(1), 75–84. Available from https://doi.org/10.1016/j.jalz.2015.04.008.

Guillozet, A. L., Weintraub, S., Mash, D. C., & Mesulam, M. M. (2003). Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Archives of Neurology*, *60*(5), 729–736. Available from https://doi.org/10.1001/archneur.60.5.729.

Henry, B. L., Minassian, A., & Perry, W. (2013). Everyday functional ability across different phases of bipolar disorder. *Psychiatry Research*, *210*(3), 850–856. Available from https://doi.org/10.1016/j.psychres.2013.04.006.

Holshausen, K., Harvey, P. D., Elvevag, B., Foltz, P. W., & Bowie, C. R. (2014). Latent semantic variables are associated with formal thought disorder and adaptive behavior in older inpatients with schizophrenia. *Cortex*, *55*, 88–96. Available from https://doi.org/10.1016/j.cortex.2013.02.006.

Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *61*(2), P102–P107.

Jack, C. R., Jr., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., ... Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 257–262. Available from https://doi.org/10.1016/j.jalz.2011.03.004.

Jajodia, A., & Borders, A. (2011). Memory predicts changes in depressive symptoms in older adults: A bidirectional longitudinal analysis. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *66*(5), 571–581. Available from https://doi.org/10.1093/geronb/gbr035.

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., ... Frolich, L. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: A systematic review. *Alzheimer's Research & Therapy*, *7*(1), 17. Available from https://doi.org/10.1186/s13195-015-0099-0.

Kalache, S. M., Mulsant, B. H., Davies, S. J., Liu, A. Y., Voineskos, A. N., Butters, M. A., ... Rajji, T. K. (2015). The impact of aging, cognition, and symptoms on functional competence in individuals with schizophrenia across the lifespan. *Schizophrenia Bulletin*, *41*(2), 374–381. Available from https://doi.org/10.1093/schbul/sbu114.

Kallenberg, M. H., Kleinveld, H. A., Dekker, F. W., van Munster, B. C., Rabelink, T. J., van Buren, M., & Mooijaart, S. P. (2016). Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD—A systematic review. *Clinical Journal of the American Society of Nephrology*, *11*(9), 1624–1639. Available from https://doi.org/10.2215/CJN.13611215.

Kaye, J., Mattek, N., Dodge, H. H., Campbell, I., Hayes, T., Austin, D., ... Pavel, M. (2014). Unobtrusive measurement of daily computer use to detect mild cognitive impairment. *Alzheimer's & Dementia*, *10*(1), 10–17. Available from https://doi.org/10.1016/j.jalz.2013.01.011.

Kaye, J. A., Maxwell, S. A., Mattek, N., Hayes, T. L., Dodge, H., Pavel, M., ... Zitzelberger, T. A. (2011). Intelligent systems for assessing aging changes: Home-based, unobtrusive, and continuous assessment of aging. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *66*(Suppl 1), i180–i190. Available from https://doi.org/10.1093/geronb/gbq095.

Koroukian, S. M., Schiltz, N., Warner, D. F., Sun, J., Bakaki, P. M., Smyth, K. A., ... Given, C. W. (2016). Combinations of chronic conditions, functional limitations, and geriatric syndromes that predict health outcomes. *Journal of General Internal Medicine*, *31*(6), 630–637. Available from https://doi.org/10.1007/s11606-016-3590-9.

Koster, N., Knol, D. L., Uitdehaag, B. M., Scheltens, P., & Sikkes, S. A. (2015). The sensitivity to change over time of the Amsterdam IADL Questionnaire((c). *Alzheimer's & Dementia*, *11*(10), 1231–1240. Available from https://doi.org/10.1016/j.jalz.2014.10.006.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*, *9*(3), 179–186.

Lin, M., Gong, P., Yang, T., Ye, J., Albin, R. L., & Dodge, H. H. (2018). Big data analytical approaches to the NACC dataset: Aiding preclinical trial enrichment. *Alzheimer Disease and Associated Disorders*, *32*(1), 18–27. Available from https://doi.org/10.1097/WAD.0000000000000228.

Loeb, M., & Jonas, B. S. (2015). Psychological and physical functioning difficulties associated with complex activity limitations among U.S. adults. *Disability and Health Journal*, *8*(1), 70–79. Available from https://doi.org/10.1016/j.dhjo.2014.08.003.

Loeb, P.A. (1996). *ILS: Independent living. Scales manual*. San Antonio, Texas: Psychological Corp, Harcourt.

Lyons, B. E., Austin, D., Seelye, A., Petersen, J., Yeargers, J., Riley, T., … Kaye, J. A. (2015). Pervasive computing technologies to continuously assess Alzheimer's disease progression and intervention efficacy. *Frontiers in Aging Neuroscience*, *7*, 102. Available from https://doi.org/10.3389/fnagi.2015.00102.

Lysaker, P. H., McCormick, B. P., Snethen, G., Buck, K. D., Hamm, J. A., Grant, M., … Dimaggio, G. (2011). Metacognition and social function in schizophrenia: Associations of mastery with functional skills competence. *Schizophrenia Research*, *131*(1−3), 214−218. Available from https://doi.org/10.1016/j.schres.2011.06.011.

Marson, D. (2015). Investigating functional impairment in preclinical Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease*, *2*(1), 4−6. Available from https://doi.org/10.14283/jpad.2015.44.

Moore, R. C., Harmell, A. L., Harvey, P. D., Bowie, C. R., Depp, C. A., Pulver, A. E., … Mausbach, B. T. (2015). Improving the understanding of the link between cognition and functional capacity in schizophrenia and bipolar disorder. *Schizophrenia Research*, *169*(1−3), 121−127. Available from https://doi.org/10.1016/j.schres.2015.09.017.

Moore, R. C., Harmell, A. L., Ho, J., Patterson, T. L., Eyler, L. T., Jeste, D. V., & Mausbach, B. T. (2013). Initial validation of a computerized version of the UCSD performance-based skills assessment (C-UPSA) for assessing functioning in schizophrenia. *Schizophrenia Research*, *144*(1−3), 87−92. Available from https://doi.org/10.1016/j.schres.2012.12.028.

Mutambudzi, M., Chen, N. W., Markides, K. S., & Al Snih, S. (2016). Effects of functional disability and depressive symptoms on mortality in older Mexican-American adults with diabetes mellitus. *Journal of the American Geriatrics Society*, *64*(11), e154−e159. Available from https://doi.org/10.1111/jgs.14432.

Naik, A. D. (2017). Evaluating capacity for safe and independent living among vulnerable older adults. In A. Catic (Eds.), *Ethical considerations and challenges in geriatric* (pp. 9−21). Cham: Springer. Available from http://dx.doi.org/10.1007/978-3-319-44084-2-2.

Ott, B. R., Davis, J. D., Papandonatos, G. D., Hewitt, S., Festa, E. K., Heindel, W. C., … Carr, D. B. (2013). Assessment of driving-related skills prediction of unsafe driving in older adults in the office setting. *Journal of the American Geriatrics Society*, *61*(7), 1164−1169. Available from https://doi.org/10.1111/jgs.12306.

Overdorp, E. J., Kessels, R. P., Claassen, J. A., & Oosterman, J. M. (2016). The combined effect of neuropsychological and neuropathological deficits on instrumental activities of daily living in older adults: A systematic review. *Neuropsychology Review*, *26*(1), 92−106. Available from https://doi.org/10.1007/s11065-015-9312-y.

Papandonatos, G. D., Ott, B. R., Davis, J. D., Barco, P. P., & Carr, D. B. (2015). Clinical utility of the trail-making test as a predictor of driving performance in older adults. *Journal of the American Geriatrics Society*, *63*(11), 2358−2364. Available from https://doi.org/10.1111/jgs.13776.

Patterson, T. L., Goldman, S., McKibbin, C. L., Hughs, T., & Jeste, D. V. (2001). UCSD performance-based skills assessment: Development of a new measure of everyday functioning for severely mentally ill adults. *Schizophrenia Bulletin*, *27*(2), 235−245.

Peetoom, K. K., Lexis, M. A., Joore, M., Dirksen, C. D., & De Witte, L. P. (2015). Literature review on monitoring technologies and their outcomes in independently living elderly people. *Disability and Rehabilitation: Assistive Technology*, *10*(4), 271−294. Available from https://doi.org/10.3109/17483107.2014.961179.

Pennarts, H., Schouws, S. N., & Bongers, I. (2014). Cognitive functioning in relation to self-care in elderly persons with a bipolar disorder. *Clinical Gerontologist*, *37*, 419−428.

Peres, K., Helmer, C., Amieva, H., Orgogozo, J. M., Rouch, I., Dartigues, J. F., & Barberger-Gateau, P. (2008). Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: A prospective population-based study. *Journal of the American Geriatrics Society*, *56*(1), 37−44. Available from https://doi.org/10.1111/j.1532-5415.2007.01499.x.

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Jr., Chance, J. M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *The Journals of Gerontology*, *37*(3), 323−329.

Rajan, K. B., Hebert, L. E., Scherr, P. A., Mendes de Leon, C. F., & Evans, D. A. (2013). Disability in basic and instrumental activities of daily living is associated with faster rate of decline in cognitive function of older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(5), 624−630. Available from https://doi.org/10.1093/gerona/gls208.

Reed, C., Belger, M., Vellas, B., Andrews, J. S., Argimon, J. M., Bruno, G., … Haro, J. M. (2016). Identifying factors of activities of daily living important for cost and caregiver outcomes in Alzheimer's disease. *International Psychogeriatrics.*, *28*(2), 247−259. Available from https://doi.org/10.1017/S1041610215001349.

Reiman, E. M., McKhann, G. M., Albert, M. S., Sperling, R. A., Petersen, R. C., & Blacker, D. (2011a). Alzheimer's disease: Implications of the updated diagnostic and research criteria. *The Journal of Clinical Psychiatry*, *72*(9), 1190−1196. Available from https://doi.org/10.4088/JCP.10087co1c.

Reiman, E. M., McKhann, G. M., Albert, M. S., Sperling, R. A., Petersen, R. C., & Blacker, D. (2011b). Clinical impact of updated diagnostic and research criteria for Alzheimer's disease. *The Journal of Clinical Psychiatry*, *72*(12), e37. Available from https://doi.org/10.4088/JCP.10087tx2c.

Robert, P., Ferris, S., Gauthier, S., Ihl, R., Winblad, B., & Tennigkeit, F. (2010). Review of Alzheimer's disease scales: Is there a need for a new multi-domain scale for therapy evaluation in medical practice? *Alzheimer's Research & Therapy*, *2*(4), 24. Available from https://doi.org/10.1186/alzrt48.

Rockwood, K. (2007). The measuring, meaning and importance of activities of daily living (ADLs) as an outcome. *International Psychogeriatrics*, *19*(3), 467−482. Available from https://doi.org/10.1017/S1041610207004966.

Rodakowski, J., Skidmore, E. R., Reynolds, C. F., 3rd, Dew, M. A., Butters, M. A., Holm, M. B., … Rogers, J. C. (2014). Can performance on daily activities discriminate between older adults with normal cognitive function and those with mild cognitive impairment? *Journal of the American Geriatrics Society*, *62*(7), 1347−1352. Available from https://doi.org/10.1111/jgs.12878.

Rog, L. A., Park, L. Q., Harvey, D. J., Huang, C. J., Mackin, S., & Farias, S. T. (2014). The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. *Clinical Neuropsychologist*, *28*(2), 215–236. Available from https://doi.org/10.1080/13854046.2013.876101.

Royall, D. R., Lauterbach, E. C., Kaufer, D., Malloy, P., Coburn, K. L., Black, K. J., & Committee on Research of the American Neuropsychiatric, A. (2007). The cognitive correlates of functional status: A review from the Committee on Research of the American Neuropsychiatric Association. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(3), 249–265. Available from https://doi.org/10.1176/jnp.2007.19.3.249.

Sajatovic, M., Forester, B. P., Gildengers, A., & Mulsant, B. H. (2013). Aging changes and medical complexity in late-life bipolar disorder: Emerging research findings that may help advance care. *Neuropsychiatry*, *3*(6), 621–633. Available from https://doi.org/10.2217/npy.13.78.

Sajatovic, M., Friedman, S. H., Sabharwal, J., & Bingham, C. R. (2004). Clinical characteristics and length of hospital stay among older adults with bipolar disorder, schizophrenia or schizoaffective disorder, depression, and dementia. *Journal of Geriatric Psychiatry and Neurology*, *17*(1), 3–8. Available from https://doi.org/10.1177/0891988703258821.

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., … Shulman, K. I. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disorders*, *17*(7), 689–704. Available from https://doi.org/10.1111/bdi.12331.

Scanlan, J. N., & Still, M. (2013). Functional profile of mental health consumers assessed by occupational therapists: Level of independence and associations with functional cognition. *Psychiatry Research*, *208*(1), 29–32. Available from https://doi.org/10.1016/j.psychres.2013.02.032.

Schmitter-Edgecombe, M., & Parsey, C. M. (2014). Assessment of functional change and cognitive correlates in the progression from healthy cognitive aging to dementia. *Neuropsychology*, *28*(6), 881–893. Available from https://doi.org/10.1037/neu0000109.

Schmitter-Edgecombe, M., Woo, E., & Greeley, D. R. (2009). Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology*, *23*(2), 168–177. Available from https://doi.org/10.1037/a0014186.

Seelye, A., Hagler, S., Mattek, N., Howieson, D. B., Wild, K., Dodge, H. H., & Kaye, J. A. (2015). Computer mouse movement patterns: A potential marker of mild cognitive impairment. *Alzheimer's & Dementia*, *1*(4), 472–480. Available from https://doi.org/10.1016/j.dadm.2015.09.006.

Seelye, A., Mattek, N., Austin, J., Alioto, A., Moseley, S., Anderson, C., … Kaye, J. (2018). *Cognitive correlates of unobtrusively monitored medication adherence in older adults*. Paper presented at the International Neuropsychological Society Annual Conference, Washington, DC.

Seelye, A., Mattek, N., Howieson, D., Austin, D., Wild, K., Dodge, H., & Kaye, J. (2015). Embedded online questionnaire measures are sensitive to identifying mild cognitive impairment. *Alzheimer's Disease & Associated Disorders, 30*, 152–159.

Seelye, A., Mattek, N., Sharma, N., Riley, T., Austin, J., Wild, K., … Kaye, J. (2017). Weekly observations of online survey metadata obtained through home computer use allow for detection of changes in everyday cognition before transition to mild cognitive impairment. *Alzheimer's & Dementia*, *14*, 187–194. Available from https://doi.org/10.1016/j.jalz.2017.07.756.

Seelye, A., Mattek, N., Sharma, N., Witter, P., Brenner, A., Wild, K., … Kaye, J. (2017). Passive assessment of routine driving with unobtrusive sensors: A new approach for identifying and monitoring functional level in normal aging and mild cognitive impairment. *Journal of Alzheimer's Disease*, *59*(4), 1427–1437. Available from https://doi.org/10.3233/JAD-170116.

Seelye, A. M., Schmitter-Edgecombe, M., Cook, D. J., & Crandall, A. (2013). Naturalistic assessment of everyday activities and prompting technologies in mild cognitive impairment. *Journal of the International Neuropsychological Society*, *19*(4), 442–452. Available from https://doi.org/10.1017/S135561771200149X.

Seligman, S. C., & Giovannetti, T. (2015). The potential utility of eye movements in the detection and characterization of everyday functional difficulties in mild cognitive impairment. *Neuropsychology Review*, *25*(2), 199–215. Available from https://doi.org/10.1007/s11065-015-9283-z.

Sikkes, S. A., de Lange-de Klerk, E. S., Pijnenburg, Y. A., Gillissen, F., Romkes, R., Knol, D. L., … Scheltens, P. (2012). A new informant-based questionnaire for instrumental activities of daily living in dementia. *Alzheimer's & Dementia*, *8*(6), 536–543. Available from https://doi.org/10.1016/j.jalz.2011.08.006.

Smith, D., Lovell, J., Weller, C., Kennedy, B., Winbolt, M., Young, C., & Ibrahim, J. (2017). A systematic review of medication non-adherence in persons with dementia or cognitive impairment. *PLoS One*, *12*(2), e0170651. Available from https://doi.org/10.1371/journal.pone.0170651.

Smith, D. J., Muir, W. J., & Blackwood, D. H. (2006). Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. *Bipolar Disorders*, *8*(1), 40–46. Available from https://doi.org/10.1111/j.1399-5618.2006.00275.x.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, *139*(1), 81–132. Available from https://doi.org/10.1037/a0028727.

Song, H. J., Meade, K., Akobundu, U., & Sahyoun, N. R. (2014). Depression as a correlate of functional status of community-dwelling older adults: Utilizing a short-version of 5-item Geriatric Depression Scale as a screening tool. *The Journal of Nutrition, Health and Aging*, *18*(8), 765–770. Available from https://doi.org/10.1007/s12603-014-0452-1.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 280–292. Available from https://doi.org/10.1016/j.jalz.2011.03.003.

Stein, M. B., & Barrett-Connor, E. (2002). Quality of life in older adults receiving medications for anxiety, depression, or insomnia: Findings from a community-based study. *The American Journal of Geriatric Psychiatry*, *10*(5), 568–574.

Thielke, S. M., Mattek, N. C., Hayes, T. L., Dodge, H. H., Quinones, A. R., Austin, D., … Kaye, J. A. (2014). Associations between observed in-home behaviors and self-reported low mood in community-dwelling older adults. *Journal of the American Geriatrics Society*, *62*(4), 685–689. Available from https://doi.org/10.1111/jgs.12744.

Thiruchselvam, T., Naglie, G., Moineddin, R., Charles, J., Orlando, L., Jaglal, S., ... Tierney, M. C. (2012). Risk factors for medication nonadherence in older adults with cognitive impairment who live alone. *International Journal of Geriatric Psychiatry*, *27*(12), 1275–1282. Available from https://doi.org/10.1002/gps.3778.

Tomita, A., & Burns, J. K. (2013). Depression, disability and functional status among community-dwelling older adults in South Africa: Evidence from the first South African National Income Dynamics Study. *International Journal of Geriatric Psychiatry*, *28*(12), 1270–1279. Available from https://doi.org/10.1002/gps.3954.

Verlinden, V. J., van der Geest, J. N., de Bruijn, R. F., Hofman, A., Koudstaal, P. J., & Ikram, M. A. (2016). Trajectories of decline in cognition and daily functioning in preclinical dementia. *Alzheimer's & Dementia*, *12*(2), 144–153. Available from https://doi.org/10.1016/j.jalz.2015.08.001.

Villarreal, A. E., Grajales, S., Lopez, L., Britton, G. B., & Panama Aging Research Initiative. (2015). Cognitive impairment, depression, and cooccurrence of both among the elderly in Panama: Differential associations with multimorbidity and functional limitations. *BioMed Research International, 2015*, 718701. Available from https://doi.org/10.1155/2015/718701.

Wadley, V. G., Okonkwo, O., Crowe, M., & Ross-Meadows, L. A. (2008). Mild cognitive impairment and everyday function: Evidence of reduced speed in performing instrumental activities of daily living. *The American Journal of Geriatric Psychiatry*, *16*(5), 416–424. Available from https://doi.org/10.1097/JGP.0b013e31816b7303.

Wesson, J., Clemson, L., Brodaty, H., & Reppermund, S. (2016). Estimating functional cognition in older adults using observational assessments of task performance in complex everyday activities: A systematic review and evaluation of measurement properties. *Neuroscience & Biobehavioral Reviews*, *68*, 335–360. Available from https://doi.org/10.1016/j.neubiorev.2016.05.024.

Wild, K. V., Mattek, N., Austin, D., & Kaye, J. A. (2016). "Are you sure?": Lapses in self-reported activities among healthy older adults reporting online. *Journal of Applied Gerontology*, *35*(6), 627–641. Available from https://doi.org/10.1177/0733464815570667.

Willis, S. L., & Marsiske, M. (1997). *Manual for the everyday problems test*. University Park, PA: Department of Human Development and Family Studies, Pennsylvania State University.

Wilms, H. U., Riedel-Heller, S. G., & Angermeyer, M. C. (2007). Limitations in activities of daily living and instrumental activities of daily living capacity in a representative sample: Disentangling dementia- and mobility-related effects. *Comprehensive Psychiatry*, *48*(1), 95–101. Available from https://doi.org/10.1016/j.comppsych.2006.04.001.

Wolf, D., Zschutschke, L., Scheurich, A., Schmitz, F., Lieb, K., Tuscher, O., & Fellgiebel, A. (2014). Age-related increases in Stroop interference: Delineation of general slowing based on behavioral and white matter analyses. *Human Brain Mapping*, *35*(5), 2448–2458. Available from https://doi.org/10.1002/hbm.22340.

Wu, K. Y., Chang, C. M., Liang, H. Y., Wu, C. S., Chia-Hsuan Wu, E., Chen, C. H., ... Tsai, H. J. (2013). Increased risk of developing dementia in patients with bipolar disorder: A nested matched case-control study. *Bipolar Disorders*, *15*(7), 787–794. Available from https://doi.org/10.1111/bdi.12116.

Zhang, Q., Karunanithi, M., Bradford, D., & van Kasteren, Y. (2014). Activity of daily living assessment through wireless sensor data. *Conference Proceedings of the IEEE Engineering in Medicine and Biology Society*, *2014*, 1752–1755. Available from https://doi.org/10.1109/EMBC.2014.6943947.

Zogg, J. B., Woods, S. P., Sauceda, J. A., Wiebe, J. S., & Simoni, J. M. (2012). The role of prospective memory in medication adherence: A review of an emerging literature. *Journal of Behavioral Medicine*, *35*(1), 47–62. Available from https://doi.org/10.1007/s10865-011-9341-9.

Chapter 22

Psychotherapeutic interventions with older adults: now and into the future

Leander K. Mitchell and Nancy A. Pachana
School of Psychology, University of Queensland, Brisbane, QLD, Australia

Introduction

The landscape of mental health has changed considerably in response to evidence-based medicine, new technologies such as telehealth and e-therapy delivery, and changes in demographics globally. Over the last three decades, research focused on older adults and their mental health has increased, although this remains an area of research that is limited compared to other age groups. More specifically in relation to psychotherapeutic interventions with older adults, much research remains to be done on larger research samples studied for longer, with attention paid to multiple comorbidities, both physical and mental, and improved knowledge of psychotherapy interventions and their outcomes in the oldest old (Laidlaw & Pachana, 2009).

Worldwide, the proportion of the population who will fit the older adult definition is increasing, with an expectation that globally, older adults (those aged 60 years and over) will represent 22% of the population by 2050 (World Health Organization (WHO), 2017). Associated with this is an increase in the number of those older persons experiencing a mental health issue; the World Health Organization estimates that approximately 15% of older adults will experience a mental health disorder (WHO, 2017). As a result, it is important for clinicians to develop a skillset that enables them to work effectively with an older adult population.

Older adults have an extended life story, which often (but not always) includes instances of coping and problem-solving that can be drawn upon within the therapeutic environment. The cohort with which they identify can also play a role in how the clinician works with them. Further, older adults can have a range of coexisting medical conditions and be on a range of different medications. This may necessarily play a role in how therapy is conducted. Finally, one of the normal processes of aging is that of a decline in certain aspects of cognitive function, including processing speed and working memory (Salthouse, 2010). Such normal declines may impact on the therapeutic process and need to be accommodated accordingly in order to make therapeutic gains with the older adults.

CALTAP: a transdisciplinary model of working with older adults

One example of a conceptualization model specifically developed with older adults in mind is the Contextual Adult Lifespan Theory for Adapting Psychotherapy (CALTAP; Knight & Poon, 2008). CALTAP offers four themes for the practitioner to consider as a guide to delivering effective interventions: developmental aging, social context, cohort differences, and cultural issues. One of the unique advantages of the CALTAP model is its transdiagnostic approach that can be used regardless of therapeutic modality. The model is considered a useful means of setting the scene for the therapeutic work to be done and the goals to be achieved, one emphasizing consideration of the late-life perspective.

Therapeutic modalities

A variety of therapeutic modalities are available to the clinician that are as effective with older adults as they are with other populations. On occasion, mention is made of making alterations to therapy in order to facilitate greater effectiveness with older adult populations; however, such modifications are often linked with the context in which the older

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00022-3

adult exists (Laidlaw & Pachana, 2009). For example, does a medical condition mean you have to consider using a well-lit room or perhaps shorter sessions occurring more frequently? Does the presence of mild cognitive impairment necessitate more scaffolding within the therapeutic environment? In general, the therapeutic modalities remain true to their beginnings and it is more likely that the therapist will need to vary the way in which they "do" the therapy.

In the following sections, a range of therapeutic modalities will be explored, highlighting their evidence-base with an older adult population. Positive modalities of therapy and those that actively draw on the experiences and life knowledge that the older adult brings to therapy are discussed. Finally, the future of therapy and what lies on the (perhaps near) horizon, including new technologies to bring therapy to more people, and in modalities that may mitigate some of the challenges that older adults face are explored.

Psychotherapeutic approaches

Psychodynamic approach

Shedler (2010) identifies the focus of brief psychodynamic therapy as a means of "... exploring those aspects of self that are not fully known, especially as they are manifested and potentially influenced in the therapy relationship" (p. 98). Shedler goes on to highlight seven core features distinguishing the psychodynamic approach from other forms of therapy: focus on affect and expression of emotion; exploration of attempts to avoid distressing thoughts and feelings; identification of recurring themes and patterns; discussion of past experience (developmental focus); focus on interpersonal relations; focus on the therapy relationship; and exploration of fantasy life.

The work of Thompson, Gallagher, and Breckenridge (1987) continues to represent one of the seminal pieces of work in this area, finding that whether using behavioral, cognitive, or brief psychodynamic therapy, an improvement in symptomology for major depressive disorder was found, with no significant differences between treatment modalities identified in older adults. In a later study, Gallagher-Thompson and Steffen (1994) compared cognitive behavior therapy (CBT) with psychodynamic therapy to mitigate the effects of depression in family caregivers. Once again, they found that both modalities were effective and that there was no clear difference between the two in terms of outcomes.

More recently, Rosebourough, Luptak, McLeod, and Bradshaw (2013) conducted a longitudinal study exploring the effectiveness of a brief psychodynamic approach in older adults. Relying on archival data collected in the general course of therapy within a community mental health context, the authors found statistically relevant reliable change and a large effect size. And in a review of various psychological treatments for depression in older adults, Scogin, Welsh, Hanson, Stump, and Coates (2005) also identified a brief psychodynamic approach as being beneficial, although the only two articles used as part of that review were the previously mentioned works of Thompson et al. (1987) and Gallagher-Thompson and Steffen (1994).

The psychodynamic approach therefore offers promise in terms of being an effective form of therapy with older adults. However, the literature in this area is lacking and would benefit from further consideration by researchers.

Cognitive behavior therapy

CBT has a large and robust evidence-base across patient ages and a range of mental and physical health contexts. Conceptualized in the 1960s by Aaron T. Beck, this form of therapy's fundamental aim is to modify dysfunctional thinking and behavior (Beck, 1964). A range of modifications and adjustments to CBT have occurred over time. For example, CBT-I has been developed for those experiencing insomnia and CBT-E for those experiencing an eating disorder.

In 2012, Gould, Coulson, and Howard conducted a metaanalysis exploring CBT for anxiety in older adults. A strict inclusion criterion was adhered to, focusing only on randomized controlled trials; 12 trials were included. Analyses suggested that CBT was more effective than both treatment as usual and waitlist control groups. Unfortunately, when CBT was compared to a more active control group, the difference in results was not significant. However, CBT did demonstrate better outcomes in terms of relapse prevention, although effect sizes were consistently small. Wilson, Mottram, and Vassilas (2008) conducted a Cochrane review looking at the effectiveness of psychotherapy for older adults experiencing depression. Seven trials met inclusion criteria using CBT. Once again, they identified that CBT was more effective than waitlist controls. They also found that CBT was superior to active control interventions (three trials) on the Hamilton Depression Rating Scale, but no significant difference was identified using the Geriatric Depression Scale. It is important to note that only a small number of trials were available for comparison and the authors concluded that the evidence is limited and therefore generalizability should be considered with caution. A further Cochrane review

conducted by Orgeta, Qazi, Spector, and Orrell (2015) looking at the efficacy of CBT in treating anxiety and depression in people living with dementia and mild cognitive impairment found improvements in well-being, but once again the number of studies meeting criteria was quite small (six studies).

CBT has also been used in populations experiencing subclinical levels of mental health concerns. For example, Bourgault-Fagnou and Hadjistavropoulos (2013) conducted a randomized controlled trial for participants experiencing subclinical health anxiety. A six-session program was used with robust improvement found in the CBT group compared to the waitlist group; gains were maintained at 3-month follow-up.

Johnco, Wuthrich, and Rapee (2014) considered the impact of cognitive inflexibility on the ability to engage in cognitive restructuring (one of the core components of the CBT model). They found that those who experienced poor cognitive flexibility were unable to engage as successfully in cognitive restructuring as those with good cognitive flexibility. As such, therapists working with older adults and considering a CBT approach would need to bear in mind the older adults' cognitive abilities to ensure optimal outcomes.

CBT research represents the most studied of all the therapeutic modalities explored in this chapter. As a result, it has more to offer in terms of a solid evidence-base. However, some caution is required in extending results to less well-studied subpopulations, particularly at advanced ages. Nonetheless, CBT remains a useful and efficacious form of therapy when working with older adults.

Interpersonal psychotherapy

Developed by Klerman, Weissman, Rounsaville, and Chevron (1984), interpersonal psychotherapy (IPT) focuses on the impact of interpersonal difficulties on the psychological well-being of the individual. It is theoretically based on attachment theory and as its broadest goal, looks to resolve interpersonal difficulties impacting on mental health issues. The therapy targets one of four interpersonal stressors: grief and loss; role transitions; interpersonal disputes; and interpersonal sensitivity. One of the most oft-quoted studies is that of Weisman et al. (1979), comparing the effectiveness of psychotropic medication and IPT. Results indicated that both treatment approaches were effective in and of themselves, but the combination was more effective than either medication or IPT alone for the treatment of adults with acute depression. Reynolds et al. (1999) found similar results in a study that focused only on participants aged 50 years and over who were experiencing bereavement-related depression. Once again, a combined treatment approach was more effective and had the highest rate of treatment completion.

IPT has been well-researched in older adults, particularly for depression (Hinrichsen & Clougherty, 2006). With respect to more recent research, studies focusing on the use of IPT with older adults have continued to focus on depression, as well as suicidality. For example, Heisel, Talbot, King, Tu, and Duberstein (2015) conducted a study offering 16 sessions of IPT adapted for use with older adults at risk of suicide. Significant reductions were noted across such factors as suicidal ideation, death ideation, and severity of depression. As an uncontrolled study, the results are to be applied with caution; however, an associated improvement in psychological well-being for participants adds to the compelling nature of IPT as a useful form of intervention in later life. Exploring bereavement-related depression, Miller et al. (1994) demonstrated a positive effect in terms of a reduction in depressive symptomatology after 17 sessions of IPT. And van Schaik et al. (2006) found that IPT was more effective than usual care in participants with depression, although remission was not attained.

IPT offers a form of therapy that focuses on the interpersonal context of the client and as such encourages a different view of the perpetuating factors contributing to the mental health concerns experienced by the older adult. Research on IPT with older adults highlights positive outcomes, although possibly not in the longer term without ongoing relapse support.

Motivational interviewing

Motivational interviewing (MI) is a form of therapy for which the primary goal is to have structured conversations about change and in such a way that those conversations motivate change in the client (Miller & Rollnick, 2013). As such, much of the literature in this area across population age groups focuses on behavior change with regards to such things as substance abuse and other health-related behaviors. And so, the technique is used within any context that would benefit from motivation to complete or engage in an activity (e.g., smoking cessation, exercise, medication adherence, healthy eating). Cummings, Cooper, and McClure Cassie (2009) conducted a literature review exploring the effectiveness of MI with older adult populations. While they highlighted that the available literature was limited, what

research was on offer identified successful results across a range of behavior change areas (e.g., physical activity, diet, smoking cessation).

More specifically, Chang, Compton, Almeter, and Fox (2015) explored MI in the domain of adherence to prescription of opioid medication in older adults with chronic pain. Their results found that after 4 weeks of MI in outpatient settings, the risk of opioid misuse was reduced. Further, despite the benefits of exercise and a good diet in mitigating negative outcomes of cardiovascular disease, diabetes, and other medical conditions being uncontested, older adults can be hesitant to engage in physical exercise due to fear of falling, fear of worsening their condition, or low selfefficacy. Research has explored the utilization of MI in this context and Hardcastle, Taylor, Bailey, Harley, and Hagger (2013) found that the use of MI was effective for some of the outcomes they measured, including walking and cholesterol levels. Interestingly, they identified that greater levels of effectiveness were found in those with higher levels of risk factors associated with cardiovascular disease.

The effectiveness of MI delivered via telephone has also been explored. Lilienthal, Pignol, Holm, and Vogeltanz-Holm (2014) randomly assigned older adults to telephone-based MI or to receive a healthy living guide. In this study, the authors also measured caloric expenditure and so were able to identify that within those who received MI, higher weekly caloric expenditure was an outcome. The effect was not maintained at 6-month follow-up, however, and the authors propose that while the technique was effective, booster sessions would need to be explored to maintain gains. A similar study looking at a telephone-based intervention using MI to reduce risky sexual behavior in older adults (Lovejoy et al., 2011) found that a brief, four-session intervention resulted in statistically greater reductions in risky behavior than the control group or briefer telephone-based MI. However, they also found that regardless of which arm of the study the older adults participated in, there was a reduction in risky behavior (potentially due simply to a greater awareness of the potential issues).

Clearly MI is an effective form of therapy when working with older adults. There remain some issues worth exploring further around relapse and maintenance of effects, however, and so future research focused on effective relapse prevention in the older adult population would be of benefit.

Third-wave therapeutic approaches

Interventions including mindfulness, acceptance and commitment therapy (ACT), and dialectical behavior therapy (DBT) focus primarily on the way in which the individual relates to their thoughts and emotions (Hayes, 2016). Evidence to date with respect to the efficacy of these third-wave approaches is mixed, with a Cochrane review article comparing therapeutic approaches in the treatment of depression finding very low-quality evidence for CBT and CBT third-wave approaches being equally effective (Hunot et al., 2013). Only three studies met the review criteria for inclusion in this study and the age of participants was not specifically older adults, but those aged between 18 and 75 years. The review nonetheless highlights the need for higher quality studies in this area in general.

Mindfulness

The fundamental basis of mindfulness is the ability to observe thoughts, emotions, and other sensations without connecting with them. The intervention encourages the individual to take a nonjudgmental stance toward their own thoughts and emotions. To facilitate this way of engaging (or rather not engaging) with one's inner self, meditation exercises are used, as is psychoeducation and in some programs, yoga exercises. Mindfulness-based stress reduction (MBSR) is one such example of a mindfulness program, as is mindfulness-based cognitive therapy (MBCT).

MBSR was originally developed as a 10-week program by Kabat-Zinn (1982) for people experiencing chronic pain, with participants in that study ranging in age from 22 to 75 years. Morone, Greco, and Weiner (2008) conducted a randomized controlled study using an 8-week program modeled on the work of Kabat-Zinn. Participants were older adults experiencing chronic lower back pain. A positive outcome was found in terms of pain acceptance and physical function, including maintenance of meditation at 3-month follow-up. Further, it was reported that the use of pain medication was reduced. Cresswell et al. (2012) used a similar approach, this time measuring loneliness and the expression of pro-inflammatory genes (i.e., genes that assist in fighting inflammation), finding that loneliness was reduced, as was the expression of pro-inflammatory genes. Other researchers have also looked at the impact of MBSR not just on mental health functioning, but also on physiological and cognitive function. For example, highlighting that there is evidence that mindfulness can assist in regulating attention, Moynihan et al. (2013) investigated the effects of MBSR on executive function abilities, as well as the immune system. While they found small but significant effects of MBSR in terms of participants more effectively completing tests of executive function, MBSR had no significant effect on immune

function. The authors attributed this in part to both the types of antibodies measured and the need for a greater understanding of variability in existing levels of antibodies at an individual level.

In a study looking at reducing worry and improving cognitive function, Lenze et al. (2014) found improvement in worry severity and in memory. However, this was a pilot study, and the improvements in memory could simply reflect the decrease in worry or, as the authors highlight, practice effects. Yet, the work of Mallya and Fiocco (2016) found no effects in using mindfulness to improve executive function. However, the participants in their study did not have cognitive impairment and by all accounts were healthy older adults. They hypothesized that their results may reflect the fact that their participants were already at optimal levels of functioning. However, they did implement an active control group comparison. Wetherell et al. (2017) conducted a randomized controlled trial to identify the impact of mindfulness in those with stress and neurocognitive difficulties. Memory improved, as did the experience of worry and depression. At follow-up, depression, worry, and anxiety had all improved.

Gallegos, Hoerger, Talbot, Moynihan, and Duberstein (2013) explored the emotional benefits of MBSR, again using an 8-week program. They found that compared to waitlist controls, the approach was most effective in improving positive affect in those older adults who began the study with a lower level of depression symptom severity.

In a study focused on older adults from a low-income minority background, Szanton, Wenzel, Connolly, and Piferi (2011) analyzed the responses of the focus groups to queries regarding what they found most important and helpful about MBSR. Themes raised by the participants included stress management and the social support provided by attending the groups. This raises the need to consider not only the effects of using the mindfulness strategies themselves, but also the impact of simply being part of a group and benefiting from the associated social engagement (e.g., Geiger et al., 2016).

Segal, Williams, and Teasdale (2002) developed MBCT for depression. Their work is based on that of Kabat-Zinn and colleagues, although MBCT is in fact a blend of mindfulness and CBT. Foulk, Ingersoll-Dayton, Kaavanagh, Robinson, and Kales (2014) explored the use of MBCT with older adults. They used an 8-week program that included a full-day retreat aimed at consolidating the strategies the group had learned during the briefer group sessions. The outcome of the study indicated reduced anxiety, symptoms of depression, and ruminative thoughts, as well as better sleep.

In 2018, Hazlett-Stevens, Singer, and Chong carried out a review of both MBSR and MBCT, identifying only one article fitting their criteria that specifically investigated MBCT in an older adult population. This article, by Helmes and Ward (2017), examined the use of MBCT for anxiety in older adults living in residential aged care. They used a randomized controlled trial approach and their program was 7-weeks in length, with significant effects shown in the study group but not the control group.

More generally, a review of the effects of mindfulness on both physical and emotional well-being in older adults conducted by Geiger et al. (2016) identified mixed support. They also noted, however, differences across these studies in terms of the mindfulness protocols used. Further, some of these studies of mindfulness interventions had significant methodological flaws, highlighting the need for more robust research in this domain. Similarly, a review by Fountain-Zaragoza and Prakash (2017) identified several ways in which mindfulness might play a role in healthy aging. These included enhancing attentional control, preserving neural functioning, improving psychological well-being, and reducing systematic inflammation. Still, the authors also highlighted that the evidence supporting these claims is tenuous at best.

Overall, and despite its long history as a therapeutic intervention, the empirical support for mindfulness could generally be described as small but effective. There is a need for more robust research if the technique (like many of the third-wave approaches) is to lose the label of being "... feasible and promising ..." (Fountain-Zaragoza & Prakash, 2017, p. 1).

Acceptance and commitment therapy

ACT is a form of therapy that focuses on mental health issues resulting from psychological inflexibility (Hayes, Strosahl, & Wilson, 1999). The model incorporates elements designed to counter psychological inflexibility by focusing the client on the present, identifying their core values, building acceptance, encouraging defusion (rather than fusion) with cognitions, building a commitment to action, and embracing the self. Contrary to CBT, for example, ACT explores the value of the self in the present and building on acceptance rather than challenging thoughts that are often valid in their content (e.g., my lifelong partner has passed away and that is very distressing; resulting in understandable symptoms of depression). There is therefore some benefit to being able to sit with such thoughts and associated emotions, rather than looking to counter them given the reality of some situations. Therefore, while ACT is considered under the umbrella of CBT-focused therapies, the focus of ACT is less on thoughts and more on process (Hayes et al., 1999).

In a small study exploring the utility of ACT for older adults experiencing generalized anxiety disorder, Wetherell, Afari, Rutledge, et al. (2011) found that the method was effective in reducing both worry and depression. In the same year, Wetherell, Afari, Ayers, et al. (2011) published another study looking at the effectiveness of ACT in the treatment of chronic pain. Once again, no significant difference in treatment effects was found between ACT and CBT, but the outcomes were positive in relation to pain interference, depression, and pain-related anxiety. However, those participants who engaged in the ACT intervention did report higher satisfaction with the modality than those who engaged in the CBT intervention. McCracken and Jones (2012) also looked at ACT in a chronic pain context and identified similarly positive results, including a 3-month follow-up. A metaanalysis conducted by Veehof, Oskam, Schreurs, and Bohlmeiher (2011) also concluded that ACT was equally effective, although once again, the participant numbers were small.

ACT has also been considered as a form of therapy for depression, with Karlin et al. (2013) finding good outcomes among older veterans. Once again, however, the number of participants was relatively small ($n = ?$), although they did obtain a 78% completion rate. Davison, Eppingstall, Runci, and O'Connor (2017) looked at ACT for people with depression and anxiety living in long-term care facilities. Compared to a waitlist condition, depression symptoms reduced in those who were engaged in the ACT intervention; results were maintained at 3-month follow-up.

ACT is a palatable form of therapy for older adults, particularly those experiencing issues impacting on mental health functioning that are unchangeable and would benefit from acceptance. There was also an indication that the effects were maintained at follow-up.

Dialectical behavior therapy

Linehan (1981) developed DBT for use in the treatment of those with highly suicidal behavior. It is underpinned by behavioral principles and social learning theory and fundamentally aims to create a synthesis between acceptance and tolerance of distress, rather than having a focus on change (Linehan & Wilks, 2015). And while there is a treatment protocol, the therapy was designed as modules such that the technique could be individualized based on the needs of the client (Linehan & Wilks, 2015). This modular approach makes comparisons across different research studies difficult given the context of the research determines the modules that are used with a group of participants. For example, the review work of Frazier and Vela (2014) discussed the various modifications made to standard DBT for the treatment of anger and aggressive behavior, finding that while overall results are positive, only one of the studies included in their review had older age participants. This was the work of Lynch et al. (2007) who looked at using DBT to treat comorbid personality disorder and depression in older adults. As has been the case in much of the research discussed in this chapter, participant numbers were again small, but standard DBT was feasible and held promise as an effective intervention.

A further challenge in considering the evidence-base for using DBT with older adults is the dearth of studies on the topic. A review by Van Alphen et al. (2015) looking at the treatment of personality disorders in older adults identified only four treatment studies, one of which used DBT (Lynch et al., 2007). Unsurprisingly, they reached the same conclusion as Lynch et al., which was to say that DBT was determined to be feasible as a treatment approach for older adults.

Based on the evidence, the third-wave approaches to therapy offer much promise in terms of their efficacy in working with older adults. Yet, research to date often relies on small participant numbers, which can result in unreliability in effect sizes. Nonetheless, what research is available highlights that these forms of therapy are effective and palatable to older adults and so should be considered as viable therapeutic options.

Problem-solving therapy

Problem-solving therapy (PST), as the name suggests, is a form of therapy that has an overarching goal of developing or building on effective problem-solving abilities as a means of "solving" what is causing the client's psychosocial distress. Nezu, Maguth Nezu, and D'Zurilla (2013) describe two key components: general orientation (i.e., seeing the problem as solvable, having selfefficacy around the ability to problem solve) and problem-solving skills (i.e., the ability to identify and carry out effective solutions to the problem).

Areán et al. (2010) compared PST with supportive therapy and found that the former not only resulted in a reduction in the severity of the symptoms of depression but also had longer term benefits (at both 9- and 12-week follow-ups). In addition, PST was found to be effective both in terms of treatment response and remission in the context of participants having executive dysfunction. Gellis and Bruce (2010) offered PST in the home for participants with cardiovascular disease and found a decrease in depression, but not anxiety. In relation to suicide risk, PST was found to reduce suicide risk in older adults at 12 weeks and 36 weeks posttreatment (Gustavson et al., 2016). In more of a theoretical offering,

Rosen, Morse, and Reynolds (2011) considered PST as a feasible treatment for depression in older adults engaging in a methadone treatment program. PST has also been suggested as useful for late-life anxiety (Beaudreau, Gould, Mashal, Huh, & Fairchild, 2019).

PST is touted as a practical therapeutic approach and, in that way, can be attractive to clients who prefer a more concrete, targeted therapeutic approach. Evidence is generally supportive of the method when working with older adults, with evidence also of maintenance of gains over time.

Strengths-based approaches

Older adults often bring knowledge and life experience to various contexts within which they might find themselves. Aging stereotypes, however, often see this quality diminished by beliefs that being old implies a lack of competence. This view is in some respects more linked to Western cultures, and while there remains a greater reverence and respect for older adults in Eastern cultures, there has also been a noted change in such sensibilities, with children moving away from rural areas, leaving aging parents behind without familial support (e.g., Liu, 2014). Nonetheless, in the context of psychotherapy, it is often of great benefit to draw on the knowledge, life experience, and wisdom of the older adult to assist not only with better therapeutic outcomes, but also longer lasting benefits (e.g., Daniels, Boehnlein, & McCallion, 2015; Linden, Baumann, Lieberei, Lorenz, & Rotter, 2011).

Positive psychology

Positive psychology focuses on flourishing and existence at optimal levels of functioning. Seligman and Csikszentmihalyi (2000) speak of "... well-being, contentment, and satisfaction (in the past); hope and optimism (for the future); and flow and happiness (in the present)" (p. 5). At an individual level, they speak of positive individual traits such as courage, perseverance, forgiveness, and wisdom. Interventions in positive psychology therefore focus on happiness, which Seligman (2002) defines as the pleasant, engaged, and meaningful life. As such, positive psychology interventions include elements such as building gratitude, increasing awareness of the positives in one's life, and identifying character strengths (Seligman, Steen, Park, & Peterson, 2005). Hill (2011) offers a positive aging framework that incorporates gratitude, forgiveness, and altruism into optimal functioning.

Ho, Yeung, and Kwok (2014) explored the use of a positive psychology intervention for older adults living in both the community and in nursing homes in Hong Kong. The themes of positive psychology explored as part of the intervention included optimism, gratitude, savoring, happiness, curiosity, courage, altruism, and meaning of life. Depressive symptoms were reduced, and sense of life satisfaction and happiness increased. Ramirez, Ortega, Chamorro, and Colmenero (2014) implemented a positive psychology intervention finding decreased state anxiety and depression, along with an associated increase in life satisfaction. A review by Sin and Lyubomirsky (2009) proffered that those who achieved the greatest gains in positive psychology-based therapy were those who were already more optimistic and positive, although the studies they included also identified improvements in depressive symptomology. They also suggested that better outcomes were seen in work with older adults as opposed to other age groups, suggesting that the presence of wisdom and better emotion regulation may play a role.

Obviously, this section offers only a sample of the literature behind positive psychology and so the reader is directed to the work of Seligman in general if they wish to explore this area further (e.g., Seligman, 2002; Seligman & Csikszentmihalyi, 2000). Focusing on work with older adults, there are positive gains to be had in using a positive psychology approach. However, when positive psychology approaches versus other forms of therapy should be used is an important consideration (e.g., Sin & Lyubomirsky, 2009). Much of the literature in this area speaks broadly to the idea of well-being and increased life satisfaction and often in contexts where psychopathology is not present (Sin & Lyubomirsky, 2009). The clinician may therefore find that a transtheoretical approach may be applicable.

Reminiscence

Bluck and Levine (1998) define reminiscence as reflecting on life past. Butler (1963) in his seminal article considering the process of life review defines this as "A naturally occurring, universal mental process characterized by the progressive return to consciousness of past experience, and particularly, the resurgence of unresolved conflicts; simultaneously, and normally, these revived experiences and conflicts can be surveyed and reintegrated ..." (p. 66). A quote by Margaret J. Wheatley captures the utility of reminiscence when she proffers that "Without reflection, we go blindly on our way, creating more unintended consequences, and failing to achieve anything useful." Therefore, part of the role of

reminiscence is to not simply engage in reflecting, but to actively engage, consolidating memories, learning from the past, and growing as a result (e.g., Bohlmeijer, Roemer, Cuijpers, & Smit, 2007).

Daniels et al. (2015) incorporated life review in group sessions with Vietnam veterans. They identified a clinically significant decrease in depressive symptoms when the group engaged in life review first, as compared to the group who focused on post-traumatic stress disorder (PTSD) first. Relevant to the next section in this chapter, they also identified that those who engaged in life review first as part of the group sessions also increased in their selfassessed wisdom scores.

The work of Cappeliez and O'Rourke (2006) identified that selfnegative forms of reminiscence have a negative impact on psychological well-being, while reminiscence that brings about meaning in life has a positive effect on psychological well-being. This is unsurprising as the links between reminiscing on emotionally negative events has been explored since the 1990s (see Fromholt, Larsen, & Larsen, 1995). As such, it should also be unsurprising that good effects have been found when using reminiscence therapy in the context of depression. For example, a metaanalysis carried out by Bohlmeijer, Smit, and Cuijpers (2003) found the effects of reminiscence and life review on depression equivalent to that found when using other forms of psychotherapy. Randomized clinical trials are, however, needed. In addition, Hallford and Mellor (2013) make an interesting observation, which is to say that reminiscence-based therapies are one of the few therapies to have only been explored in older adult populations as a treatment approach for depression. Their work concludes that the therapy should be explored with other age groups as it shows the potential to be useful in reducing symptoms of depression in groups other than older adults.

Reminiscence therapy builds on what many would say is a natural occurrence, taking the general act of reminiscing and encouraging a more active approach to life reflections. Research to date offers positive support, however, randomized controlled trials would build a more robust evidence-base.

Wisdom

Wisdom is highlighted as a multidimensional construct that at its most basic level incorporates such characteristics as having expertise in the fundamental pragmatics of life, being able to cope with uncertainty, and being able to offer good judgment and advice, taking into account the life spectrum (Baltes & Smith, 1990). Other authors highlight the element of tacit knowledge (Sternberg, 2003) and cognitive, reflective, and affective components (e.g., Ardelt, 1997; Clayton & Birren, 1980). Eastern definitions of wisdom tend to focus on benevolence and compassion and other interpersonal factors, therefore being less focused on intelligence (e.g., Takayama, 2002; Sung, 2011; Yang, 2001).

In a theoretical piece written by Linley (2003), he explores the adaptation and wisdom that comes from experiencing challenging life events. Referred to as posttraumatic positive adaptation, Linley (2003) proposes a theoretical framework that incorporates three elements of wisdom: the recognition and management of uncertainty; the integration of affect and cognition; and the recognition of acceptance of the limitations of humans. He also proposes that wisdom is both a process within and an outcome of positive adaptation to trauma. There are some overlaps here between positive psychology and wisdom, however, Linley's work links specifically to what is loosely termed the potential positive growth that comes from trauma and the associated development of wisdom as a result.

In an older adult context, one might assume that the potential to experience some form of trauma or challenging life experience is increased purely by virtue of having lived longer. As such, the therapist may look to such experiences and draw out and encourage the recognition and understanding of the growth and wisdom that may have occurred, despite the challenges said trauma may have invoked. Linley (2003) emphasizes that positive adaptation to trauma is a growth process, one that "... propels the survivor to a higher level of functioning than that which they held previously" (p. 602).

More specifically, in relation to wisdom having utility within psychotherapy, Linden et al. (2011) speak to the notion that wisdom is a quality that can assist us in dealing more effectively with negative life events. As such, wisdom is linked with resilience. However, there is likely more to the relationship between wisdom and resilience. While resilience (as defined in the next section) is the ability to bounce back after a negative event, wisdom is the ability to travel alongside the negative event, accept it, and grow from the experience (taking on board the lessons learnt to assist with future calls on our coping abilities). Indeed, Sternberg (1990) links wisdom with a means of problem-solving, particularly in the context of those problems that do not have a clear response or certain outcome, as well as those with a more metacognitive frame.

The utilization of wisdom therapeutically is an emerging field of research. In another theoretical piece, Hanna and Ottens (1995) posited that wisdom not only be considered an important technique to be used within therapy, but also a worthy outcome of therapy. So-called wisdom psychotherapy has been placed under the umbrella of CBT and

fundamentally relies on the idea that the goal of therapy is the development of qualities associated with wisdom (Linden et al., 2011). However, it is worth noting at this point that Sternberg (1990) emphasized that a wise person would be someone who was able to think independently, that is, not be a product of automatic thoughts, a common goal within CBT frameworks of therapy. Going back to wisdom psychotherapy, Linden et al. (2011) offer this form of therapy as a treatment for posttraumatic embitterment disorder (PTED; a form of adjustment disorder in reaction to a negative life experience that results in the onset of illness). Unfortunately, their focus was not specifically on older adults; however, their work refers specifically to the utility of wisdom psychotherapy. Fundamentally, the method links closely with the definitional work of Baltes and colleagues (e.g., Baltes & Smith, 1990) and attempts to encourage the building of such things as factual knowledge regarding the problem at hand, to be able to cope with the uncertainty element, and see the problem at its broadest level rather than be too closely entwined (which can hamper problem-solving ability, in keeping with the adage that one cannot see the forest for the trees).

Wisdom therapy is clearly an area in need of further exploration to establish an evidence-base. One could even draw links between ACT and mindfulness with wisdom in that both forms of therapy work more toward accepting and walking alongside everyday challenges, which loosely relates to the notion of the tolerance of uncertainty.

Resilience

As has been highlighted at various points so far in this chapter, older adults often have life experience encompassing coping with a range of stressful situations within their past and at the present time, including loss and bereavement as well as trauma. The ability to adapt and work through such challenges can be important in maintaining mental health and well-being.

Broadly defined as the ability to bounce back after experiencing difficult life events, resilience (while not a form of therapy in and of itself) is often encouraged, developed, and/or maintained to help the older adult face their current challenges and adapt effectively. As such, the encouraging of resilience often draws on the past experiences of the older adult, particularly times when they have been resilient. In the midst of a stressful or challenging time, the fact of having dealt with challenging events in the past is often forgotten. The role of the therapist becomes one of assisting the older adult in exploring how they have coped in the past and guiding them in using similar strategies in the present.

A literature review conducted by MacLeod, Musich, Hawkins, Alsgaard, and Wicker (2016) sought to identify ways to incorporate resilience as an intervention given resilience has been linked with such positive outcomes as successful aging, lower depression, and longevity. Their review highlighted that interventions incorporating adaptive coping, optimism, positive emotion, and social connectedness—that were individualized to the needs of the client—offer the most evidence in terms of building and maintaining resilience.

Gooding, Jurst, Johnson, and Tarrier (2012) conducted a study that compared psychological resilience in older adults compared to younger adults, and what factors might predict resilience. Their findings indicated that older adults are higher in resilience due to having greater abilities in the regulation of emotion and problem-solving. Younger adults, on the other hand, with a higher sense of social support were more resilient. The authors also found that poor selfrated health and a sense of hopelessness were associated with low resilience. Such knowledge can be important for the clinician as it may guide how best to promote resiliency in older adults. That is, if the client is experiencing hopelessness, then working with this may need to be a target of therapy as it may then enhance resilience. In a similar vein, Cheavons, Cukrowicz, Hansen, and Mitchell (2016) posit that in the context of suicidality, resilience factors should be incorporated in models of suicidal ideation, particularly in relation to selfforgiveness. More work needs to be done in this area, but it speaks to the potential for late-life interventions targeting resilience as a means of building mental health and well-being.

Strengths-based approaches have common themes of growth from trauma, being able to step back from problems in order to be able to disentangle oneself and explore wider options of solutions, acceptance of the uncertain nature of some circumstances and soldiering on regardless, and of using the lessons of the past in order to more effectively challenge and solve the problems of the present. Given that not all problems have concrete solutions, and that older adults can be more likely to experience problems without a solution (e.g., diagnosis of chronic medical condition, the loss of a partner of many number of years), the therapist is encouraged to consider such approaches in their work with older adults.

Future focus

In 1983, when the first cellular phone became a tool of the present, “Baby Boomers” were of an age when such technology would start to play a key role at least in their working careers. Fast forward to the present day and few people

outside of technologically savvy organizations such as Apple™ and Google™ could have predicted how embedded such technology would become in terms of everyday living. Grandparents are texting their grandchildren from their smartwatches, retirees are monitoring their health, exercise load, and sleep routines daily, and those still in the workforce are working from home (using videoconferencing and cloud technology, while achieving greater work efficiencies than their younger adult selves could have imagined).

Baby Boomers are now of an age where they are either firmly in older adulthood or approaching older adulthood. And what they bring (or will bring) to older adulthood is not only an openness to mental health and well-being, but also a willingness and ability to use technology (Karel, Gatz, & Smyer, 2012). Developments in the technology domain have included the utilization of telehealth for mental health sessions, websites that take the user through psychotherapy sessions via selfhelp models (including with and without coaching options), apps that engage the user in strategies and techniques for managing such diagnoses as depression and anxiety, as well as mental well-being more generally, and virtual reality (VR) technology that immerses the user in a virtual environment for such things as exposure therapy and relaxation.

While technological development in the area of mental health has been quite prolific, and there is much excitement about the use of such tools in the area, the associated evidence-base is often lacking and what evidence does exist indicates that technology may have limited clinical relevance. It is therefore a field in need of further, and more robust, research in order to tease out the evidence-base and establish the utility of what is a very exciting, but still research lacking, area for therapy.

Telehealth modalities

Telehealth offers the opportunity for clients to engage in therapeutic services via the internet rather than in person. This modality has obvious benefits, particularly in relation to those clients who experience barriers to regular participation in face-to-face interventions.

Using a telehealth approach, Choi et al. (2014) offered PST to low-income older adults who were experiencing depression. Labeled as tele-PST, they compared the modified therapy with in-person PST and telephone support calls using a randomized controlled trial approach. The results demonstrated that both in-person and tele-PST produced the same effective results when compared to telephone support calls, with treatment effects also maintained 6 months later. Steffen and Gant (2016) offered telehealth programs to women caring for an older adult with a neurocognitive disorder. They used an active, behavioral intervention that incorporated instructional videos and coaching, finding that those who received treatment had reduced levels of depression and generally coped better with challenging situations (including having higher levels of selfefficacy).

Web-based interventions

The internet has also broadened the scope of therapy by offering an online means of accessing mental health support independently. This is advantageous in many ways. For example, it offers access to such therapy by those who live in regional and remote areas and who would otherwise not be able to access such services. It also offers an alternative form of therapy for those who might otherwise be hesitant to engage in face-to-face, direct therapy. Web-based interventions therefore offer a viable alternative for those who would otherwise not have access to therapy due to caring responsibilities or other forms of accessibility issues.

Scott et al. (2016) reviewed the utility of technology-based CBT (TB-CBT) as an intervention for dementia caregivers. Small effects were identified, and the authors also acknowledged that this form of treatment approach was convenient and economically viable. As with other research discussed in this chapter, the authors highlighted that more research is needed in this area, particularly with regard to the long-term efficacy of the modality.

Mobile applications ("Apps")

The advent of apps has similarly seen an increase in the development of apps seen as potentially useful within the domain of mental health. The research behind such apps is quite limited, however, and the support for the efficacy of such tools is poor. People report good effects, but the research base is lacking. In a single case study conducted by Chen, Hung, and Chen (2016), they demonstrated that an older female was better able to manage her sleep without the use of medication after engaging with the Win-Win aSleep app (using six sessions of CBT for insomnia).

A review by Bhattarai, Newton-John, and Phillips (2018) on pain management apps primarily identified the need for apps to be older adult user friendly, a view shared by Gao, Zhou, Wang, and Bowers (2017). Other authors such as Whitlock, McLaughlin, Harris, and Bradshaw (2015) offer ideas as to how apps should be designed (in this case with regards diabetes and selfmanagement in older adults). Other studies highlight the lack of robust research to establish the efficacy of apps in general (e.g., Garabedian, Ross-Degnan, & Wharam, 2015; Marley & Farooq, 2015).

While certainly an exciting and potentially efficacious modality of therapy, there is clearly much work to be done in the area of apps and their actual degree of utility.

Gaming and virtual reality

Hall, Chavarria, Maneeratana, Chaney, and Bernhardt (2012) conducted a literature review exploring the health benefits of video games for older adults. Overall, their review highlighted that such game play identified positive mental health, physical health, and social health outcomes. Allaire et al. (2013) found that those older adults who engaged in playing digital games experienced a better sense of well-being, lower levels of negative affect (including lower levels of depression), and higher social functioning compared to those not playing digital games. An online, multiplayer form of bingo that aimed to help older adults learn about nutrition and health was explored by Seah, Kaufman, Sauvé, and Zhang (2018). The benefits included learning about the content, social connectedness, and having fun.

Much of the research to date looking at the utility of VR when working with older adults has focused on physical benefits, such as improved balance, rehabilitation efforts, and increased exercise more generally. However, Chan, Ngai, Leung, and Wong (2010) looked at using VR as a cognitive training program for older adults with schizophrenia. They found that after 10 sessions of training, those in the intervention group performed better than the control group in terms of overall cognitive function. Other researchers such as Grenier et al. (2015) have considered the use of VR as a means of enhancing CBT. Their review considered older adults with anxiety and the use of VR as an exposure strategy (rather than more traditional imaginal or in vivo strategies). The method was identified as effective in older veterans, but they also highlight that such research is very limited, focusing more on those younger than age 65.

Clearly gaming has benefits, including at its most fundamental level, positive activity engagement. Research to date has also identified related benefits including a greater sense of well-being, connecting and engaging with others, and reduced levels of negative affect. Similarly, VR offers much promise, but there is certainly more research to be done in this area in specific reference to mental health concerns and with older adults. The use of gaming is therefore worthwhile considering as a means of engaging an older adult in positive event scheduling and behavioral activation if they would see such an activity as both feasible and something they would like to try.

Technology offers much promise in terms of expanding the availability of therapy (particularly to those who for various reasons are unable or unwilling to attend sessions in person), building on the array of options available that may enhance the effectiveness of "regular" modalities of therapy and offer more palatable solutions to maintaining gains from therapy for longer term. However, there is much work to do not only more broadly in terms of establishing a more robust evidence-base, but with older adult populations who are sometimes stereotyped as being technology averse.

Conclusion

Many forms of psychotherapy have garnered at least modest efficacy bases in the literature, and e-health variants of these also have growing research bases, as well as important clinical applications. In many instances, however, the research surrounding therapeutic work with older adults remains limited, particularly for those with multiple comorbidities or at more advanced ages. What research is available offers support for good outcomes or at least the feasibility and promise of using the variety of forms of therapy available with older adults to positive effect.

Technological advancements offer the opportunity to build on existing research, incorporating telehealth and online methods of therapy. Once again there is a dearth of studies in this domain in specific reference to older adults, however, what scientific evidence is available again offers much promise. This is important for a variety of populations of underserved older adults, including those living in more rural areas, those with mobility restrictions, and those who might wish to connect with a therapist with expertise or cultural background.

Although CBT variants of psychotherapy have the largest empirical database, other forms of therapy such as ACT and mindfulness have been usefully applied to a growing number of presenting problems. Moreover, the ability of older adults to have choice among therapy offerings and for research to make improvements on which therapies work best for which older adults in which contexts are both crucial to deliver the best possible mental health outcomes to older people.

References

Allaire, J. C., McLaughlin, A. C., Trujillo, A., Whitlock, L. A., LaPorte, L., & Gandy, M. (2013). Successful aging through digital games: Socioemotional differences between older adult gamers and non-gamers. *Computers in Human Behavior*, *29*, 1302−1306. Available from https://doi.org/10.1016/j.chb.2013.01.014.

Ardelt, M. (1997). Wisdom & life satisfaction in old age. *Journal of Gerontology: Psychological Sciences*, *52B*(1), 15−27. Available from https://doi.org/10.1093/geronb/52b.1.p15.

Areán, P. A., Raue, P., Mackin, R. S., Kanellopoulos, D., McCulloch, C., & Alexopoulos, G. S. (2010). Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. *American Journal of Psychiatry*, *167*, 1391−1398. Available from https://doi.org/10.1176/appi.ajp.2010.09091327.

Baltes, P. B., & Smith, J. (1990). Toward a psychology of wisdom and its ontogenesis. In R. J. Sternberg (Ed.), *Wisdom: Its nature, origins, and development* (pp. 87−120). Cambridge: Cambridge University Press.

Beaudreau, S. A., Gould, C. E., Mashal, N. M., Huh, J. T., & Fairchild, J. K. (2019). Application of problem solving therapy for late-life anxiety. *Cognitive and Behavioral Practice*, *26*, 381−394. Available from https://doi.org/10.1016/j.cbpra.2018.05.003.

Beck, A. T. (1964). Thinking and depression: Theory and therapy. *Archives of General Psychiatry*, *10*, 561−571. Available from https://doi.org/10.1001/archpsyc.1964.01720240015003.

Bhattarai, P., Newton-John, T. R. O., & Phillips, J. L. (2018). Quality and usability of arthritic pain self-management apps for older adults: A systematic review. *Pain Medicine*, *19*, 471−484. Available from https://doi.org/10.1093/pm/pnx090.

Bluck, S., & Levine, L. (1998). Reminiscence as autobiographical memory: A catalyst for reminiscence theory development. *Ageing and Society*, *18*, 185−208. Available from https://doi.org/10.1017/S0144686X98006862.

Bohlmeijer, E., Roemer, M., Cuijpers, P., & Smit, F. (2007). The effects of reminiscence on psychological well-being in older adults: A meta-analysis. *Aging & Mental Health*, *11*, 291−300. Available from https://doi.org/10.1080/13607860600935547.

Bohlmeijer, E., Smit, F., & Cuijpers, P. (2003). Effects of reminiscence and life review on late-life depression: A meta-analysis. *International Journal of Geriatric Psychiatry*, *18*, 1088−1094. Available from https://doi.org/10.1002/gps.1018.

Bourgault-Fagnou, M. D., & Hadjistavropoulos, H. D. (2013). A randomized trial of two forms of cognitive behavior therapy for an older adult population with subclinical health anxiety. *Cognitive Behavior Therapy*, *42*, 31−44. Available from https://doi.org/10.1080/16506073.2012.717302.

Butler, R. N. (1963). The life review: An interpretation of reminiscence in the aged. *Psychiatry: Interpersonal and Biological Processes*, *26*, 65−76. Available from https://doi.org/10.1080/0332747.1963.11023339.

Cappeliez, P., & O'Rourke, N. (2006). Empirical validation of a model of reminiscence and health in later life. *The Journals of Gerontology: Series B, Psychological Sciences and Social Sciences*, *61*, 237−244. Available from https://doi.org/10.1093/geronb/61.4.P237.

Chan, C. L., Ngai, E. K., Leung, P. K., & Wong, S. (2010). Effect of the adapted virtual reality cognitive training program among Chinese older adults with chronic schizophrenia: A pilot study. *International Journal of Geriatric Psychiatry*, *25*, 643−649. Available from https://doi.org/10.1002/gps.2403.

Chang, Y.-P., Compton, P., Almeter, P., & Fox, C. H. (2015). The effect of motivational interviewing on prescription opioid adherence among older adults with chronic pain. *Perspectives in Psychiatric Care*, *51*, 211−219. Available from https://doi.org/10.1111/ppc.112082.

Cheavons, J. S., Cukrowicz, K. C., Hansen, R., & Mitchell, S. M. (2016). Incorporating resilience factors into the interpersonal theory of suicide: The role of hope and self-forgiveness in an older adult sample. *Journal of Clinical Psychology*, *72*, 58−69. Available from https://doi.org/10.1002/jclp.22230.

Chen, Y. X., Hung, Y. P., & Chen, H. C. (2016). Mobile application-assisted cognitive behavioral therapy for insomnia in an older adult. *Telemedicine Journal and e-Health*, *22*, 332−334. Available from https://doi.org/10.1089/tmj.2015.0064.

Choi, N. G., Hegel, M. T., Marti, N., Marinucci, M. L., Sirrianni, L., & Bruce, M. L. (2014). Telehealth problem-solving therapy for depressed low-income homebound older adults: Acceptance and preliminary efficacy. *American Journal of Geriatric Psychiatry*, *22*, 263−271. Available from https://doi.org/10.1097/JGP.0b013e318266b356.

Clayton, V. P., & Birren, J. E. (1980). The development of wisdom across the life span: A reexamination of an ancient topic. In P. B. Baltes, & O. G. Brim, Jr. (Eds.), *Life span development and behavior* (Vol. 3, pp. 103−135). New York: Academic Press.

Cresswell, J. D., Irwin, M. R., Burkland, L. J., Lieberman, M. D., Arevalo, J. M. G., Ma, J., … Cole, S. W. (2012). Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: A small randomized controlled trial. *Brain Behavior Immunology*, *26*, 1095−1101. Available from https://doi.org/10.1016/j.bbi.2012.07.006.

Cummings, S. M., Cooper, R. L., & McClure Cassie, K. (2009). Motivational interviewing to affect behavioural change in older adults. *Research on Social Work Practice*, *19*, 195−204. Available from https://doi.org/10.1177/1049731508320216.

Daniels, L. R., Boehnlein, J., & McCallion, P. (2015). Aging, depression, and wisdom: A pilot study of life-review intervention and PTSD treatment with two groups of Vietnam veterans. *Journal of Gerontological Social Work*, *58*, 420−436. Available from https://doi.org/10.1080/01634372.2015.1013657.

Davison, T. E., Eppingstall, B., Runci, S., & O'Connor, D. W. (2017). A pilot trial of acceptance and commitment therapy for symptoms of depression and anxiety in older adults residing in long-term care facilities. *Aging & Mental Health*, *21*, 766−773. Available from https://doi.org/110.1080/13607863.2016.1156051.

Foulk, M. A., Ingersoll-Dayton, B., Kaavanagh, J., Robinson, E., & Kales, H. C. (2014). Mindfulness-based cognitive therapy with older adults: An exploratory study. *Journal of Gerontological Social Work*, *57*, 498−520. Available from https://doi.org/10.1080/01634372.2013.869787.

Fountain-Zaragoza, S., & Prakash, R. S. (2017). Mindfulness training for healthy aging: Impact on attention, well-being, and inflammation. *Frontiers in Aging Neuroscience*, *9*, 11. Available from https://doi.org/10.3389/fnagi.2017.00011.

Frazier, S. N., & Vela, J. (2014). Dialectical behavior therapy for the treatment of anger and aggressive behavior: A review. *Aggression and Violent Behavior*, *19*, 156–163. Available from https://doi.org/10.1016/j.avb.2014.02.001.

Fromholt, P., Larsen, P., & Larsen, S. F. (1995). Effects of late-onset depression and recovery on autobiographical memory. *The Journals of Gerontology: Series B, Psychological Sciences and Social Sciences*, *50*, 74–81. Available from https://doi.org/10.1093/geronb/50B.2.P74.

Gallagher-Thompson, D., & Steffen, A. M. (1994). Comparative effects of cognitive-behavioral and brief psychodynamic psychotherapies for depressed family caregivers. *Journal of Consulting and Clinical Psychology*, *62*, 543–549.

Gallegos, A. M., Hoerger, M., Talbot, N. L., Moynihan, J. A., & Duberstein, P. R. (2013). Emotional benefits of mindfulness-based stress reduction in older adults: The moderating roles of age and depressive symptom severity. *Aging Mental Health*, *17*, 823–829. Available from https://doi.org/10.1080/13607863.2013.799118.

Gao, C., Zhou, L., Wang, H., & Bowers, B. (2017). Mobile application for diabetes self-management in China: Do they fit for older adults? *International Journal of Medical Informatics*, *101*, 68–74. Available from https://doi.org/10.1016/j.ljmedinf.2017.02.005.

Garabedian, L. F., Ross-Degnan, D., & Wharam, J. F. (2015). Mobile phone and smartphone technologies for diabetes care and self-management. *Current Diabetes Reports*, *15*, 109. Available from https://doi.org/10.1007/s11892-015-0680-8.

Geiger, P. J., Boggero, I. A., Brake, C. A., Caldera, C. A., Combs, H. L., Peters, J. R., & Baer, R. A. (2016). Mindfulness-based interventions for older adults: A review of the effects on physical and emotional well-being. *Mindfulness*, *7*, 296–307. Available from https://doi.org/10.1007/s12671-015-0444-1.

Gellis, Z. D., & Bruce, M. L. (2010). Problem solving therapy for subthreshold depression in home healthcare patients with cardiovascular disease. *American Journal of Geriatric Psychiatry*, *18*, 464–474.

Gooding, P. A., Jurst, A., Johnson, J., & Tarrier, N. (2012). Psychological resilience in young and older adults. *International Journal of Geriatric Psychiatry*, *27*, 262–270. Available from https://doi.org/10.1002/gps.2712.

Gould, R. L., Coulson, M. C., & Howard, R. J. (2012). Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *Journal of the American Geriatrics Society*, *60*, 218–229. Available from https://doi.org/10.1111/j.1532-5415.2011.03824.x.

Grenier, S., Forget, H., Bouchard, S., Isere, S., Belleville, S., Potvin, S., ... Talbot, M. (2015). Using virtual reality to improve the efficacy of cognitive-behavioral therapy (CBT) in the treatment of late-life anxiety: Preliminary recommendations for future research. *International Psychogeriatrics*, *27*, 1217–1225. Available from https://doi.org/10.1017/S1041610214002300.

Gustavson, K. A., Alexopoulos, G. S., Niu, G. C., McCulloch, C., Meade, T., & Arean, P. A. (2016). Problem-solving therapy reduces suicidal ideation in depressed older adults with executive dysfunction. *American Journal of Geriatric Psychiatry*, *24*(1), 11–17. Available from https://doi.org/10.1016/j.jagp.2015.07.010.

Hall, A. K., Chavarria, E., Maneeratana, V., Chaney, B. H., & Bernhardt, J. M. (2012). Health benefits of digital videogames for older adults: A systematic review of the literature. *Games for Health Journal*, *1*, 402–410. Available from https://doi.org/10.1089/g4h.2012.0046.

Hallford, D. J., & Mellor, D. (2013). Cognitive-reminiscence therapy and usual care for depression in young adults: Study protocol for a randomized controlled trial. *Trials*, *14*, 1–8. Available from https://doi.org/10.1186/1745-6215-14-343.

Hanna, F. J., & Ottens, A. J. (1995). The role of wisdom in psychotherapy. *Journal of Psychotherapy Integration*, *5*, 195–219. Available from https://doi.org/10.1037/h0101273.

Hardcastle, S. J., Taylor, A. H., Bailey, M. P., Harley, R. A., & Hagger, M. S. (2013). Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: A randomized controlled trial with a 12-month post-intervention follow-up. *International Journal of Behavioral Nutrition and Physical Activity*, *10*, 40. Available from https://doi.org/10.1186/1479-5868-10-40.

Hayes, S. C. (2016). Acceptance and commitment therapy, relational frame theory, and third wave of behavioral and cognitive therapies. *Behavior Therapy*, *47*, 869–885. Available from https://doi.org/10.1016/S0005-7894(04)80013-3.

Hayes, S. C., Strosahl, K. D., & Wilson, K. G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. New York: Guilford Press.

Heisel, M. J., Talbot, N. L., King, D. A., Tu, X. M., & Duberstein, P. R. (2015). Adapting interpersonal psychotherapy for older adults at risk for suicide. *American Journal of Geriatric Psychiatry*, *23*, 87–98. Available from https://doi.org/10.1016/j.jagp.2014.03.010.

Helmes, E., & Ward, B. G. (2017). Mindfulness-based cognitive therapy for anxiety symptoms in older adults in residential care. *Aging & Mental Health*, *21*, 272–278. Available from https://doi.org/10.1080/13607863.2015.1111862.

Hill, R. D. (2011). A positive aging framework for guiding geropsychology interventions. *Behavior Therapy*, *42*, 66–77. Available from https://doi.org/10.1016/j.beth.2010.04.006.

Hinrichsen, G. A., & Clougherty, K. F. (2006). *Interpersonal therapy for depressed older adults*. Washington, DC, USA: American Psychological Association.

Ho, H. C. Y., Yeung, D. Y., & Kwok, W. Y. C. L. (2014). Development and evaluation of the positive psychology intervention for older adults. *The Journal of Positive Psychology*, *9*, 187–197. Available from https://doi.org/10.1080/17439760.2014.888577.

Hunot, V., Moore, T. H. M., Caldwell, D. M., Furukawa, T. A., Davies, P., Jones, H., ... Churchill, R. (2013). 'Third wave' cognitive behavioural therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*, *10*. Available from https://doi.org/10.1002/14651858.CD008704.pub2, CD008704.

Johnco, C., Wuthrich, V. M., & Rapee, R. M. (2014). The influence of cognitive flexibility on treatment outcome and cognitive restructuring skill acquisition during cognitive behavioural treatment for anxiety and depression in older adults: Results of a pilot study. *Behaviour Research and Therapy*, *57*, 55−64. Available from https://doi.org/10.1016/j.brat.2014.004.005.

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*, *4*, 33−47. Available from https://doi.org/10.1016-0163-8343(82)90026-3.

Karel, M. J., Gatz, M., & Smyer, M. A. (2012). Aging and mental health in the decade ahead: What psychologists need to know. *American Psychologist*, *67*, 184−198. Available from https://doi.org/10.1037/a0025393.

Karlin, B. E., Walser, R. D., Yesavage, J., Zhang, A., Trockel, M., & Taylor, C. B. (2013). Effectiveness of acceptance and commitment therapy for depression: Comparison among older and younger veterans. *Aging & Mental Health*, *17*, 555−563. Available from https://doi.org/10.1080/13607863.2013.789002.

Klerman, G. L., Weissman, M. M., Rounsaville, B. J., & Chevron, E. (1984). *Interpersonal psychotherapy of depression*. New York: Basic Books.

Knight, B. G., & Poon, C. Y. M. (2008). Contextual adult lifespan theory for adapting psychotherapy with older adults. *Journal of Rational-Emotive & Cognitive-Behavior Therapy*, *26*(4), 232−249. Available from https://doi.org/10.1007/s10942-008-0084-7.

Laidlaw, K., & Pachana, N. A. (2009). Aging, mental health, and demographic change: Challenges for psychotherapists. *Professional Psychology: Research and Practice*, *40*(6), 601−608. Available from https://doi.org/10.1037/a0017215.

Lenze, E. J., Hickman, S., Hershey, T., Wendleton, L., Ly, K., Dixon, D., … Wetherell, J. L. (2014). Mindfulness-based stress reduction for older adults worry symptoms and co-occurring cognitive dysfunction. *International Journal of Geriatric Psychiatry*, *29*, 991−1000. Available from https://doi.org/10.1002/gps.4086.

Lilienthal, K. R., Pignol, A. E., Holm, J. E., & Vogeltanz-Holm, N. (2014). Telephone-based motivational interviewing to promote physical activity and stage of change progression in older adults. *Journal of Aging and Physical Activity*, *22*, 527−535. Available from https://doi.org/10.1123/JAPA.2013-0056.

Linden, M., Baumann, K., Lieberei, B., Lorenz, C., & Rotter, M. (2011). Treatment of posttraumatic embitterment disorder with cognitive behaviour therapy based on wisdom psychology and hedonia strategies. *Psychotherapy and Psychosomatics*, *80*, 199−205. Available from https://doi.org/10.1159/000321580.

Linehan, M. M. (1981). A social-behavioral analysis of suicide and parasuicide: Implications for clinical assessment and treatment. In H. Glazer, & J. F. Clarkin (Eds.), *Depression, behavioural and directive intervention strategies* (pp. 229−294). New York: Garland Press.

Linehan, M. M., & Wilks, C. R. (2015). The course and evolution of dialectical behavior therapy. *American Journal of Psychotherapy*, *69*, 97−110. Available from https://doi.org/10.1176/appi.psychotherapy.2015.69.2.97.

Linley, P. A. (2003). Positive adaptation to trauma: Wisdom as both process and outcome. *Journal of Traumatic Stress*, *16*, 601−610. Available from https://doi.org/10.1023/B.JPOTS.0000004086.64509.09.

Liu, J. (2014). Ageing, migration and familial support in rural China. *Geoforum*, *51*, 305−312. Available from https://doi.org/10.1016/j.geoforum.2013.04.013.

Lovejoy, T. I., Heckman, T. G., Suhr, J. A., Anderson, T., Heckman, B. D., & France, C. R. (2011). Telephone-administered motivational interviewing reduces risky sexual behaviour in HIV-positive late middle-age and older adults: A pilot randomized controlled trial. *AIDS Behavior*, *15*, 1623−1634. Available from https://doi.org/10.1007/s10461-011-0016-x.

Lynch, T. R., Cheavons, J. S., Cukrowicz, K. C., Thorp, S. R., Bronner, L., & Beyer, J. (2007). Treatment of older adults with co-morbid personality disorder and depression: A dialectical behavior therapy approach. *International Journal of Geriatric Psychiatry*, *22*, 131−143. Available from https://doi.org/10.1002/gps.1703.

MacLeod, S., Musich, S., Hawkins, K., Alsgaard, K., & Wicker, E. R. (2016). The impact of resilience among older adults. *Geriatric Nursing*, *37*, 266−272. Available from https://doi.org/10.1016/j.gerinurse.2016.02.014.

Mallya, S., & Fiocco, A. J. (2016). Effects of mindfulness training on cognition and well-being in healthy older adults. *Mindfulness*, *7*, 453−465. Available from https://doi.org/10.1007/s12671-015-0438-6.

Marley, J., & Farooq, S. (2015). Mobile telephone apps in mental health practice: Uses, opportunities and challenges. *BJPsych Bulletin*, *39*, 288−290. Available from https://doi.org/10.1192/pb.bp.114.050005.

McCracken, L. M., & Jones, R. (2012). Treatment for chronic pain for adults in the seventh and eight decades of life: A preliminary study of acceptance and commitment therapy (ACT). *Pain Medicine*, *13*, 861−867. Available from https://doi.org/10.1111/j.1526-4637.2012.01407.x.

Miller, M. D., Frank, E., Cornes, C., Imber, S. D., Anderson, B., Ehrenpreis, S. D., … Reynolds, C. F., III (1994). Applying interpersonal psychotherapy to bereavement-related depression following loss of a spouse in late life. *The Journal of Psychotherapy Practice and Research*, *3*, 149−162.

Miller, W. R., & Rollnick, S. (2013). *Motivational interviewing: Helping people change* (3rd edition). New York: Guilford Press.

Morone, N. E., Greco, C. M., & Weiner, D. K. (2008). Mindfulness meditation for the treatment of chronic low back pain in older adults: A randomized controlled pilot study. *PAIN*, *134*, 310−319. Available from https://doi.org/10.1016/j.pain.2007.04.038.

Moynihan, J. A., Chapman, B. P., Klorman, R., Krasner, M. S., Duberstein, P. R., Brown, K. W., & Talbot, N. L. (2013). Mindfulness-based stress reduction for older adults: Effects on executive function, frontal alpha asymmetry and immune function. *Neuropsychobiology*, *68*, 34−43. Available from https://doi.org/10.1159/000350949.

Nezu, A. M., Maguth Nezu, C., & D'Zurilla, T. J. (2013). *Problem-solving therapy: A treatment manual*. New York: Springer Publishing Co.

Orgeta, V., Qazi, A., Spector, A., & Orrell, M. (2015). Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *207*. Available from https://doi.org/10.1192/bjp.bp.114.148130, 293−293.

Ramirez, E., Ortega, A. R., Chamorro, A., & Colmenero, J. M. (2014). A program of positive intervention in the elderly: Memories, gratitude and forgiveness. *Aging & Mental Health*, *18*, 463–470. Available from https://doi.org/10.1080/13607863.2013.856858.

Reynolds, C. F., III, Miller, M. D., Pasternak, R. E., Frank, E., Perel, J. M., Cornes, C., ... Kupfer, D. J. (1999). Treatment of bereavement-related major depressive episodes in later life: A controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *American Journal of Psychiatry*, *156*, 202–208. Available from https://doi.org/10.1176/ajp.156.2.202.

Rosebourough, D. J., Luptak, M., McLeod, J., & Bradshaw, W. (2013). Effectiveness of psychodynamic psychotherapy with older adults: A longitudinal study. *Clinical Gerontologist*, *36*, 1–16. Available from https://doi.org/10.1080/07317115.2012.731476.

Rosen, D., Morse, J. Q., & Reynolds, C. F., III (2011). Adapting problem-solving therapy for depressed older adults in methadone maintenance treatment. *Journal of Substance Abuse Treatment*, *40*, 132–141. Available from https://doi.org/10.1016/j.jsat.2010.09.003.

Salthouse, T. A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society*, *16*, 754–760. Available from https://doi.org/10.1017/S1355617710000706.

Scogin, F., Welsh, D., Hanson, A., Stump, J., & Coates, A. (2005). Evidence-based psychotherapies for depression in older adults. *Clinical Psychology: Science and Practice*, *12*, 222–237. Available from https://doi.org/10.1093/clipsy.bpi033.

Scott, J. L., Dawkins, S., Quinn, M. G., Sanderson, K., Elliott, K. E., Stirling, C., ... Robinson, A. (2016). Caring for the carer: A system review of pure technology-based cognitive behavioral therapy (TB-CBT) interventions for dementia carers. *Aging & Mental Health*, *20*, 793–803. Available from https://doi.org/10.1080/13607863.2015.1040724.

Seah, E. T. W., Kaufman, D., Sauvé, L., & Zhang, F. (2018). Play, learn, connect: Older adults' experience with a multiplayer, educational, digital bingo game. *Journal of Educational Computing Research*, *56*, 675–700. Available from https://doi.org/10.1177/0735633117722329.

Segal, Z. V., Williams, J. M. G., & Teasdale, J. D. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford Press.

Seligman, M. E. P. (2002). *Authentic happiness: Using the new positive psychology to realize your potential for lasting fulfillment*. New York: Free Press.

Seligman, M. E. P., & Csikszentmihalyi, M. (2000). Positive psychology: An introduction. *American Psychologist*, *55*(1), 5–14. Available from https://doi.org/10.1037//0003-066X.55.1.5.

Seligman, M. E. P., Steen, T. A., Park, N., & Peterson, C. (2005). Positive psychology: Empirical validation of interventions. *American Psychologist*, *60*, 410–421. Available from https://doi.org/10.1037/0003-066X.60.5.410.

Shedler, J. (2010). The efficacy of psychodynamic psychotherapy. *American Psychologist*, *65*, 98–109. Available from https://doi.org/10.1037/a0018378.

Sin, N. L., & Lyubomirsky, S. (2009). Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: A practice-friendly meta-analysis. *Journal of Clinical Psychology: In Session*, *65*, 467–487. Available from https://doi.org/10.1002/jclp.20593.

Steffen, A. M., & Gant, J. R. (2016). A telehealth behavioural coaching intervention for neurocognitive disorder family carers. *International Journal of Geriatric Psychiatry*, *31*, 195–203. Available from https://doi.org/10.1002/gps.4312.

Sternberg, R. (1990). Wisdom and its relations to intelligence and creativity. In R. J. Sternberg (Ed.), *Wisdom: Its nature, origins, and development* (pp. 142–159). Cambridge: Cambridge University Press.

Sternberg, R. J. (2003). *Wisdom, intelligence, and creativity synthesized*. New York: Cambridge University Press.

Sung, K. (2011). Exploring wisdom in the Korean elderly: A Q methodology study. *Asian Nursing Research*, *5*(2), 128–140. Available from https://doi.org/10.1016/s1976-1317(11)60021-2.

Szanton, S. L., Wenzel, J., Connolly, A. B., & Piferi, R. L. (2011). Examining mindfulness-based stress reduction: Perceptions from minority older adults residing in a low-income housing facility. *BMC Complementary & Alternative Medicine*, *11*, 44. Available from https://doi.org/10.1186/1472-6882-11-44.

Takayama, M. (2002). *The concept of wisdom and wise people in Japan* (Unpublished doctoral dissertation). Tokyo University, Japan.

Thompson, L. W., Gallagher, D., & Breckenridge, J. S. (1987). Comparative effectiveness of psychotherapies for depressed elders. *Journal of Consulting and Clinical Psychology*, *55*, 385–390.

Van Alphen, S. P., van Dijk, S. D., Videler, A. C., Rossi, G., Dierckx, E., Bouckaert, F., & Voshaar, R. C. (2015). Personality disorder in older adults: Emerging research issues. *Current Psychiatry Reports*, *17*, 538. Available from https://doi.org/110.1007/s11920-014-0538-9.

van Schaik, A., van Marwijk, H., Adèr, H., van Dyck, R., de Haan, M., Penninx, B., ... Beekman, A. (2006). Interpersonal psychotherapy for elderly patients in primary care. *American Journal of Geriatric Psychiatry*, *14*, 777–786. Available from https://doi.org/10.1097/01.JGP.0000199341.25431.4b.

Veehof, M. M., Oskam, M.-J., Schreurs, K. M. G., & Bohlmeiher, E. T. (2011). Acceptance-based interventions for the treatment of chronic pain: A systematic review and meta-analysis. *PAIN*, *152*, 533–542. Available from https://doi.org/10.1016/j.pain.2010.11.002.

Weisman, M. M., Prusoff, B. A., DiMascio, A., Neu, C., Goklaney, M., & Klerman, G. L. (1979). The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. *The American Journal of Psychiatry*, *136*, 555–558.

Wetherell, J. L., Afari, N., Ayers, C. R., Stoddard, J. A., Ruberg, J., Sorrell, J. T., ... Patterson, T. L. (2011). Acceptance and commitment therapy for generalized anxiety disorder in older adults: A preliminary report. *Behavior Therapy*, *42*, 127–134. Available from https://doi.org/10.1016/j.beth.2010.07.002.

Wetherell, J. L., Afari, N., Rutledge, R., Sorrell, J. T., Stoddard, J. A., Petkus, A. J., ... Atkinson, J. H. (2011). A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *PAIN*, *152*, 2098–2107. Available from https://doi.org/10.1016/j.pain.2011.05.016.

Wetherell, J. L., Hershey, T., Hickman, S., Tate, S. R., Dixon, R., Bower, E. S., & Lenze, E. J. (2017). Mindfulness-based stress reduction for older adults with stress disorders and neurocognitive difficulties: A randomized controlled trial. *The Journal of Clinical Psychiatry*, *78*(7), 734–743. Available from https://doi.org/10.4088/JCP.16m10947.

Whitlock, L. A., McLaughlin, A. C., Harris, M., & Bradshaw, J. (2015). *The design of mobile technology to support diabetes self-management in older adults*. Paper presented at the meeting of International Conference on Human Aspects of IT for the Aged Population.

Wilson, K., Mottram, P. G., & Vassilas, C. (2008). Psychotherapeutic treatments for older depressed people. *Cochrane Database of Systematic Reviews*. Available from https://doi.org/10.1002/14651858.CD004853.pub2, CD004853.

World Health Organization (WHO). (2017). *Mental health of older adults*. <http://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults>.

Yang, S.-Y. (2001). Conceptions of wisdom among Taiwanese Chinese. *Journal of Cross-Cultural Psychology*, *32*, 662–680. Available from https://doi.org/10.1177/0022022101032006002.

Further reading

Hazlett-Stevens, H., Singer, J., & Chong, A. (2019). Mindfulness-based stress reduction and mindfulness-based cognitive therapy with older adults: A qualitative review of randomized controlled outcome research. *Clinical Gerontologist*, *42*, 347–358. Available from https://doi.org/10.1080/07317115.2018.1518282.

Chapter 23

Psychopharmacologic treatment

Vimal M. Aga[1], Mujeeb U. Shad[2], Hongru Zhu[3] and Carl Salzman[4,5]

[1]Layton Aging and Alzheimer's Disease Center, Oregon Health and Science University, Portland, OR, United States, [2]Department of Psychiatry, Oregon Health and Science University, Portland, OR, United States, [3]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [4]Department of Psychiatry, Harvard Medical School, Boston, MA, United States, [5]Beth Israel Deaconess Medical Center & Massachusetts Mental Health Center, Boston, MA, United States

Overview

Geriatric psychopharmacology requires an understanding of several age-related physiological and psychological factors that impact not just the phenomenology of psychiatric disorders in older adults but several aspects of the patient−drug interaction. Various factors play a significant role in psychopharmacologic treatment, which are not directly drug-related. These include the patient−physician relationship, the patient−caregiver relationship, prior experience with psychotropic drugs, and the ability to understand the nature of the illness and the treatment being prescribed, all of which impact medication adherence. A successful patient−provider relationship starts with treating the older patient with respect and recognizing and addressing the common prejudices and negative perceptions, which are an impediment to providing adequate health care services to older adults.

The United States Census Bureau data from July 1, 2018, indicates that 16% of adults in the country are aged 65 and above, and they are typically referred to as "older," "elderly," or "geriatric." This is not a homogenous population, however. The "oldest-old"—those aged 85 and over—are the most rapidly growing demographic subgroup, and their numbers will increase from 10% of older adults in 1994 to almost 25% of older adults, and 5% of all Americans, by 2050. Unfortunately, not all studies have adhered to this convention and some have used arbitrary age cutoffs to define "elderly," which can be as low as 55, so the mean age of the study sample is noted whenever studies are discussed in the chapter, if available. Furthermore, studies that have included the oldest-old subsegment of the population are not common at all, one notable exception being the 90 + Study at the University of California-Irvine Institute for Memory Impairments and Neurological Disorders, which was initiated in 2003 and continues to be funded. Data from studies conducted in "young-old" subjects should be extrapolated to the oldest-old with an abundance of caution.

Some other terminology issues are worth noting at the beginning. In keeping with the 2017 modifications of the American Medical Association Manual of Style by the Journal of the American Geriatric Society (Lundebjerg, Trucil, Hammond, & Applegate, 2017), this text will eschew the use of pejorative terms such as aged, elderly, and seniors, and preferentially use the more respectful term "older adults" throughout the text to refer to individuals aged 65 and older who are the primary focus of this chapter. Disorders due to other medical conditions will be referred to as physical illnesses rather than medical illnesses, as the latter term implies that psychiatric illnesses are not "medical" in nature. Another terminology issue to note is that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) terminology (American Psychiatric Association, 2013) will be used for psychiatric disorders throughout the text, with two exceptions. The DSM-5 term *neurocognitive disorder* has not yet been widely adopted in research thus far, and it is not synonymous with previous definitions of dementia. Since the research reviewed in this chapter has been on patients diagnosed with dementia using older diagnostic criteria, the older term has been retained for continuity. Terminology for the clinical syndrome and the underlying neuropathology is often used interchangeably in the dementias. In this chapter, Alzheimer's disease (AD) dementia refers to a clinically ascertained predominantly amnestic syndrome with resulting functional decline, while AD itself refers to the underlying neuropathology. Finally, various terminologies have been used in studies to refer to behavioral symptoms in the dementias, which are all synonymous. The newer National Institute on Aging-Alzheimer's Association term neurobehavioral symptoms (Jack et al., 2018) will be used in this chapter to denote all neuropsychiatric symptoms in the dementias.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00023-5

This chapter is organized into several sections. The first section covers basic psychopharmacological principles with a focus on older adults. This includes the impact of aging-related changes in body physiology on pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body). The second section will cover several clinical issues that specifically impact the practice of geriatric psychopharmacology, including multimorbidity, polypharmacy, and sociocultural factors. The next section is devoted solely to a detailed discussion of drug interactions of all types. The final section will cover drug treatment of several major psychiatric disorders with a focus on recent data and studies in older adults where available, and practical recommendations will be made where possible. In the interest of brevity, only select topics will be covered in this section and the interested reader is referred to a textbook of psychopharmacology for further details.

Basic psychopharmacological principles

Pharmacokinetics

Pharmacokinetics can be described as what the body does to a drug in terms of its absorption, distribution, metabolism, and elimination. Aging has a differential effect on all four phases of pharmacokinetics, some of which are more clinically relevant than others.

Absorption

There is an age-related decrease in small-bowel surface area, slowed gastric emptying time, reduced splanchnic blood flow, and an increase in gastric pH, but they do not appear to affect time to maximum concentration of a drug in older adults (Catterson, Preskorn, & Martin, 1997). Age-related increase in gastric pH, such as in atrophic gastritis or due to administration of proton pump inhibitors, results in decreased absorption of the drugs that require an acidic environment for optimal absorption. Drugs with intrinsic anticholinergic activity, such as the first-generation low-potency antipsychotics and tricyclic antidepressants (TCAs), reduce gastric motility. Absorption of some psychotropic drugs, such as vilazodone, ziprasidone, and lurasidone (the three "done" drugs), is decreased significantly if taken without food.

Distribution

With advancing age, there is an increase in body fat and a decrease in plasma volume, extracellular fluid, and total body water (Klotz, 2009). These changes may result in decreased volume of distribution (*Vd*) for most hydrophilic drugs with a shorter elimination half-life, and vice-versa for the lipophilic drugs.

Most drugs circulate bound to plasma proteins, with the bound and unbound ("free") fractions of the drugs existing in equilibrium. The free fraction of a drug is also the fraction that is pharmacologically active. The "total" drug level is the sum of both the free and the bound fractions of a drug, and it remains unchanged where there is an increase in the pharmacologically active free fraction relative to the protein-bound fraction of a drug. Acidic drugs mostly bind to albumin, a low-affinity/high-capacity transport protein, while basic drugs mostly bind to alpha-1 (α_1)-acid glycoprotein, a high-affinity/low-capacity transport protein (Butler & Begg, 2008). Aging reduces circulating albumin levels by 10%–20% (McLean & Le Couteur, 2004), while its impact on α_1-acid glycoprotein is less clear (McLachlan & Pont, 2011).

P-glycoprotein (P-gp) belongs to a superfamily of transporter proteins whose role is to function as "chemical pumps" and mediate the efflux of foreign chemical substances called xenobiotics from cells. Xenobiotics include harmful substances such as carcinogens, as well as useful compounds, such as drugs. P-gp belongs to the ATP-binding cassette (ABC) transporter superfamily, thus named because the hydrolysis of adenosine triphosphate (ATP) is their driving force, and they have a distinctive sequence of ATP-binding domains. Seven subfamilies of the ABC transporter superfamily are known, labeled A–G. The P-gp protein was previously known as multidrug resistance protein 1 (MDR1), while its current name is ABCB1 since it belongs to the B subfamily, encoded for by the *ABCB1 (MDR1)* gene. Note that by convention, the name of the gene is the same as the name of the protein, except that it is written in italics. The effects of P-gp are widespread, as it can affect a drug's absorption (P-gp in the intestinal epithelium), distribution (P-gp in the capillary endothelium of the blood–brain barrier), and elimination (P-gp in the hepatic and renal cells) (Terada & Hira, 2015). It often works in conjunction with CYP3A4 as a "drug efflux-metabolism alliance," where one of its roles is to manage the amount of substrate that is presented to CYP3A4 (Benet & Cummins, 2001). In the blood–brain barrier, P-gp provides a mechanism for disposal of waste products of normal metabolism from the brain and prevents xenobiotics from entering the brain (Saidijam, Karimi Dermani, Sohrabi, & Patching, 2018). P-gp and other transporters in the blood–brain barrier regulate the concentrations of various chemicals, including psychotropic

drugs, in the central nervous system (CNS). With increasing age, there is a downregulation of the ABC transporter proteins, which in turn potentially increases the exposure of the brain to xenobiotics (Erdő & Krajcsi, 2019; Toornvliet et al., 2006), the clinical significance of which is unknown. Many drugs are substrates and modulators of both CYP3A4 and P-gp (Kim et al., 1999). Such dual inhibitors can obviously be involved in significant drug−drug interactions (DDIs), but they do not always inhibit both P-gp and CYP3A4 with equal potency. A more detailed discussion of this issue can be found in Lund, Petersen, and Dalhoff (2017).

Metabolism

Once a drug is absorbed, it either undergoes metabolism in the liver or is excreted unchanged, mostly in bile and urine. Metabolism of xenobiotics, as well as of endogenous compounds (endobiotics), occurs in two phases. Phase I metabolism is mediated in the liver by oxygen-dependent hemoprotein enzymes, commonly known as the cytochrome (CYP) enzymes, via oxidative phosphorylation. In the CYP nomenclature, CYP indicates the superfamily, followed by a number indicating the gene family, then a capital letter indicating the subfamily, and then another number indicating the individual gene, such as CYP2(gene family)D(subfamily)6(gene). Individual alleles are designated with an * such as CYP2D6*1, where 1 is the wild-type allele. The CYP450 isoenzymes in superfamilies 1−3 are responsible for 70%−80% of all phase I-dependent metabolism of clinically used drugs, of which the enzymes that are responsible for more than 90% of known oxidative drug metabolism in humans include CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, and CYP3A3/4 (Harvey & Preskorn, 1996). Of these, the five CYP enzymes most commonly involved in human metabolism and responsible for the bulk of the pharmacokinetic DDIs are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/3A5. CYP2D6 is the most clinically relevant of these enzymes. Although CYP2D6 accounts for only about 5% of the total hepatic CYP enzymes (Zhou, Ingelman-Sundberg, & Lauschke, 2017), it contributes significantly to the metabolism of roughly 25% of all drugs in clinical use (He, Chen, Zhou, & Zhou, 2015). CYP3A4 is the most abundant of the CYP enzymes in the adult human liver and intestine, both in terms of its drug-metabolizing activity and its quantitative dominance, and is involved in the metabolism of about 50% of drugs used clinically (Zhou, 2008). CYP3A5 is structurally very similar to CYP3A4, resulting in overlapping substrate selectivity, and these are usually considered together. Based on the metabolic capacity of the different CYP enzymes, they can be classified into two groups: low-affinity/ high-capacity or high-affinity/ low-capacity. CYP2D6, CYP2C9, and CYP2C19 are high-affinity/ low-capacity enzymes, as these bind avidly to and metabolize specific substrates at low concentrations. As the concentration of a substrate increases, the capacity of these enzymes to metabolize it becomes saturated, and the metabolism then spills over to CYP3A4 and CYP1A2, which are low-affinity/ high-capacity enzymes that function as a "sink" (Wijnen et al., 2007).

Phase II metabolism is the primary detoxification step, which mainly involves transferases, such as glutathione S-transferases, uridine 5′-diphospho-glucuronosyltransferases (UGTs), sulfotransferases, *N*-acetyltransferases, and epoxide hydrolases, that biotransform both endobiotics and xenobiotics into hydrophilic products, which are then easily eliminated (Jancova, Anzenbacher, & Anzenbacherova, 2010). These reactions occur mostly in the liver and partly in the small intestine (Zhang & Benet, 2001). The UGTs are the most abundant of the phase II enzymes, which are also found in the intestine, kidneys, brain, and placenta, and they catalyze the conjugation of substrates with glucuronic acid to form polar glucuronides that can be excreted in bile or urine. As in the case of the CYP enzymes, the nomenclature for naming the UGT enzymes includes an Arabic numeral for the superfamily, an uppercase letter for the subfamily, and an Arabic numeral for the individual gene, while the name of the corresponding gene is written in italics. The 18 active human UGTs belong to three superfamilies (1, 2, and 3) and four subfamilies (1A, 2A, 2B, 3A) (Knights, Rowland, & Miners, 2013). UGTs have lower affinity for drug substrates and substantial overlap in substrates specificities, leading to less potential for DDIs (Williams et al., 2004). A more extended discussion of the UGTs, including their role in DDIs, can be found in Rowland, Miners, and Mackenzie (2013).

Phase I metabolism appears to be affected more with age due to the indirect effect of reduced oxygen delivery on the CYP enzymes, as noted above, while existing evidence does not support any significant age-related effects on phase II reactions (Klotz, 2009).

Finally, in accordance with the Phase I and Phase II terminology, the efflux of xenobiotics from cells via the ABC transporters described in the section on distribution is also referred to as Phase III *elimination* (not Phase III *metabolism*), as the efflux across the plasma membrane of cells occurs without chemical modification of the substrate (Döring & Petzinger, 2014).

The clearance of drugs that are highly extracted by the liver is rate-limited by hepatic blood flow (flow-limited), while the clearance of drugs that are extracted poorly is rate-limited by hepatic enzyme activity as well as protein

binding (capacity-limited) (Hilmer, Shenfield, & Le Couteur, 2005; Le Couteur & McLean, 1998). Metabolism of a drug in the liver independent of blood flow and protein binding is referred to as its *intrinsic clearance*. Metabolism of the highly extracted flow-limited drugs is highly efficient and both the free and the protein-bound fractions are extracted equally, which leaves their ratio unchanged. Flow-limited clearance is reduced by almost 50% in older adults due to a reduction in hepatic blood flow (Butler & Begg, 2008; McLean & Le Couteur, 2004). High hepatic extraction of flow-limited drugs is responsible for presystemic (first-pass) metabolism, although first-pass metabolism also occurs via the CYP enzymes in the intestinal epithelium. Reduction in flow-limited clearance in the liver in older adults increases the bioavailability of drugs that exhibit very high first-pass elimination in young adults, which assumes clinical significance only with drugs that also have a narrow therapeutic window (Wilkinson, 1997). Examples of flow-limited psychotropic drugs include TCAs, venlafaxine, sertraline, and bupropion (Telles-Correia et al., 2017). Metabolism of capacity-limited drugs depends upon the dual impact of protein binding and age-related changes in intrinsic clearance. The free fraction of drugs with low protein binding is relatively high to begin with, and the free-to-bound drug ratio is not substantially increased due to an age-related reduction in transport proteins; the total hepatic clearance therefore approximates the intrinsic clearance of capacity-limited drugs with low protein binding. On the other hand, the free-to-bound drug ratio of highly protein-bound capacity-limited drugs is substantially increased due to age-related reduction in transport proteins, and the total clearance of the drug obscures the true intrinsic clearance. Therefore measuring the free fraction provides the true estimate of intrinsic clearance with these drugs and not the total drug level which estimates both the free and bound fractions. When the true intrinsic clearance is thus estimated, it is found to be 30%−50% decreased in older adults for capacity-limited drugs as well (Butler & Begg, 2008). Examples of capacity-limited psychotropic drugs with high protein binding include valproic acid, temazepam, lorazepam, and diazepam (Butler & Begg, 2008), and the clearance of the free fraction of these drugs is disproportionately reduced with age. The clinical impact of age-related reduction in protein binding on the free valproic acid level will be discussed in more detail in the section on bipolar disorder.

Elimination

A decrease in the renal elimination of drugs is one of the most significant pharmacokinetic changes in older adults. In order to measure the true rate of glomerular filtration (glomerular filtration rate or GFR in mL/min/1.73 m^2), an exogenous substance that is freely filtered at the glomerulus but neither secreted nor reabsorbed at the level of the renal tubules is used, such as the polysaccharide inulin. The endogenously produced chemical creatinine is normally secreted by the renal tubule, and therefore the clearance of creatinine (CrCl), expressed in mL/min, overestimates the clearance of inulin by about 22%−24% (Glassock & Winearls, 2009a, 2009b). There is a reduction in CrCl at an average rate of −0.8 mL/min annually after 40 years of age, reaching a nadir at around age 80 (Lindeman, Tobin, & Shock, 1985). This involutional reduction in CrCl is unrelated to disease, and worsens further with physical illnesses in older adults such as cardiac and liver dysfunction or dehydration (Glassock & Winearls, 2009a, 2009b). The Cockcroft−Gault (C−G) equation is the most commonly used formula to estimate creatinine clearance (Cockcroft & Gault, 1976). The first formula to estimate GFR (eGFR) from serum creatinine was the modification of diet in renal disease (MDRD) study equation (Levey et al., 1999), and others have been proposed since. An eGFR below 60 mL/min/1.73 m^2 is now routinely reported by most laboratories as part of the routine blood chemistry results, but the laboratories usually do not specify which equation has been used. The C−G equation was exclusively used by the United States Food and Drug Administration (FDA) for drug studies and for stratifying renal function−based dosing schedules in the product label, and has been the historical gold standard for estimating drug dosing in renal impairment.

However, preliminary guidance provided by the FDA in 2010 allowed use of either the C−G or MDRD equation to specify the stage of renal impairment, and specified that pharmacokinetic results "should be shown for both C−G estimates of creatinine clearance and eGFR," a shift in regulatory guidelines that is nontrivial (Crass & Pai, 2019). Providers should note that CrCl and eGFR are not synonymous, and use of the MDRD eGFR equation instead of the C−G equation classifies about twice more patients into the higher stages 1 and 2 (normal or mild GFR reduction) than the C−G equation and erroneously leads to higher estimates (mean positive bias was 34% ± 20% in one study) of renal function in older adults (Cartet-Farnier, Goutelle-Audibert, Maire, De la Gastine, & Goutelle, 2017; Dowling, Wang, Ferrucci, & Sorkin, 2013). The discrepancy between MDRD eGFR and the C−G equation increases with age due to the nature of the equations.

As is evident, there is much uncertainty about renal dosing and even regulatory guidelines are in a state of flux, so practical clinical recommendations are necessary, and the recommendations that follow have been adapted from Hudson and Nolin (2018). If the reported eGFR is <60 mL/min/1.73 m^2, calculate the CrCl using the C−G equation,

which can be done quickly using cellphone apps or calculators embedded in electronic medical records (EMRs) that can be pulled into initial evaluation templates. CrCl and eGFR have different units, so in order to compare them directly, the standard "normalized" eGFR value expressed in mL/min/1.73 m^2 should be multiplied by (individual patient's body surface area/1.73 m^2) to yield the "individualized" eGFR in mL/min, which is then directly comparable to CrCl. The more conservative kidney function and corresponding renal dose should be selected in the case of drugs with a narrow therapeutic window, especially when therapeutic drug monitoring is not an option; for drugs with a wide therapeutic window, and especially if therapeutic failure has significant clinical implications, a more aggressive dosing strategy should be selected instead. Where endogenous creatinine-based kidney functions (i.e., both C−G and MDRD eGFR equations) are expected to be unreliable (e.g., frail older adults with a low muscle mass), creatinine clearance should be measured via a timed urine collection, especially when a drug with a narrow therapeutic window is being used and therapeutic drug monitoring is not an option. A good discussion of the concept of therapeutic window can be found in Eppenga et al., 2016. Psychotropic drugs with a narrow therapeutic window include carbamazepine, oxcarbazepine, pregabalin, amantadine, lithium, and memantine, of which therapeutic drug monitoring is recommended only for carbamazepine and lithium.

Pharmacodynamics

Altered psychotropic drug response and tolerability in older adults occur at least partly due to age-related changes in receptor sensitivity and neurotransmitter function. Common changes within the dopaminergic system include a reduction in the dopamine D_2 receptors in the striatum (Roth & Joseph, 1994), which increases the sensitivity of older adults to D_2-blockers and thereby the risk of drug-induced parkinsonism. Within the noradrenergic system, there is a reduction in β-receptor responsiveness in older adults, with reduction in both β-receptor numbers and affinity with age (Scarpace, Tumer, & Mader, 1991). There is also reduction in presynaptic α_2-autoreceptor responsiveness. The decreased sensitivity of α_2-autoreceptors may contribute to increased CNS noradrenergic activity with aging (Raskind et al., 1988), with increased noradrenaline biosynthesis and release (Raskind, Peskind, Holmes, & Goldstein, 1999). Within the cholinergic system, a reduction in cholinergic cells as well as a reduction in the activity of choline acetyltransferase, an enzyme that is contained only in the cholinergic cells and is involved in the biosynthesis of acetylcholine, occurs later, which is preceded by a reduced responsiveness of the cholinergic system with aging (Decker, 1987). This partly explains the increase in sensitivity to anticholinergic drugs in older adults (Campbell et al., 2009). Regarding the serotonergic or 5-hydroxytryptamine (5HT) system, there appears to be a general reduction in serotonergic transmission with increasing age that appears to be compensated by fewer 5HT transporters, which prolongs the activity of 5HT in the synaptic cleft. Presynaptic $5HT_{1A}$ autoreceptors appear to remain relatively preserved in older adults, while there is a large negative effect of age on the postsynaptic $5HT_{2A}$ receptors (Karrer, McLaughlin, Guaglianone, & Samanez-Larkin, 2019). Finally, glutamate is the major excitatory neurotransmitter in the human brain. Glutamate release appears to remain unaltered in the aging brain; however, glutamate uptake may be reduced and there is a reduction in the density of *N*-methyl-D-aspartate (NMDA) receptors in the brains of older rodents (Segovia, Porras, Del Arco, & Mora, 2001).

Issues specific to psychotropic drug prescribing in older adults

Diagnostic issues

Late-onset primary psychiatric disorder or harbinger of a physical illness?

There is some evidence that late-onset psychiatric disorders have a clinical presentation that is often distinct from similar disorders with onset in younger adults, but it is not yet clear if this is because of the effects of aging on phenomenology or because psychiatric disorders with onset in older adults are distinct from their young-onset counterparts. Specific criteria for late-onset psychiatric disorders have not been adopted in the major diagnostic frameworks; in fact, specifiers related to age of onset have been removed from more recent editions of the DSM. Some specific examples are noted later in the chapter in the sections on psychotic disorders and major depressive disorder. However, due to the rather restricted repertoire of psychiatric symptomatology, psychiatric symptoms that mimic those seen in the primary psychiatric disorders can also herald the onset of a physical illness months or even years before the appearance of nonpsychiatric symptomatology, but diagnosing the physical illness can be virtually impossible in these early stages and such patients are often erroneously given the diagnosis of a primary psychiatric disorder initially.

Mild behavioral impairment (MBI) is a relatively new non-DSM-5 construct that is still in evolution and describes patients who develop psychiatric symptoms as a prodrome of a dementia (Ismail et al., 2016). In one study, more than

50% of the participants had developed neuropsychiatric symptoms prior to the onset of dementia, of which depression and irritability were the most common (Wise, Rosenberg, Lyketsos, & Leoutsakos, 2019). In a blinded, retrospective chart review, the mean time to accurate diagnosis of a neurodegenerative dementia was 33.3 ± 3.4 months from the onset of psychiatric symptoms (Woolley, Khan, Murthy, Miller, & Rankin, 2011). A study comparing patients with mild cognitive impairment (MCI) with or without neurobehavioral symptoms vis-à-vis patients with MBI with or without cognitive symptoms found that the rate of conversion to dementia was the highest for MBI without cognitive symptoms (Taragano, Allegri, & Lyketsos, 2008). Therefore, making an accurate early diagnosis of MBI requires a high index of suspicion as well as familiarity with the provisional research diagnostic criteria for MBI proposed by the Alzheimer's Association-International Society to Advance Alzheimer's Research and Treatment (AA-ISTAART) (Ismail et al., 2016). The biggest drawback of this construct is that it remains a retrospective diagnosis for now, and criteria that can identify such patients prospectively who will eventually go on to develop a dementia have yet to be identified.

Effect of concurrent physical illness

Comorbid medical and psychiatric illnesses are common in older adults. The sickest psychiatric patients are usually found in the inpatient setting, and up to 90% of the inpatient geriatric psychiatric population have at least one comorbid physical illness (Goh et al., 2016). There is a bidirectional impact of medical and psychiatric illnesses on each other, each exacerbating the symptoms of the other and making overall care of the complicated patient even more complex. Physical illnesses can concurrently present with new-onset psychiatric symptoms, the commonest example in older adults being psychosis due to a delirium, the definitive treatment of which involves identification and treatment of the underlying physical illness. Physical illnesses such as pancreatic carcinoma, endocrine disorders (hypothyroidism, hyperthyroidism, hyperparathyroidism, hypo- and hyperadrenal states), and chronic viral infection are known to produce psychiatric disturbances. Neurological illnesses directly affect that brain and commonly result in psychiatric symptoms, and some common examples are idiopathic Parkinson's disease and stroke. In fact, idiopathic Parkinson's disease is the quintessential neuropsychiatric disorder that can present with psychiatric symptoms that run the entire gamut, from depression to psychosis to anxiety to impulse control disorders to dementia, with psychiatric symptoms that are relatively specific to idiopathic Parkinson's disease (e.g., minor hallucinations, and impulse control disorders such as hobbyism and punding). Drugs and deep brain stimulation (DBS) surgery used to treat idiopathic Parkinson's disease can also result in psychiatric symptoms. Psychotropic drugs used to treat these psychiatric symptoms can counteract the effects of the antiparkinsonian drug (Weintraub & Mamikonyan, 2019), while antiparkinsonian drugs can cause and/or exacerbate the psychiatric disorder(s).

DDIs between medications used to treat the physical illness and psychotropic medications will be covered later in the section on DDIs.

Importance of a comprehensive evaluation

Obtaining an accurate history is essential in all patients, but even more so in older adults, so that accurate determinations can be made regarding onset, presence of underlying physical illness(es) that may be contributing, treatment history, and any resulting functional impairment. Enquiring about onset and course of symptoms can yield important clues about etiology, yet this is often very difficult due to the absence of a reliable informant or any collateral information. Patients and significant others can both have cognitive decline. Sensory deficits in patients and informants, such as impaired hearing and vision, may contribute to the lack of an adequate history. Cultural and language barriers can also make it difficult to obtain information. Finally, intentional withholding of critical information is always a possibility in older adults, just as it is in younger adults; some of the reasons are similar in both age groups, such as a spouse or significant other omitting a history of substance use because both partners are using the substance together, while other reasons are more specific to older adults, such as elder abuse.

Medication history and treatment adherence

There may be nothing more important, and yet more elusive, than obtaining an accurate medication history in older adults. In order to save time in a busy practice, office staff should be instructed to obtain the medication list in advance, but the provider should always cross-check it for accuracy with the patient, caregiver, or the facility medication administration record, before finalizing it in the EMR. If the patient is residing in a facility, a copy of the medication administration record should be obtained in advance.

Providers should always enquire about who manages the patient's medications if they reside at home, and if it is not the patient himself or herself, they should ask about any problems with medication adherence when they were last managing their own medications. Competent medication self-management requires multiple skills. Impairment in time-based prospective memory significantly increases the risk of medication nonadherence (Woods et al., 2009). While a focused cognitive assessment is necessary for all such patients (Hsu, Huang, Tu, & Hua, 2015), it lacks sensitivity and specificity to identify safe medication self-management practices. As cognitive impairment progresses, the ability to self-manage medications declines further, leading to increased risk of unintentional nonadherence (Elliott, Goeman, Beanland, & Koch, 2015). Standardized instruments for assessing patients' capacity to self-manage medications exist and may be used in exceptional situations; a review of these instruments is available here in Elliott and Marriott (2009). In a busy practice, a brown-bag review where the patient is asked to bring in *all* of their medications in a bag to the office for review is an excellent method of obtaining an accurate medication history quickly from patients residing independently (Steinman & Hanlon, 2010). Additionally, such a review can provide clues about medical history (e.g., why are you on warfarin? Has someone diagnosed you with atrial fibrillation?), nonadherence (e.g., as evidenced by partially used antibiotic bottles), and poor safety awareness (e.g., as evidenced by multiple expired pill bottles).

Physical illness, including sensory deficits, that are common in older adults can impact medication adherence. Containers commonly used for dispensing prescriptions are sometimes exceedingly difficult for an older patient to open; arthritic fingers, poor vision, tremor, and muscle weakness often interfere with the ability to reach medications, and "safety" tops may be too "safe" and nearly impossible for older people to open. Frustration, embarrassment, and anger are not unusual responses in such situations and can understandably lead to reduced adherence. Physicians' instructions on labels of these containers may be too small to be read easily, and verbal instructions are often forgotten.

Adverse effects of psychotropic drugs may contribute to poor adherence; particularly the anticholinergic effects of constipation, blurred vision, and dry mouth may be so severe that older patients do not take their medicine at all or take lower-than-prescribed doses. Tremor due to lithium and sedation from some antianxiety agents are other common side effects poorly tolerated by older persons that may result in nonadherence or underdosing of prescription medications.

Medication adherence improves in the context of a good therapeutic relationship and open communication with the provider. Use of technology to improve adherence is still in its infancy. One novel recent development has been the digital ingestion tracking system first marketed in Abilify MyCite, which was approved by the FDA in 2017. Each pill is embedded with an ingestible event marker sensor, which is 1 mm in size and activates in contact with gastric fluid. The biodegradable sensor then communicates with a wearable band aid−sized sensor worn on the left rib cage and replaced every 7 days (the MyCite patch), which records the ingestion and transmits the data via Bluetooth to the MyCite app in the patient's smartphone. However, the evidence that it improves medication adherence is weak (Cosgrove, Cristea, Shaughnessy, Mintzes, & Naudet, 2019), and its official website does not make any claims about improving adherence but emphasizes tracking instead. Experts have highlighted its ability to provide "important information to patients about their own medication-taking habits" (Kane, 2018). Certainly, use of a digital ingestion tracking system is quite labor-intensive and requires some degree of motivation on part of the patient, and is not the panacea for medication nonadherence.

Confounding effects of substance use

Substance use disorders can also precipitate the entire gamut of psychiatric disorders, from psychosis to depression to anxiety and even mania. Substance use is increasing among older adults, which is often underrecognized and can often unexpectedly confound the psychiatric diagnosis. The use of illicit drugs among adults aged 50 or older is projected to increase from 2.2% to 3.1% between 2001 and 2020 (Colliver, Compton, Gfroerer, & Condon, 2006). The combined 2007−14 National Survey on Drug Use and Health (NSDUH) data found that nearly 16.2 million adults aged 65 or older used alcohol in the past month, while nearly 469,000 older adults used an illicit drug in the past month (Mattson, Lipari, Hays, & Van Horn, 2013). Over a tenth of the older adults aged 65 and older in the United States were binge drinkers (2015−17 administrations of the NSUDH) (Han, Moore, Ferris, & Palamar, 2019), who were identified using the thresholds for younger adults that are defined below. Substance use admissions among older adults increased from 3.4% to 7.0% between 2000 and 2012 (Chhatre, Cook, Mallik, & Jayadevappa, 2017), and alcohol was the most common substance requiring inpatient treatment. However, a declining trend has been noted for inpatient admissions for alcohol use, while an increasing trend has been noted for inpatient admissions due to cocaine/crack, marijuana/hashish, heroin, nonprescription methadone, and other opiates and synthetics (Chhatre et al., 2017). Adults with mental illness smoke at about twice the rate of those without mental illness, the rate being the highest for those with comorbid substance use (Lawrence, Mitrou, & Zubrick, 2009).

No discussion of substance use is complete without mentioning cannabinoids. Cannabinoids are chemical compounds that act on the endogenous cannabinoid system, which consists of the cannabinoid receptor type-1 (CB1R) and the cannabinoid receptor type-2 (CB2R), their endogenous ligands or endocannabinoids *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for endocannabinoid catabolism (Di Marzo & Piscitelli, 2015). The plant-derived phytocannabinoids are derivatives of the cannabis plant, *Cannabis sativa*, while synthetic cannabinoids are a large family of chemically unrelated compounds that are full agonists at cannabinoid receptors (Antoniou & Juurlink, 2014). Cannabinoids can be smoked, inhaled, ingested orally as edibles of various kinds, absorbed sublingually, or applied topically.

The recreational use of marijuana is legal in 12 states and the District of Columbia as of December 2019, while medical marijuana is legal in several more states. A recent review (Lloyd & Striley, 2018) found that the greatest increase in marijuana use was observed among those in the older adult population 50 years or older, and among these older users, those 65 years or older had the greatest increase in marijuana use. Most of the use was "medicinal" rather than recreational. Marijuana consists of the dried flowers of *C. sativa*, and cannabis preparations include crude marijuana as well as medications that contain either phytocannabinoids or synthetic cannabinoids. The primary psychoactive component of marijuana is delta-9-tetrahydrocannabinol (THC), which is only a partial agonist at the CB1R and CB2R (Pertwee, 2008). Cannabidiol (CBD), also a phytocannabinoid, differs from THC by lacking psychoactive properties by virtue of having a low affinity for CB1 and CB2 receptors; instead, multiple mechanisms of action have been proposed for CBD involving activity at numerous noncannabinoid receptors (Premoli et al., 2019). Marijuana contains multiple chemically active compounds in different proportions, making it difficult to know what one is buying and even more difficult to compare different crude marijuana preparations. It is a schedule I controlled substance in the United States under the 1970 Controlled Substance Act. However, changes in the United States Agriculture Improvement Act of 2018 removed industrial hemp (a different strain of *C. sativa*) and its derivatives that contain 0.3% or less of THC on a dry weight basis from the Controlled Substances Act. FDA-approved cannabinoids commercially available in the United States in end-2019 for treatment of select disorders include synthetic oral cannabinoids dronabinol (Marinol, Syndros) and nabilone (Cesamet), as well as cannabidiol itself (Epidiolex). Nabiximols (Sativex) is a buccal spray that is available outside the United States and contains THC and CBD in a 1:1 ratio.

To summarize, the data indicate increasing rates of nonalcohol substance use in older adults, and providers need to consider substance use to be causing or contributing to psychiatric symptoms in older adults, as well as to possible DDIs. It is therefore imperative that they how to obtain a relevant history and interpret blood and urine tests for substance use disorders, which includes familiarity with new biomarkers for objective identification of ongoing substance as well as the performance of such biomarkers in the presence of physical illnesses which older adults often have. As an example, ethyl glucuronide and ethyl sulfate are relatively new biomarkers for verification of alcohol abstinence (Junghanns et al., 2009), but in older adults, the impact of ongoing liver disease on these biomarkers also needs to be considered during interpretation of test results (Stewart, Koch, Burgess, Willner, & Reuben, 2013). Also, providers need to be familiar with the lower diagnostic thresholds for substance use disorders in older adults. For example, binge-drinking in young adults is defined as having more than five drinks for men and four drinks for women on a single occasion, but the threshold is lower in older adults, just three drinks for men and two drinks for women on a single occasion, and the prevalence of binge-drinking older adults in the United States would be much higher if these thresholds had been used in the survey above (Kranzler, Babor, & Lauerman, 1990). Last but not least, use of screening instruments specific to older adults needs to be adopted in routine clinical practice when they are available, such as the use of the 10-item Short Michigan Alcoholism Screening Test-Geriatric Version (SMAST-G) to screen older adults for alcohol use (Naegle, 2008).

Need for cross-disciplinary expertise

Given the close interaction between physical and psychiatric disorders in older adults, a comprehensive initial evaluation should necessarily go beyond the conventional psychiatric mental status examination and include an assessment of geriatric syndromes that may be contributing to the clinical presentation. Use of a standardized assessment to conduct such an evaluation, such as the St. Louis Rapid Geriatric Assessment (RGA) (Morley & Adams, 2015), is highly recommended. The RGA is in the public domain and can be incorporated into EMRs without prior approval and free of cost. It screens for not just cognitive impairment, but also for frailty, sarcopenia, and nutritional status, and checks for the presence or absence of an advance directive. Frailty is a geriatric syndrome that is becoming especially important in predicting possible adverse drug events (Cullinan, O'Mahony, O'Sullivan, & Byrne, 2016). It is also an independent predictor of nonadherence to both pharmacological as well as nonpharmacological treatments, as seen in a study

conducted in frail hypertensive patients (Jankowska-Polanska et al., 2018). Patient information sheets in simple language are part of the RGA tool which can be used as handouts for patients.

There is also a great deal of overlap between psychiatry and neurology, which increases exponentially in older adults, where split treatment between psychiatry and neurology providers is often the norm for disorders such as Parkinson's disease and all the dementias. Psychiatric providers should have an in-depth understanding of these neuropsychiatric disorders in order to contribute to the patient's care in a meaningful way. This requires some expertise in interpreting diagnostic biomarkers, including neuroimaging. DSM-5 includes 13 specific etiological subtypes of neurocognitive disorders and requires clinicians to make a dichotomous "probable" versus "possible" distinction in 5 of the 13 neurocognitive disorders. Imaging is necessary to *rule in* the probable neurocognitive disorder in 2 of these 5 disorders (vascular and frontotemporal) and is required to *rule out* mixed etiology due to concurrent cerebrovascular disease in all the others. Newer specialized imaging modalities, such as the use of the dopamine transporter (DaT) scan (Bajaj, Hauser, & Grachev, 2013) and the cardiac metaiodobenzylguanidine single-photon emission computed tomography scan (Yoshita et al., 2006) for diagnosing the Lewy body disorders, have become fairly routine in clinical practice, and psychiatric providers who work with dementia patients should become familiar with these. Even accurate interpretation of routine structural imaging studies, such as a magnetic resonance imaging (MRI) scan, by general radiologists is known to be problematic in patients with the dementias. In a study performed predominantly in an academic setting, a diagnosis of behavioral-variant frontotemporal dementia (bv-FTD) was considered by the radiologists in only 10% of all cases (Suarez et al., 2009), though the characteristic atrophy pattern was identified in half the cases. Psychiatric providers are possibly the most imaging-averse of all providers working in the clinical neurosciences, and at the very least the providers routinely seeing dementia patients should aspire to personally review brain scans themselves and not depend solely on the radiology report for establishing a clinical diagnosis. An introductory neuroimaging text specifically written for psychiatric providers working with dementia patients, such as the one by Aga (2018), can be helpful for this purpose.

Multimorbidity

Multimorbidity is the norm and not the exception in older adults, but systems to manage multiple chronic conditions in the community are inadequate and fragmented (Ploeg et al., 2017). Multimorbidity is defined as "the presence of two or more long-term conditions … that cannot currently be cured but can be controlled through medications or other treatments" (Yarnall et al., 2017). Multimorbidity rates are the highest among nursing home residents. A nursing home study out of Sweden captures some of the key problems associated with multimorbidity—the 70 residents in the study exhibited 275 different health problems, the top three being neuropsychiatric, cardiovascular, and gastrointestinal (GI), had a mean of 17 different chronic health problems and were prescribed a mean of 6.6 continuous medications per day (Akner, 2009). The 2016 guidelines from the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) identified five target groups of patients who will benefit the most from a comprehensive approach to their multimorbidity, and one of these was patients with long-term physical and mental health conditions.

Patients with multimorbidity are usually older, receive a lot more consultations and less continuity of care in primary care practices (Salisbury, Johnson, Purdy, Valderas, & Montgomery, 2011). Even when there are teams of health care professionals taking care of such patients in the community, the evidence base to guide appropriate treatment is very limited and leads to uncertain outcomes. A recent Cochrane collaboration review identified only 18 randomized controlled trials (RCTs) of interventions designed to improve outcomes in patients with multimorbidity in primary care settings; while the findings regarding outcome were mixed, mental health outcomes improved the most with such interventions (Smith, Wallace, O'Dowd, & Fortin, 2016).

Polypharmacy and older adults

Appropriate versus problematic polypharmacy

Polypharmacy, or concurrent use of multiple medications by one individual, is common in older adults. Even though 138 different definitions of polypharmacy and associated terms were retrieved in a 2017 review (Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017), a threshold of five concurrent medications is the definition most commonly used. Such polypharmacy can be appropriate, when medications are prescribed based on best evidence, or problematic, when multiple medications are prescribed inappropriately or when the intended benefit of the medications is not realized (McCarthy, Visentin, & Rochon, 2019). Appropriate polypharmacy is quite routine in clinical practice and includes not only use of medications to counteract treatment-emergent adverse effects but also use of two or more medications to

treat the disorder itself. The latter strategy is common in the treatment tuberculosis and human immunodeficiency virus (HIV) in infectious diseases, and in the treatment of epilepsy and idiopathic Parkinson's disease in neurology. In psychiatry, after a decades-long quest for the ideal antipsychotic monotherapy for schizophrenia, evidence is emerging in favor of rational polypharmacy, and recent studies show that appropriate antipsychotic polypharmacy is more effective in lowering psychiatric rehospitalization rates in mixed-age adults with schizophrenia than antipsychotic monotherapy (Tiihonen et al., 2019).

Fixed-dose combinations of several medications, called polypills, are the best example of more loosely defined appropriate polypharmacy. Initially proposed by the World Health Organization (WHO) in 2001 for the secondary prevention of cardiovascular diseases in low socioeconomic countries, polypills were popularized by a British Medical Journal article (Wald & Law, 2003) and its accompanying cover illustration. In neurology, polypills are commonly used in the treatment of idiopathic Parkinson's disease—Sinemet is a two-drug fixed-dose combination of levodopa and carbidopa, while Stalevo is a three-drug fixed-dose combination of levodopa, carbidopa, and entacapone. An example of a recently introduced polypill in psychiatry is Symbyax, which is a fixed-dose combination of olanzapine and fluoxetine approved for the treatment of bipolar depression and treatment-resistant major depressive disorder. Polypills require the provider to be knowledgeable about not just pharmacological properties of the individual medications in the combination, but also about any potential pharmacokinetic and pharmacodynamic interactions between them.

Unfortunately, problematic polypharmacy is much more common, which not only increases costs to the patient but also the risk of adverse drug effects, nonadherence, and DDIs (Steinman & Hanlon, 2010). In one study, the risk for adverse drug events was increased by 3.5-fold in older adults taking four to six medications, 4.5-fold in those taking seven to nine medications and by almost sixfold in those taking 10 or more medications, versus those taking three drugs or less; also, polypharmacy and not inappropriate medication use was associated with adverse drug events after multivariate analysis (Laroche, Charmes, Nouaille, Picard, & Merle, 2007). Unfortunately, polypharmacy seems to be on the rise, and in a survey of a nationally representative sample of older adults who were surveyed in 2005−06 and again in 2010−11, concurrent use of at least five prescription medications had increased from 30% to 35% (Qato, Wilder, Schumm, Gillet, & Alexander, 2016). Polypharmacy is common in hospitalized patients and directly contributes to medication nonadherence in older adults recently discharged from the hospital (Pasina et al., 2014). A prospective cohort study that looked at adverse drug effects in ambulatory care found that they were related to the patient's failure to inform the physician of the adverse effects in a little more than a third of the patients surveyed, and that the medication class most commonly involved in causing adverse drug events was the selective serotonin reuptake inhibitors (SSRIs) in 10% of all cases (Gandhi et al., 2003), likely due to the potent inhibitory effects of some SSRIs on the CYP450 enzymes, as discussed later in the section on pharmacokinetic DDIs. After adjusting for multiple confounders, only polypharmacy was significantly associated with adverse drug events.

However, problematic polypharmacy involving psychotropic medications is usually not serious enough to result in emergency hospitalization. Adverse-event data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (2007−09) were used to estimate the frequency and rates of hospitalization after emergency department visits for adverse drug events in older adults (Budnitz, Lovegrove, Shehab, & Richards, 2011). The study found that nearly 50% of the hospitalizations were among adults 80 years of age or older, and four medication classes were implicated in two-thirds of the adverse effects, either alone or in combination, none of which were psychotropics—warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). This suggests that psychiatric medications are not a major contributor to serious adverse effects stemming from problematic polypharmacy in older adults, while simultaneously underscores the need for providers treating older adults to be knowledgeable about DDIs involving nonpsychiatric medications as well.

Reducing polypharmacy in older adults requires a collaborative and individualized approach. Among younger adults, guideline-driven care is one approach to reducing polypharmacy, but it does just the opposite in older adults, simply because very few guidelines exist for older adults with multimorbidity. An average guideline for younger adults recommends three drugs per disease on average (Wehling, 2011). Extrapolating from the nursing home multimorbidity study above, such a guideline-based approach would hypothetically lead to the average nursing home resident receiving 17×3 drugs (the residents had a mean of 17 different chronic health problems), which would paradoxically increase polypharmacy!

Prescribing cascade

A prescribing cascade is such an important contributor to polypharmacy that it deserves special mention. The term was first introduced in 1995 (Rochon & Gurwitz, 1995), and research on the concept has exploded since. A prescribing

cascade is initiated when a drug-related adverse effect is recognized as a new medical condition and a second drug is prescribed to treat it. Use of anticholinergic medications to treat antipsychotic-induced extrapyramidal symptoms (EPS) is perhaps the commonest example in psychiatry. This is an example of an intentional prescribing cascade, where the adverse effect is recognized and attributed to the offending drug. When the benefits of such an intentional prescribing cascade outweigh the risks, it is termed as an appropriate prescribing cascade (McCarthy et al., 2019). An unintentional prescribing cascade begins when the adverse effect is erroneously recognized as a new medical condition or the exacerbation of a preexisting condition, and a new medication is inadvertently prescribed to treat it. When the benefits of a prescribing cascade do not outweigh the risks, it is termed as problematic, which may be intentional or not. Inadvertently adding a bladder antispasmodic to treat the urinary frequency arising from the prescription of a cholinesterase inhibitor instead of reducing the dose of the cholinesterase inhibitor is one example of a problematic prescription cascade, whether intentional or not, since new-onset or worsening urinary incontinence is a well-known side effect of cholinesterase inhibitors, and bladder antispasmodic that penetrates the CNS opposes the effects of cholinesterase inhibitors (Gill et al., 2005). Conversely, an example of an intentional prescribing cascade, which may or may not become problematic, is the use of antipsychotics to treat the psychosis that may be precipitated by dopamine agonists in the treatment of idiopathic Parkinson's disease.

When a prescribing cascade is initiated intentionally, ongoing monitoring of the risk-benefit ratio should always be initiated. An algorithm for detecting and evaluating prescribing cascades has been published, which consists of four questions, each with 2–4 options (Ponte, Wachs, Wachs, & Serra, 2017). The total score ranges from 0–8, and a cutoff of 4/8 is proposed to identify a prescribing cascade. The higher the score, the greater the severity of the cascade. Using the algorithm in complex clinical cases is suggested to help identify unintentional problematic prescription cascades.

Nonprescription medication use

In addition to prescription medications, one should always ask for nonprescription medication use. These medications are commonly referred to as over-the-counter (OTC) medications. Older adults are the largest consumers of OTC medications. A nationally representative sample of community-dwelling older adults 62–85 years old that was surveyed in 2005–06, and again in 2010–11, had sobering findings (Qato et al., 2016). The study found that while the use of OTC medications declined from 45% to 38% between the two survey periods, the use of dietary supplements increased from 52% to 64%, and the proportion of older adults at risk for a possible major DDI increased from about 8% to 15%. Among prescription medication users, concurrent use of nonprescription medications (OTC or dietary supplements) remained relatively stable at about 71%. Older adults are especially vulnerable, not just due to their excessive OTC medication use, but also due to their limited knowledge about potential problems associated with such use. A small study screened community-dwelling older adults for their knowledge about risks associated with the use of OTC products and found that 95% of those interviewed screened positive for at least one instance of potential misuse, including a DDI, drug–disease interaction, drug–age interaction, or excessive usage (Stone et al., 2017).

DDIs involving OTC medications will be covered later in the section on drug interactions. However, adverse drug effects involving OTC medications are not only due to DDIs, and even monotherapy with an OTC medication in older adults can lead to significant adverse effects. One such example is the use of OTC "sleep aids," the active ingredient of which is typically a first-generation histaime-1 receptor (H_1) blocker such as diphenhydramine or doxylamine, which are highly anticholinergic and can lead to cognitive impairment and even delirium in higher doses. Doxylamine toxicity can also result in seizures and rhabdomyolysis (Syed, Som, Khan, & Faltas, 2009).

Complementary and alternative medications and medical "foods"

Prevalence of concurrent use of complementary and alternative medications (CAMs) and prescription medications in adults varied widely across studies, ranging from around 5% to almost 90% in one systematic review (Agbabiaka, Wider, Watson, & Goodman, 2017). Ginkgo biloba, garlic, ginseng, St. John's Wort (SJW), Echinacea, saw palmetto, evening primrose oil and ginger were the CAMs most reported in this review. In the previously mentioned survey, most of the interacting regimens involved prescription medications and dietary supplements that were increasingly being used by 2010–11 (Qato et al., 2016). Fish oil was the commonest CAM in the survey (18% of older adults in 2010–11), and there are case reports of fish oil supplementation significantly increasing the international normalization ratio (INR) in patients already on warfarin (Gross, Gillio, Rinehart, Lynch, & Rogers, 2017); this interaction was noted in about 1% of older adults in the survey in 2010–11.

Use of medical foods has become fairly ubiquitous in dementia patients, and older adults are often on one or more of these "foods," leading to questionable benefits and increased risk of drug–medical food interactions. Section 5(b)(3)

of the United States Orphan Drug Act (21 U.S.C. 360ee(b)(3)) defines medical foods as "a food which is formulated to be consumed or administered parenterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." The FDA requires medical foods to be specially formulated and processed "for the specific dietary management of a medical condition ... to provide nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition... (that must be) used under medical supervision... wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food" [FDA Regulations 21 CFR 101.9(j)(8)]. Once these conditions are met, the medical food is exempt from nutritional labeling requirement. Since these are not approved drugs, they lack rigorous FDA review prior to being marketed and lack regulatory oversight of their manufacturing process, which can result in poor quality control, and even the ingredients listed on the label may not even accurately represent the contents of the medical foods. In the absence of well-designed RCTs, the claims regarding the benefits of such medical foods remain unverifiable.

Medical foods are most commonly marketed for the treatment of AD dementia, including caprylic triglyceride (brand-name Axona), a combination of omega-3 fatty acids with phospholipids, choline, uridine monophosphate, vitamin E, selenium, vitamin B6, vitamin B12, and folic acid (brand-name Souvenaid), a combination of L-methylfolate, methylcobalamin, and *N*-acetylcysteine (brand-name CerefolinNAC) and apoaequorin (brand-name Prevagen). All medical foods are backed by a miniscule evidence base and a massive advertising budget, and none can be recommended for use at this time. Providers should take the time to educate themselves and their patients about known adverse effects of these products and their contents. Patients who remain desirous of adding a "natural" or "organic" product to their prescription medication(s) for the prevention of AD can be directed to simply increase their fish consumption instead. An autopsy-based study (Morris et al., 2016) found that moderate seafood consumption (one or more meals per week) was correlated with lower levels of AD neuropathology, but only among ApoE ε4 carriers, which is an example of a gene−food interaction; the higher mercury levels in these brains was not correlated with neuropathology, but this may not hold true for those with even higher brain mercury levels.

Potentially inappropriate medication use in older adults

The drug list approach

Adverse drug effects in older adults have been the focus of attention for a long time. A 1997 study (Hanlon et al., 1997) found that 35% of ambulatory older adults experienced an adverse drug effect, and 29% required health care services for it, resulting in billions of dollars in health care costs. Adverse drug effects ranked between the fourth and the sixth leading cause of death in hospitalized patients in a 1998 meta-analysis (Lazarou, Pomeranz, & Corey, 1998), so avoiding them as much as possible is imperative.

Dr. Mark Beers and colleagues published the first list of potentially inappropriate medications (PIMs) in 1991, which was focused on nursing home residents (Beers et al., 1991). The list was updated in 1997 to make them more generally applicable to all older adults (Beers, 1997), and PIMs were spilt into medications inappropriate for older adults in general, and medications that were inappropriate for use by older adults with 15 specific medical conditions. The list was adopted by the Centers for Medicare and Medicaid Services (CMS) (then Health Care Finance Administration) in July 1999 for nursing home regulation. Dr. Mark Beers was last involved in revising the criteria in 2003 (Fick et al., 2003). Unfortunately, he passed away in 2009 at the young age of 54 (Lau, 2009), and the list languished for a while before being taken over by the American Geriatrics Society (AGS) in 2011. The AGS published updates of the criteria in 2012, 2015, and 2019. The 2015 update included a selective list of DDIs as well as PIMs based on renal functions. Pocket cards containing the most current 2019 criteria are available for providers from the AGS.

A study out of Quebec, Canada, looked at PIM use in older community-dwelling adults using the 2015 Beers criteria and found that almost one-half of them were receiving at least one PIM (Roux, Sirois, Simard, Gagnon, & Laroche, 2019). Among the five most prevalent PIMs in this study, three were psychotropic medications—benzodiazepines (25%), first- and second-generation antipsychotics (6%), and antidepressants (5%). Polypharmacy and number of comorbid chronic illnesses, especially psychiatric illness (after adjusting for polypharmacy), were two of four factors strongly associated with PIM exposure, the other two being female sex and older age.

The Beers list has been critiqued for being a "negative" list that only informs providers about what not to prescribe (Wehling, 2016). In contrast, positive-negative lists do not only inform the provider about what not to do but about the alternatives as well. These include the Irish STOPP-START criteria, first proposed in 2008 and updated in 2015

(O'Mahony et al., 2015), as well as the FORTA (Fit fOR The Aged) list first developed in 2008 in Germany (Wehling, 2008), which has since been updated in 2012, 2015, and 2018 (Pazan, Weiss, & Wehling, 2019), and expanded from the original Germany/Austria-centric list into the European EUR-FORTA list in 2018 (Pazan, Weiss, & Wehling, 2018). The FORTA list classifies drugs as A (indispensable), B (beneficial), C (questionable), or D (avoid), based on current evidence about safety, efficacy, and age appropriateness, and it is embedded in an "implicit" process that requires in-depth knowledge about the patient and their diagnosis, which is in contrast to the "explicit" negative-list process that requires the provider to know not much more than the patient's age (Wehling, 2016).

The STOPP/START criteria cover not only PIM use in older adults (STOPP medications), but also errors of omission, that is medications that should have been started for a particular indication (START medications), and both lists are arranged by physiological system, an approach that was also adopted by the Beers list starting with the 2012 revision. The 2015 START-STOPP2 criteria have been incorporated into the SENATOR software engine, which is an international collaboration funded by the European Union (EU) and includes 12 European organizations, and is being developed for the optimization of medical and nondrug therapy in older adults with multimorbidity and polypharmacy (Soiza et al., 2017). STOPP criteria have also been adapted for frail, older adults with limited life expectancy (Lavan, Gallagher, Parsons, & O'Mahony, 2017), and these STOPPFrail criteria have been shown to have a positive predictive value of almost 90% in predicting systematic geriatrician-led deprescribing in hospitalized adults at or over the age of 65 with advanced frailty receiving five or more medications (Curtin et al., 2019), and may be used as an alternative to a specialist-led review in resource-poor areas.

Deprescribing in older adults

The term "deprescribing" was first described in 2003 (Woodward, 2003) but the terminology has been used inconsistently. A systematic review (Reeve, Gnjidic, Long, & Hilmer, 2015) found 37 different definitions of deprescribing and proposed a consensus definition which is as follows: "Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes." Assessment of PIM use with the help of one of the explicit or implicit drug lists is the first step in deprescribing. Tools have also been constructed to aid deprescribing in specific conditions, such as the medication appropriateness tool for comorbid health conditions in dementia (MATCH-D), which consists of 67 consensus statements that describe appropriate medication management in people with dementia (Page, Potter, Clifford, McLachlan, & Etherton-Beer, 2016). Deprescribing is generally feasible and safe, but benefits have not been consistently demonstrated in RCTs. A systematic review of deprescribing interventions in RCTs (Page, Clifford, Potter, Schwartz, & Etherton-Beer, 2016) found no reduction in mortality, although nonrandomized data suggest that it reduces mortality; a trend to reduced mortality was noted in the 65−80-year-old age group but not in those above the age of 80, and there was no significant change in quality of life.

One of the largest ongoing projects in deprescribing is the CAnadian DEprescribing Network or CaDeN, described as "a national network of individuals and organizations interested in the deprescribing of PIMs in Canada" (Tannenbaum et al., 2017). It has an ambitious goal of curbing the use of PIMs among older people by 50% by the year 2020. Educational material is available in the public domain on the website, including educations videos for clinicians and patient handouts. As of January 11, 2019, algorithms for deprescribing five commonly used medication classes in older adults had been posted to the website—proton pump inhibitors, antihyperglycemics, antipsychotics, benzodiazepines, and antidementia medications (cholinesterase inhibitors and memantine)—which may be accessed free of cost at https://www.deprescribingnetwork.ca/algorithms. As is evident, three of these five are psychotropic medication classes.

Sociocultural factors

The patient−caregiver dyad

One should always enquire about the presence or absence of social support type of support available (tangible or intangible), and presence or absence of any surrogate decision-makers. If a surrogate decision-maker has been appointed by the courts, a copy of the court order should always be incorporated into the EMR or paper chart. Unusual medication effects that occur when a caregiver is managing medications, such as a persistent and unusually high INR in a patient on warfarin, should lead to enquiries about caregiver stress and elder abuse. Caregiver stress can adversely impact the patient's medication adherence (Foebel, Hirdes, & Heckman, 2012), while the suffering of a loved one with dementia can increase caregiver depression and increase caregiver medication use (Schulz et al., 2008). One should enquire about the caregiver's physical and emotional health in all patient−caregiver dyads, whether the caregiver is a professional or

a family member. Concealing a history of physical or financial abuse by a family member is common among patients, since patients are dependent upon that family member in some way and/or is too ashamed to report the abuse (Lachs & Pillemer, 2015). Separate interviews with patients and caregivers, use of a professional medical interpreter where indicated, and indirect questioning about safety and available community resources are just some of the interviewing strategies that may help uncover a history of elder abuse.

The impact of ageism

Ageism impacts health care delivery at multiple levels and adversely affects health care delivery to older adults. Common beliefs among patients, caregivers, and even providers include that ill-health is inevitable in older adults and interventions are usually ineffective, and late-onset behavioral and psychiatric symptoms are often erroneously attributed to old age. Even when correctly identified, pharmacological options for older adults are limited by the underrepresentation of older adults in RCTs (Konrat et al., 2012), and the fact that under-representation of older people in trials causes difficulties for prescribers and patients alike was endorsed in a survey of 521 health professionals in nine EU countries (Crome et al., 2011). Lack of an evidence base leads to therapeutic uncertainty, as medications that are prescribed have usually not been adequately tested in older adults, especially in the oldest-old.

Drug interactions in older adults

Drug interactions are a critical topic in psychopharmacology in general, and in older adults in particular. These not only include pharmacokinetic and pharmacodynamic DDIs, but also drug–herb interactions, drug–food interactions, drug–disease interactions, drug–substance interaction, and drug–gene interactions. The last are better known as genetic biomarkers for drug response and tolerability, or pharmacogenomics. Drug interactions assume special significance in older adults due to the age-related changes in drug pharmacology, increased frequency of multimorbidity, and the high prevalence of polypharmacy, all of which have already been discussed.

Drug–drug interactions

DDIs can be of two types—pharmacokinetic and pharmacodynamic—and each one will be discussed in some detail. However, not all DDIs can be neatly classified into one or the other category. Lithium levels are increased by nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors via an unknown mechanism, since the increase in serum lithium concentration with these drugs is not directly proportional to the renal prostaglandin synthesis inhibiting effect of these drugs which was conventionally thought to be the mechanism of action for these DDIs (Phelan, Mosholder, & Lu, 2003). Another example is the risperidone–furosemide interaction noted in the FDA label for Risperdal. The label notes that "in placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years) or furosemide alone (4.1%; mean age 80 years). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of four clinical trials. No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed."

Pharmacokinetic drug–drug interactions

Pharmacokinetic DDIs occur when a concomitantly administered drug alters the serum concentration of another drug at the site of action. These can occur at the level of absorption, distribution, metabolism, or elimination.

Absorption

An age-related increase in gastric pH in older adults increasingly impacts absorption of drugs as patients grow older. The increase in gastric pH is further exacerbated by antacids which interfere with GI absorption of drugs (Romankiewicz, 1976). Cimetidine used for the treatment of acid-peptic diseases delays gastric emptying by causing relative achlorhydria and reducing gastric pepsin activity (Kerrigan, Mangnall, Read, & Johnson, 1991), and drug absorption may be impaired by delayed gastric emptying. Antiulcer therapy has other effects on drug absorption as well. Ionized medications can bind to the divalent cations of antacids and sucralfate to result in complexes that are poorly absorbed, and reduced gastric acid may decrease the absorption of medications that are weak bases, while enhancing the absorption of those that are weak acids (Reynolds, 1990).

Distribution

Changes in absorption and the volume of distribution, alteration in hepatic clearance, reduction in protein binding due to a reduction in synthesis or increase in excretion of the transport proteins, breakdown of the blood−brain barrier leading to increased penetration of the drug into the CNS, and reduced clearance of drugs by the kidneys can all increase the risk of pharmacokinetic DDIs in older adults. Highly protein-bound can also potentially displace a less avidly bound drug from its protein binding sites, which can assume clinical significance when the displaced drug has an extremely narrow therapeutic window. DDIs involving the P-gp system will not be covered here, but an excellent discussion can be found in Lund et al., 2017.

Metabolism

These are some of the most clinically relevant pharmacokinetic DDIs and involve one drug (an enzyme inducer or inhibitor that may or may not be a substrate of that enzyme) altering the metabolism of another concomitantly administered drug, which is a substrate of that enzyme.

Only DDIs involving the CYP drugs will be discussed in this section, which disproportionately affect older adults due to the impact of aging on the CYP enzymes, as discussed in the section on pharmacokinetics. All SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), except levomilnacipran, inhibit at least one cytochrome P450 enzyme, but in some cases the inhibition is not clinically significant. Fluoxetine is a pan-inhibitor of the clinically relevant CYPP450 enzymes—it inhibits CYP2D6 and CYP2C9/10 to a substantial degree, CYP2C19 moderately, and its active metabolite norfluoxetine inhibits CYP3A3/4 moderately. Fluvoxamine inhibits four of the five common CYP enzymes, except CYP2D6. Paroxetine is a potent inhibitor of CYP2D6, sertraline and duloxetine are moderate inhibitors of CYP2D6 (Kennedy et al., 2016), and citalopram and escitalopram are weak inhibitors of CYP2D6 (Gram et al., 1993; Preskorn et al., 2007). Venlafaxine is a weak CYP2D6 inhibitor (Ball, Ahern, Scatina, & Kao, 1997), as is desvenlafaxine (Nichols et al., 2013). Sertraline, citalopram, and escitalopram are the safest SSRIs to use in older adults, since the inhibition of CYP2D6 by sertraline is dose-dependent, occurring only above 200 mg/day, while the weak inhibition by citalopram and escitalopram is not clinically significant. Unlike other SSRIs, fluvoxamine inhibits CYP1A2, which primarily metabolizes two important second-generation antipsychotics, olanzapine, and clozapine (Wang et al., 2004).

Antipsychotics are more likely to be involved in DDIs as substrates of the CYP enzymes rather than as inducers or inhibitors. Several common antipsychotics are metabolized by CYP2D6 (see Table 23.1 for details), which means that caution will be required to coadminister these with antidepressants that are potent CYP2D6 inhibitors (fluoxetine, paroxetine, bupropion). Some antidepressants and benzodiazepines are metabolized by CYP2C19, which is inhibited by fluvoxamine and omeprazole, and extreme caution should be used when co-administering fluvoxamine or omeprazole with such antidepressants (escitalopram, citalopram) and benzodiazepines (diazepam) (Perucca et al., 1994).

DDIs involving the SSRIs and SNRIs affect not only psychotropic medications, but also other medications commonly used in older adults. For example, when choosing a beta-blocker in patients with ischemic heart disease, their metabolic route should be considered in addition to their cardio-selectivity. Preference may be given to the use of beta-blockers that are metabolized via multiple cytochrome P450 enzymes such as propranolol, and those that are mainly excreted unchanged via the kidneys such as atenolol, over those that are predominantly metabolized by CYP2D6, such as carvedilol, metoprolol, and nebivolol (mnemonic CarMeN), and therefore have a greater potential for DDIs (Andrade, 2013).

Other DDIs involve enzyme induction instead of inhibition. Of note, none of the SSRIs or SNRIs induce any of the CYP enzymes. Carbamazepine is an important example of a drug that is metabolized via CYP3A4 but also induces its own metabolism. When a drug induces its own metabolism by being both a substrate and an inducer of the same enzyme, it is called autoinduction. The clearance of carbamazepine increases by 300% within 30 days after initiation of therapy due to autoinduction, and stable carbamazepine concentrations are usually attained within 2−3 weeks of starting therapy (Tolou-Ghamari, Zare, Habibabadi, & Najafi, 2013). Carbamazepine, along with other older enzyme-inducing antiepileptic drugs (AEDs; phenytoin, phenobarbital and its prodrug primidone) reduce the levels of many psychotropic and nonpsychotropic medications by inducing the activity of CYP1A2, CYP2C9, CYP2C19, and CYP3A4, as well as the UGTs (Spina, Pisani, & de Leon, 2016).

Pharmacokinetic DDIs can also involve OTC drugs and prescription drugs. OTC drugs can increase or reduce the efficacy of the psychotropic medication via a pharmacokinetic interaction. Almost 15% of older adults in 2010−11 used omeprazole OTC, making it the second most commonly used OTC drug in the previously mentioned survey (Qato et al., 2016). Omeprazole is a CYP2C19 blocker but induces CYP1A2 in the presence of an inducible CYP1A2*1F

allele, and therefore has potential for multiple pharmacokinetic DDIs. It can increase serum levels of citalopram and escitalopram (via CYP2C19 inhibition) but lower serum levels of clozapine and olanzapine (in patients with the inducible allele). It can also block the conversion of the prodrug clopidogrel into its active form (also via CYP2C19 inhibition). This clopidogrel−omeprazole OTC interaction was noted in about 1% of older adults in the abovementioned survey in 2010−11 (Qato et al., 2016).

DDIs involving the UGT enzymes have not been covered in the interest of brevity but are also important, and an excellent discussion of the topic can be found in Rowland et al. (2013).

Elimination

DDIs involving elimination are less frequent. One clinical example is the interaction between lithium and thiazide diuretics; when used concurrently, thiazides can significantly increase the plasma levels of lithium due to reabsorption of lithium in the proximal tubules, thereby increasing the risk of lithium toxicity (Finley, Warner, & Peabody, 1995).

Pharmacodynamic drug−drug interactions

Pharmacodynamic interactions comprised almost one-half of all the DDIs in one study (Sonnerstam, Sjolander, Lovheim, & Gustafsson, 2018). Older antidepressants (tertiary amine TCAs, such as amitriptyline and imipramine) and first-generation antipsychotics (such as chlorpromazine and thioridazine) are problematic due to their potent muscarinic, α_1 and H_1-receptor blockade, all of which can contribute to pharmacodynamic DDIs in older adults when administered with other anticholinergic, antihypertensive, or sedative drugs, respectively. The α_1 antagonists have several uses, including in the treatment of hypertension (doxazosin), posttraumatic stress disorder (prazosin), and benign prostatic hyperplasia (tamsulosin), but when α_1-blockers are administered concurrently with psychotropic drugs that also block α_1 receptors (clozapine, trazodone), the risk of orthostatic hypotension is greatly increased.

Monoamine oxidase inhibitors (MAOIs) also have the potential for a large number of DDIs, including the risk of a serotonin syndrome when concomitantly used with serotonergic drugs (such as SSRIs, SNRIs, buspirone, and triptans), and a hypertensive crisis when combined with noradrenergic drugs, stimulants, and pressors. One exception is combining MAO-B inhibitors, such as rasagiline, in therapeutic doses with an SSRI, which is not an uncommon situation in the treatment of depression in idiopathic Parkinson's disease and appears to be relatively safe (Aboukarr & Giudice, 2018). Drugs that are not "known" to be MAOIs can also have potent MAOI properties, such as the antibiotic linezolid (Aga, Barklage, & Jefferson, 2003) and can have similar DDIs. Opioid analgesics can be classified into weak SSRIs (meperidine, tramadol, methadone, dextromethorphan, and propoxyphene) and those that have no serotonergic activity (morphine, codeine, oxycodone, and buprenorphine); even though all opioids are thought to be contraindicated for concurrent administration with the MAOIs, the latter can be safely used concurrently (Gillman, 2005).

The QTc-prolonging effects of some antidepressants and antipsychotics may be lethal in older adults, and these risks may be further enhanced if two drugs that can cause QTc prolongation are prescribed together, such as some antipsychotics (chlorpromazine, thioridazine, clozapine, ziprasidone) with some TCAs (amitriptyline, imipramine, desipramine, nortriptyline) (Wisniowska, Tylutki, Wyszogrodzka, & Polak, 2016).

Significant pharmacodynamic DDIs can occur with the antidementia medications. Cholinesterase inhibitors can potentiate the bradycardia caused by other drugs that have a negative chronotropic effect, such as beta-blockers. QT prolongation and torsades de pointes were added to the list of adverse reactions in the postmarketing experience section of the donepezil prescribing information in 2015 by the FDA, but a recent meta-analysis found that individuals treated with cholinesterase inhibitors have a significant prolongation of the PR interval and no significant changes in the QRS or QT/QTc intervals (Isik et al., 2018). Regardless, it should be combined with caution with other drugs that can prolong the QTc, such as antipsychotics, citalopram, and escitalopram. Memantine is a glutamate NMDA receptor antagonist that may potentiate the effects of antiparkinsonian treatments (levodopa, dopamine agonists) and anticholinergic agents, while reducing the effects of barbiturates and neuroleptics (Jones, 2010).

OTC drugs can result in pharmacodynamic DDIs with prescription drugs. In the survey mentioned previously (Qato et al., 2016), aspirin OTC was the most commonly used prescription or OTC drug, which was used by 40% older adults in 2010−11. Antiplatelet therapy is well known to increase the risk of bleeding, and the addition of an SSRI further potentiates the risk via a pharmacodynamic interaction. Also, H_1-blockers sold as OTC sleep aids can interact with psychotropic medications that cause sedation or have anticholinergic side effects, such as benzodiazepines and antipsychotics respectively, thereby increasing the risk of these adverse effects.

Drug–herb interactions

As with prescription drugs, drug–herb interactions can be pharmacokinetic or pharmacodynamic, and a single herb will be used to illustrate some interactions. The flowering tops of the plant St. John's wort (SJW; *Hypericum perforatum)* have some efficacy in treating mild-to-moderate depression (Sarris, 2013), but the evidence is inconsistent and the quality of commercially available preparations varies considerably (Linde, Mulrow, Berner, & Egger, 2005). Its use can result in several drug–herb interactions. An example of a pharmacokinetic interaction involving SJW is the induction of the metabolism of drugs that are substrates for CYP3A4 and P-gp (Nicolussi, Drewe, Butterweck, & Meyer Zu Schwabedissen, 2019), and there are case reports of rejection after organ transplants in patients on cyclosporine (a CYP3A4 substrate) after the patients inadvertently started using SJW postsurgery on their own. Similarly, a reduction in effective levels of prescribed protease inhibitors (all of which are CYP3A4 substrates) may result in worsening of HIV infection if taken concurrently with SJW (Mannel, 2004). An example of a pharmacodynamic interaction involving SJW is the increased risk of serotonin syndrome if it is used concurrently with other serotonergic drugs such as triptans or SSRIs (Bonetto, Santelli, Battistin, & Cagnin, 2007). Older adults are at higher risk of such interactions due to polypharmacy, and its risk-benefit profile does not support its use in older adults.

Drug–food interactions

These can again be pharmacokinetic or pharmacodynamic. One example of the former is that grapefruit juice significantly inhibits the metabolism of CYP3A4 substrates in a dose-dependent manner (Veronese et al., 2003). As discussed in the section on metabolism, CYP3A4 in the intestinal epithelium is also involved in first-pass metabolism, and the effects of food on the enzyme are more pronounced in the intestinal epithelium than in the liver. Its inhibition greatly increases the bioavailability of drugs, but the magnitude of the effect is unpredictable and there is interindividual variability (Wilkinson, 1997). As little as 200 mL of grapefruit juice is enough to cause this inhibition, which is clinically significant in medications taken by the oral route that have a low to intermediate oral bioavailability (i.e., high first-pass metabolism), a narrow therapeutic window and are mainly metabolized by CYP3A4; this pharmacokinetic interaction becomes even more pronounced in those above age 70 (Bailey, Dresser, & Arnold, 2013). A list of drugs that interact with grapefruit juice can be found in Bailey et al. (2013). Brassica (family Cruciferae) vegetables such as broccoli and Brussel sprouts increase, apiaceous (family Umbelliferae) vegetables such as carrots and parsnips decrease, and allium (family Liliaceae) vegetables such as onions and leeks have no effect on CYP1A2 activity, compared to a basal, vegetable-free diet (Lampe et al., 2000). Regular consumption of charcoal-broiled food also induces CYP1A2 activity in the intestinal epithelium and liver (Wilkinson, 1997). However, such CYP1A2 induction is usually not clinically significant in psychiatry since only a few psychotropic drugs are metabolized by this enzyme.

The best-known example of a pharmacodynamic drug–food interactions is the interaction between MAOIs and tyramine-containing foods (aged cheese, processed beer, fava beans, and monosodium glutamate or MSG), which can result in a hypertensive crisis ("cheese reaction") when they are taken together that can be lethal, especially in older adults. The recent availability of the selegiline transdermal system (Emsam-TD) provides an attractive alternative to oral selegiline as it bypasses the first-pass metabolism effect and the lowest 6 mg daily dose does not increase the risk of drug–food interaction, but higher doses do (Goodnick, 2007).

Similarly, a pharmacodynamic medical food–prescription drug interaction may occur. CAMs, which are often a component of a medical food, can increase the risk of bleeding in patients who are already on aspirin or warfarin (Agbabiaka et al., 2017), which can be further potentiated by the concurrent use of SSRIs in psychiatric patients. The risk of bleeding with SSRIs is discussed further in the section on the treatment of major depressive disorder.

Drug–disease interactions

The impact of physical illness on psychopharmacology in older adults cannot be emphasized enough. Changes in the circulating low-affinity/high-capacity albumin and high-affinity/low-capacity α_1-acid glycoprotein levels occur in older adults more as a function of physical disease rather than age per se (Grandison & Boudinot, 2000). Decrease in intravascular serum albumin in disease can occur due to reduced protein intake, reduced albumin synthesis, extravascular shifts, or increased losses. Circulating α_1-acid glycoprotein is an acute-phase reactant and its level increases with physiological trauma (cancer, inflammatory disease, trauma, and surgery) or stress, and falls with reduced production (e.g., liver disease) or increased losses (e.g., nephrotic syndrome). The clinical impact of changes in the circulating transport proteins on drug concentrations depends upon the extent of the protein binding and whether the drug's hepatic clearance

is capacity-limited or flow-limited, which have already been discussed in the section on hepatic metabolism. Any kind of stress, including infections or trauma, can also directly inhibit hepatic metabolism of drugs, which can result in drug toxicity in older adults. There is evidence to suggest that some CYP enzymes can be downregulated by pro-inflammatory cytokines; of the common human CYP enzymes, CYP1A2 appears to be affected the most and CYP2D6 the least (Zídek, Anzenbacher, & Kmoníčková, 2009). The FDA drug labels contain information on adjusting a drug's dose in patients with liver disease, and dosing recommendations for the newer antipsychotics and antidepressants in the presence of hepatic impairment (called *hepatic dosing*) are listed in Tables 23.1 and 23.3.

A practical example will illustrate the clinical impact of drug−disease interactions on drug transport and metabolism. The hepatic clearance of clozapine is capacity-limited and 95% of the circulating clozapine is bound to α_1-acid glycoprotein, which predicts a higher circulating free fraction of the drug in older adults. About 70% of clozapine is metabolized to norclozapine via CYP1A2 (Eiermann, Engel, Johansson, Zanger, & Bertilsson, 1997). In acute infections, there is an increase in circulating α_1-acid glycoprotein as it is an acute-phase reactant, as already discussed. This reduces the free fraction of the drug (Man et al., 2019), which should neutralize the effects of downregulation of CYP1A2 by pro-inflammatory cytokines. However, the rate and level of increase in α_1-acid glycoprotein in infections is variable, which explains why it does not exert more of a protective effect (Clark et al., 2018), and the net effect is usually a large increase in the clozapine serum level with a higher risk of clozapine toxicity (Darling & Huthwaite, 2011; Matthews & Hall, 2014). Additionally, due to the opposing and variable effect of increased α_1-acid glycoprotein, there is also a dissociation between the clozapine level and the extent of toxicity in acute infections (Clark et al., 2018).

Reduced creatinine clearance due to renal disease especially impacts those drugs that are excreted mainly unchanged by the kidneys without undergoing significant biotransformation. Creatinine clearance has already been discussed in detail in the section on elimination.

Drug−substance interactions

Since substance use is still relatively uncommon in the older population, as discussed in the section on the confounding effects of substance use, and only select drug−substance interactions will be discussed here. Pharmacokinetic interactions involving smoking, caffeine, cannabis, and alcohol are most encountered in geriatric clinical practice today. Like omeprazole, smoking induces the expression of CYP1A2*1F, which in turn lowers serum concentrations of CYP1A2 substrates such as clozapine and olanzapine. It is the polycyclic aromatic hydrocarbons in cigarette smoke and not nicotine itself that is responsible for the enzyme induction (Kroon, 2007). After cessation of heavy smoking (defined as 20 or more cigarettes/day), CYP1A2 activity declines rapidly until a new steady state is established by the end of the first week (Faber & Fuhr, 2004). One common situation where this becomes important is when psychotic patients are stabilized on one of these two antipsychotic medications on a nonsmoking psychiatric inpatient unit and discharged to the community, where they resume smoking and quickly relapse as their serum drug concentration plummets.

Psychiatric patients consume much more coffee than the general population (De Freitas & Schwartz, 1979), which sets the stage for important drug−caffeine interactions. Ninety-five percent of the primary metabolism of caffeine is via CYP1A2 and most of the rest is via CYP2E1, which is induced by alcohol (Gu, Gonzalez, Kalow, & Tang, 1992). Caffeine also induces CYP1A2*1F, but it is the relative concentrations and enzyme affinity of substrates and inhibitors that determines the extent of interaction. Caffeine has a lower affinity for CYP1A2 than clozapine, but higher concentrations of caffeine displace clozapine from the CYP1A2 binding sites, thereby competitively inhibiting rather than inducing clozapine metabolism (Carrillo & Benitez, 2000). Caffeine consumption also increases the renal clearance of lithium, and conversely, caffeine withdrawal can precipitate lithium toxicity (Mester et al., 1995).

Cannabis and cannabinoids have significant pharmacokinetic drug−substance interactions. THC inhibits CYP2C9, CBD potently inhibits CYP2C19 and perhaps CYP2D6, and both inhibit CYP3A4 (Anderson & Chan, 2016; Jiang, Yamaori, Okamoto, Yamamoto, & Watanabe, 2013; Rong et al., 2018; Yamaori, Okamoto, Yamamoto, & Watanabe, 2011). The full clinical implications of these interactions are as yet unclear, especially with respect to route of administration (e.g., smoking vs ingestion) and the amount consumed. An extensive review of the topic concluded that the inhibition of the cytochrome P450 enzymes by THC is "probably too weak to cause a clinically significant interaction with coadministered drugs," but inhibition of CYP3A4 by higher doses of CBD may be clinically relevant (Zendulka et al., 2016). Thus, drugs that are mostly metabolized via CYP3A4 appear to be at the highest risk of having a pharmacokinetic interaction with CBD. Pharmacodynamic interactions include possibly increasing the anticoagulant effect of warfarin by smoking marijuana (Yamreudeewong, Wong, Brausch, & Pulley, 2009), which can be clinically significant in the many many older adults who are on warfarin.

The drug–substance interactions involving alcohol are mainly pharmacodynamic in nature. The most reliable estimates for the concurrent use of psychotropic medications and alcohol is in the range of around 7.5% in older adults, and falls appear to be the most common adverse effect seen with concurrent use of alcohol and psychotropic drugs (Holton, Gallagher, Fahey, & Cousins, 2017), although fatal poisoning is possible due to the concurrent consumption of alcohol and benzodiazepines (Tanaka, 2002).

Drug–gene interactions

A detailed discussion of this vast topic is beyond the scope of this chapter. Many pharmacokinetic and pharmacodynamic genetic biomarkers are now available for use in clinical practice due to the availability of several gene assay panels that are relatively inexpensive. For-profit companies such as 23&Me have made these gene assays available to the lay public without a provider's orders, which creates problems due to the consumers' inadequate understanding of the test results. Provider-ordered genetic assays are being increasingly utilized to optimize efficacy and tolerability of psychotropic drugs, especially antidepressants, but evidence supporting such use in clinical practice is still equivocal (Goldberg, 2017).

Pharmacokinetic drug–gene interactions

There is robust evidence supporting the use of pharmacokinetic genetic biomarkers, such as genetic variance in drug-metabolizing cytochrome P450 enzymes. As discussed in the section on metabolism, the alleles of the *CYP* genes are defined by star (*) nomenclature for which the Human CYP Allele Nomenclature Database serves as a central repository. The functional status of the variant alleles can range from no function to increased function, and therefore the phenotypes can range from poor metabolizer (PM) to ultra-rapid metabolizer (UM) status, depending upon the genotype (Tornio & Backman, 2018). Patients homozygous for wild-type alleles are known as extensive (normal) metabolizers (EMs), those homozygous for a loss-of-function allele are PMs, and those heterozygous for a loss of function and a wild-type allele are intermediate metabolizers (IMs). UMs may have multiple copies of a normal function allele (e.g., CYP2D6*1xN), a gain-of-function allele whose expression is induced only in the presence of an inducer (CYP1A2*1F), or a gain-of-function allele that is independent of an inducer (CYP2C19*17). As is obvious, PMs require lower doses and UMs require higher doses of the substrate drug relative to EMs in order to avoid toxicity and enhance effectiveness, respectively.

Since the early 2000s, the FDA has been working toward encouraging drug manufacturers to voluntarily submit pharmacogenomics data, and guidelines on voluntary genomic data submissions were finally finalized in 2005 (Lesko & Zineh, 2010). Based on this data, a number of drug labels have been updated, such as the one for carbamazepine in 2007 mentioned in the next section. The FDA does not recommend CYP genotyping as a prerequisite for dosing any drug, but the FDA drug labels do recommend lowering drug doses based on CYP genotyping specifically for the following psychotropic drugs: pimozide, clozapine, aripiprazole, iloperidone and brexpiprazole, all antipsychotics, citalopram and vortioxetine, both antidepressants, and atomoxetine, a selective norepinephrine reuptake inhibitor. When such testing should be done, and which commercially available assay should be used, are issues that are not clarified by the FDA.

Pharmacodynamic drug–gene interactions

The pharmacodynamic interactions between drugs and genetic polymorphisms are not as well studied, but there are some interesting preliminary findings. Of the many reported drug–gene interactions, two are selected here for a brief discussion and the clinical significance of each is somewhat different.

SSRIs increase the availability of serotonin in the synaptic cleft by inhibiting the SERotonin (or 5HT) transporter (5HTT or SERT). The gene *SLC6A4* encodes for the 5HTT and it has a promoter region that modulates the expression of the gene. This promoter region contains a polymorphic segment called the 5HTT-linked polymorphic region (5HTTLPR), which has a short (S) and a long (L) allele. The L allele is further subdivided into L(A) and L(G), where adenine (A) at one location in the L allele is replaced by guanine (G). The L(G) and S alleles are low-expression genes that reduce the expression of the 5HTT gene while L(A) is a high-expression gene, but both the S and L alleles act codominantly. Individuals with the homozygous S allele of 5HTTLPR polymorphism are at increased risks of major depressive disorder, as well as alcohol dependence (Oo, Aung, Jenkins, & Win, 2016). In a posthoc analysis of patients treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a positive association was found between the L/L genotype and remission in those with onset of major depressive disorder *after*

age 55 compared to the S genotype, and multivariate analysis demonstrated that the genetic effect of the promoter region on remission increased with age at onset (Shiroma, Drews, Geske, & Mrazek, 2014).

Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but potentially life-threatening side effects of carbamazepine, which are more common in Asian individuals, especially the Han Chinese. These have been linked to the human leukocyte antigen (HLA) antigen B*1502, and in 2007 the FDA-recommended genetic screening for all patients of Asian ancestry before initiating carbamazepine therapy, which has since been included as a black box warning on the label (Ferrell & McLeod, 2008).

Drug treatment of common psychiatric disorders in older adults

Psychotic disorders in older adults

Introduction

Nonaffective psychotic disorders in older adults include persisting young-onset schizophrenia, schizophrenia with onset later in life (late-onset schizophrenia), and new-onset psychosis in the dementias. The latter is much more common in older adults than the former two, and will be covered in the section on neurobehavioral symptoms in the dementias. This section will focus on late-onset psychosis that does not occur in the context of a pre-existing dementia. Psychosis that occurs in the presence of a known dementia will be covered later in the section on neurobehavioral symptoms. A little less than a fourth of all patients with schizophrenia have onset after age 40 (Harris & Jeste, 1988). The DSM-III criteria had implied that a diagnosis of new-onset schizophrenia with onset above age 45 could not be made. DSM-III-R changed this by adding a late-onset specifier instead, and the age cutoff for diagnosis was completely done away with in DSM-IV and DSM-5 (Tandon et al., 2013), thereby acknowledging the existence of late-onset schizophrenia.

Schizophrenia with onset in late life presents in ways that are distinct from schizophrenia with onset in younger adults. The International Late-Onset Schizophrenia Group published a consensus statement (Howard, Rabins, Seeman, & Jeste, 2000) that proposed criteria for late-onset (age 40–60 years) schizophrenia and very late–onset schizophrenia-like psychosis (after age 60). Female sex is associated with late-onset schizophrenia and there is a lower prevalence of formal thought disorder and affective blunting with a higher prevalence of visual hallucinations (Howard et al., 2000). Patients with very late–onset schizophrenia-like psychosis, especially men, have higher mortality rates than adults in whom early-onset schizophrenia has continued into late life (Talaslahti et al., 2015). Late-onset psychosis appears to increase the risk of progression to dementia. In a community-based study in adults aged 70–90 years (Ostling, Palsson, & Skoog, 2007), 25% of those with no psychotic symptoms versus 44% with any first-onset psychotic symptoms developed dementia during the 20-year follow-up period. The hazard ratio (HR) for development of dementia for any psychosis was 3.5, which was higher for hallucinations (HR 3.8) than for delusions (HR 2.9) and lowest for paranoid ideations "of less than delusional proportions" (HR 0.8). The mean interval between the first onset of psychotic symptoms and development of dementia was 5 ± 4.7 years. In the largest study to date, 37,770 dementia-free men aged 65–85 years were prospectively followed for almost 18 years (Almeida et al., 2019). The risk ratio of incident dementia was more than twice as high among those who had received a diagnosis of psychotic disorder at baseline or were diagnosed with a psychotic disorder during follow-up, and the risk was the highest in those with the shortest duration of the psychosis, that is those with a late-onset psychosis.

In summary, the incidence rate of dementia in older adults is higher in those with late-onset psychosis versus those without, the risk being greatest in those with recent-onset psychosis, but overall the progression to dementia can still take many years from onset of psychosis.

Drugs for the treatment of psychotic disorders

All antipsychotics can be classified into one of two large groups, first-generation and second-generation antipsychotics, although there is a great deal of pharmacological heterogeneity within both groups. The older, first-generation *typical* antipsychotics are rarely used nowadays, especially in older adults. The decline in use, especially of low-potency first-generation antipsychotics, is due to their multiple clinically serious adverse effects in old age, including but not limited to dryness of mouth, blurring of vision, tachycardia, retention of urine, constipation, confusion and memory problems, sedation, increased appetite, postural hypotension, and reflex tachycardia. The only apparent advantage of low-potency first-generation antipsychotics is their low potential for causing EPS and hyperprolactinemia, which justifies their continued use in select young adults. The first-generation high-potency antipsychotics are more selective dopamine-2 receptor blockers, a mechanism considered central to the antipsychotic effects of all *typical* antipsychotics. At higher

doses and especially in older adults, these high-potency first-generation antipsychotics can significantly increase the risk for EPS, neuroleptic malignant syndrome, and hyperprolactinemia.

The newer or second-generation antipsychotics (also called *atypical,* as D_2 receptor antagonism is not the predominant mechanism of action) are preferred in older adults when indicated compared to the first-generation D_2 receptor antagonists. However, their receptor profile is highly variable, and several second-generation antipsychotics have a side effect profile that is similar to that of first-generation low-potency antipsychotics, most notably clozapine. Partial D_2/D_3 agonists and inverse $5HT_{2A}$ agonists are relatively new classes of second-generation antipsychotics with new indications, such as augmenting antidepressants in treatment-refractory depression and treating Parkinson's disease psychosis.

Of the first-generation antipsychotics, haloperidol is still commonly used in clinical practice, based on many decades of clinical experience. A Cochrane collaboration review (Donnelly, Rathbone, & Adams, 2013) that reviewed the use of haloperidol in the treatment of acute schizophrenia in mixed-age adults found that the overall quality of evidence was poor. Doses in excess of 7.5 mg/day were not more effective than doses in the range of 3−7.5 mg/day, and the higher dose range caused more EPS. Another Cochrane collaboration review (Adams, Bergman, Irving, & Lawrie, 2013) that looked at the benefits of haloperidol vis-à-vis placebo in a mixed-age schizophrenia population also found that the evidence base was of rather poor quality, and while it was certainly an effective antipsychotic, the risk of inducing a movement disorder in the short-term (parkinsonism, acute akathisia, acute dystonia) was high. Haloperidol has not been systematically studied in late-onset psychosis. The one published case report (McClure, Gladsjo, & Jeste, 1999) underscores all the points that have already been made—the patient was finally stabilized on a dose as low as 2 mg/day, his response was partial and he developed parkinsonism and akathisia in the short term and tardive dyskinesia (TD) within 1 year of initiating treatment. Hyperprolactinemia is another well-known adverse effect. Haloperidol is a potent mesolimbic D_1 and D_2 blocker with negligible effects on other receptors, and therefore causes minimal sedation and orthostasis in therapeutic doses (Patteet et al., 2012). In terms of its metabolism, it is a "dirty" drug, in that it is metabolized via several CYP and UGT enzymes. Its serum concentrations are affected by CYP3A4 and CYP2D6 inducers and inhibitors, while its inhibitory effects on these two enzymes are not clinically significant (Kudo & Ishizaki, 1999). Its main advantages are that it is rapidly effective in managing acute psychotic agitation and is available as oral tablet, oral liquid, short-acting injectable and long-acting injectable formulations, and providers are generally familiar with its use. Another advantage is that therapeutic drug monitoring yields clinically meaningful information; serum levels of 5−17 ng/mL are considered therapeutic *in young adults* with maximum benefit around 10 ng/mL, and levels above 18 ng/mL are not more effective (Coryell, Miller, & Perry, 1998; Ulrich, Neuhof, Braun, & Meyer, 1998). In older adults, the goal should be to keep the serum level at the lower end of the therapeutic range. Haloperidol has a limited role in the psychopharmacologic armamentarium for the rapid treatment of acute psychotic agitation in older adults using very low doses, but it should be avoided in dementia-related psychosis due to the much higher risk of morbidity and mortality.

The second-generation antipsychotic clozapine has a special place in the treatment of psychosis and also deserves special mention. Clozapine remains the gold standard for treatment-refractory schizophrenia and is the only other antipsychotic apart from pimavanserin that has been shown to be effective in treating Parkinson's disease psychosis (Zhang et al., 2019). However, its use in older adults is quite limited due to the higher incidence of postural hypotension, confusion, leukopenia and agranulocytosis, and slower titration and lower final doses are recommended (Bishara & Taylor, 2014). In 2015, the FDA started a new program called Clozapine Risk Evaluation and Mitigation Strategy (REMS) to replace the individual patient registries and the National Non-Rechallenge Master File. This lowered the threshold of the absolute neutrophil count for treatment interruption from 1500 to 1000/μL and removed white blood cell count thresholds from the monitoring algorithm (Sultan, Olfson, Correll, & Duncan, 2017).

A full list of second-generation antipsychotics currently available in the United States can be found in Table 23.1. The table lists the receptor activity that is thought to contribute to their antipsychotic effect, along with their major metabolic pathway(s), requirement for renal and hepatic dosing (if any), and recommendations from the FDA for use in older adults. Second-generation antipsychotics are also now approved for a number of nonpsychotic indications, which are also listed in the table. Specific data regarding safety and effectiveness in older adults are largely unavailable for the newer second-generation antipsychotics, because too few patients aged 65 and above were included in the pivotal drug trials that were conducted to obtain FDA approval.

Since all first- and second-generation antipsychotics have generally comparable efficacy, adverse effects can help differentiate between available agents.

Anticholinergic activity

Antipsychotic drugs such as chlorpromazine, thioridazine, clozapine, and olanzapine have intrinsic muscarinic-blocking properties and should be used with extreme caution in older adults due to their increased sensitivity for anticholinergic

TABLE 23.1 Comparison of the second-generation antipsychotics available in the United States in 2019.

Antipsychotic (Brand name) *Available formulations*	Predominant receptor activity	Metabolic pathway(s) (major pathway(s) in bold)	FDA-approved indications other than for the treatment of psychotic disorders	Comments
Clozapine (Clozaril) *Avail as tab, ODT*	D_2 (weak), D_4, $5HT_{2A}$, $5HT_{2C}$ and $5HT_{3C}$ antagonist, partial agonist at $5HT_{1A}$; D_4 affinity particularly high	**CYP1A2**, CYP2D6, CYP3A4	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder	Dose reduction may be required in renal and hepatic disease; multiple adverse effects possible in older adults—orthostatic hypotension, tachycardia, anticholinergic side effects—requiring careful titration of dose
Risperidone (Risperdal, Risperdal Consta) *Avail as tab, ODT, solution, long-acting injection*	D_2 and $5HT_{2A}$ antagonist	**CYP2D6**	Bipolar I disorder—acute mania/mixed episodes; irritability in autistic disorder in children and adolescents	Renal and hepatic dosing required; monitor for orthostatic hypotension in the elderly; risk of mortality may be higher in older adults with dementia who receive risperidone with furosemide
Olanzapine (Zyprexa, Zyprexa Relprevv) *Avail as tab, ODT, injection, long-acting injection with limited distribution in the United States*	D_{1-4}, $5HT_{2A}$, $5HT_{2C}$, and $5HT_6$ antagonist	**CYP1A2**, CYP2D6, flavin mono-oxygenase system	Bipolar I disorder—acute mania/mixed episodes; agitation due to schizophrenia or bipolar I disorder; acute depression in bipolar I disorder; acute treatment of treatment-resistant major depressive disorder (with fluoxetine as Symbyax)	No renal or hepatic dosing required; mean elimination t1/2 1.5 times greater in those 65 and above compared to younger adults
Quetiapine (Seroquel, Seroquel XR) *Avail as tab, ER tab*	D_2 and $5HT_{2A}$ antagonist	**CYP3A4**	Bipolar I disorder manic/mixed episodes; depressive episodes in bipolar disorder; adjunctive treatment of major depressive disorder (XR only)	Only hepatic dosing required; oral clearance of quetiapine reduced by 40% in patients above age 65 compared to young patients requiring dosing adjustment
Ziprasidone (Geodon) *Avail as cap, injection*	D_2, $5HT_{2A}$, and $5HT_{1D}$ antagonist; $5HT_{1A}$ agonist; inhibits synaptic reuptake of serotonin and norepinephrine	**Aldehyde oxidase** (two-thirds), CYP3A4 and CYP1A2 (one-third)	Bipolar I disorder, manic/mixed episodes	No renal or hepatic dosing required; pharmacokinetics not altered in adults above age 65
Aripiprazole (Abilify, Abilify MyCite, Abilify Maintena, Aristada, Aristada Initio) *Avail as tab, ODT, solution, long-acting injection; short-acting injection has been discontinued*	Partial D_2 and $5HT_{1A}$ agonist, $5HT_{2A}$ antagonist	**CYP2D6, CYP3A4**	Acute treatment of manic/mixed episodes in bipolar I disorder; adjunctive treatment of major depressive disorder; irritability associated with autistic disorder; treatment of Tourette's disorder	No renal or hepatic dosing required; no data regarding use in older adults

Paliperidone ER (Invega, Invega Sustenna) *Available as ER tab, long-acting injection*	D_2 and $5HT_{2A}$ antagonist	Minimal CYP metabolism	Schizoaffective disorder as monotherapy or adjunctive treatment	Renal dosing required; data in older adults with schizophrenia suggests no change in dose if renal function is adequate
Asenapine (Saphris) *Avail as sublingual tab, transdermal patch has been approved by the FDA*	$5HT_{2A}$, $5HT_{2C}$, $5HT_6$, $5HT_7$, D_2, D_3, and D_4 antagonist, highest affinity for $5HT_{2C}$ and low affinity for D_2 receptors, clinical significance of this is unknown	**CYP1A2, UGT1A4**	In bipolar I disorder—acute treatment of manic or mixed episodes; adjunctive treatment to lithium or valproate in adults; maintenance monotherapy in adults	Renal dosing not required; contraindicated in severe hepatic disease; no data regarding use in older adults but caution advised
Brexpiprazole (Rexulti) *Avail as tab*	Partial D_2 and $5HT_{1A}$ agonist with less intrinsic D_2 receptor activity than aripiprazole, $5HT_{2A}$ antagonist	**CYP2D6, CYP3A4**	Adjunctive treatment in major depressive disorder	Renal and hepatic dosing required; start lower doses in older adults
Lurasidone (Latuda) *Avail as tab*	D_2, $5HT_{2A}$, and $5HT_7$ antagonist; clinical benefit of $5HT_7$ antagonism is unknown	**CYP3A4**	Acute treatment of depressive episodes in bipolar I disorder as monotherapy or adjunct treatment	Only renal dosing required; no data regarding use in older adults
Iloperidone (Fanapt) *Avail as tab*	D_2 and $5HT_{2A}$ antagonist	**CYP2D6, CYP3A4**	None	Renal dosing not required; contraindicated in severe hepatic disease; no data regarding use in older adults
Cariprazine (Vraylar) *Avail as cap*	Potent D_3 and D_2 receptor partial agonist, partial agonist at $5HT_{1A}$ receptors, antagonist at $5HT_{2B}$, $5HT_{2A}$, and H_1 receptors	**CYP3A4**, CYP2D6	Acute treatment of manic or mixed episodes in bipolar I disorder	Renal and hepatic dosing not required; start lower doses in older adults
Pimavanserin (Nuplazid) *Avail as cap*	Potent and selective $5HT_{2A}$ inverse agonist	**CYP3A4**, CYP2J2, CYP2D6		Contraindicated in severe renal impairment and in hepatic impairment; no dose adjustments in older adults required

ODT, orally dissolving tablet; *t1/2*, elimination half-life; *ER*, extended release; *FDA, united states food and drug administration; 5HT*, 5-hydroxytryptamine; *D*, dopamine; *CYP*, cytochrome P450; *UGT*, uridine 5′-diphospho-glucuronosyltransferases; *GAD*, generalized anxiety disorder.

side effects, as discussed in the section on pharmacodynamics earlier. Use of second-generation antipsychotics such as quetiapine, risperidone, asenapine, lurasidone, aripiprazole, brexpiprazole, or cariprazine should be favored due to their low intrinsic anticholinergic activity.

Antihistaminic activity

Antipsychotics with potent intrinsic H_1-blocking activity, such as chlorpromazine, thioridazine, clozapine, olanzapine, and quetiapine, can lead to excessive sedation in older patients and should be avoided in older adults, while less sedating agents such as ziprasidone, risperidone, aripiprazole, and brexpiprazole should be preferred. However, sedation can also be useful; for example, a very low dose of quetiapine 12.5−25 mg at bedtime is often used to treat insomnia.

Dizziness and hypotension

Antipsychotics such as chlorpromazine, thioridazine, clozapine, olanzapine, quetiapine, and iloperidone are potent adrenergic α_1-receptor blockers, which can increase the risk of dizziness, orthostasis, and falls in older adults.

QTc interval prolongation

Drugs that can cause QTc prolongation, especially haloperidol, thioridazine, ziprasidone, clozapine, and quetiapine, should be used with caution and preferably after obtaining a baseline electrocardiogram (EKG) to help track any treatment-induced QTc changes. Other risk factors include congenital long QT syndrome, bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Ziprasidone initially received a lot of attention due to its QTc-prolonging effect, but postmarketing evidence revealed that the cardiac concerns with ziprasidone vis-à-vis other second-generation antipsychotic were largely unfounded (Camm et al., 2012).

Metabolic syndrome

Metabolic syndrome in the medically vulnerable older population is another serious adverse effect, which is seen most frequently seen with clozapine and olanzapine. In the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's disease (CATIE-AD) study, olanzapine and quetiapine were significantly associated with weight gain, and olanzapine was significantly associated with decreases in high-density lipoprotein cholesterol and increased girth vis-à-vis placebo (Zheng et al., 2009). On the other hand, there was no evidence of weight gain for up to one year in an open-label study of risperidone in older adults with psychosis (Barak, 2002). When metabolic syndrome is a concern, use of risperidone, ziprasidone, aripiprazole, asenapine, or lurasidone is preferable, as they all appear to carry a lower risk for inducing a metabolic syndrome.

Extrapyramidal symptoms

EPS are directly related to the D_2-blocking potency of antipsychotics and include drug-induced parkinsonism and acute akathisia. A lower D_2/D_3 receptor occupancy threshold of around 60% is adequate for EPS to occur in older adults (Graff-Guerrero et al., 2015). The risk of EPS appears to be related to both dose and duration of treatment. A meta-analysis of trials that compared risperidone to placebo in AD dementia found that the risk of EPS with risperidone was dose-related over the first 12 weeks (Ballard & Howard, 2006). In a one-year multicenter open-label study of risperidone in older adults with psychosis (mean age 72 years) (Davidson et al., 2000), 41% patients required concurrent anti-parkinsonian medication initially but the need dropped to 26% patients over the course of the study. Among the second-generation antipsychotics, aripiprazole and olanzapine particularly worsen parkinsonism (Goetz, Blasucci, Leurgans, & Pappert, 2000; Friedman et al., 2006) and should be avoided in patients with idiopathic Parkinson's disease, while clozapine and quetiapine have a lower potential to cause parkinsonism. Unlike aripiprazole, brexpiprazole has a much lower propensity to cause EPS, both acute akathisia and parkinsonism, likely due to its 10-fold higher binding affinities for $5HT_{1A}$ and $5HT_{2A}$ receptors and lower intrinsic D_2 receptor activity compared to aripiprazole (Maeda et al., 2014). Its relatively benign side-effect profile suggests that it may be an effective treatment for Parkinson's disease psychosis, but this has only been reported in a single case report so far (Sanagawa, Shiraishi, Sekiguchi, Akechi, & Kimura, 2019).

Olanzapine, quetiapine, ziprasidone, and risperidone among the older second-generation antipsychotics, and asenapine, lurasidone, cariprazine, and especially aripiprazole among the newer second-generation antipsychotics have a higher propensity to cause acute akathisia (Kahn et al., 2008; McCormack, 2015; Thomas, Caballero, & Harrington, 2015). Mirtazapine should be tried first (off-label use) to treat drug-induced acute akathisia in older adults, since

treatment of akathisia with propranolol can cause or worsen bradycardia and hypotension; the efficacy of mirtazapine in treating acute akathisia is thought to be related to its $5HT_{2A}$ antagonism (Poyurovsky, Bergman, Pashinian, & Weizman, 2014).

Hyperprolactinemia

This is directly related to the central D_2-blocking effects of antipsychotics, as dopamine from the hypothalamic neurons exerts the major inhibitory effect on the pituitary lactotrophs. Risperidone, and especially its active metabolite 9-hydroxy-risperidone, cause the most hyperprolactinemia among the second-generation antipsychotics, which may occur early during treatment and a dose−response relationship may not exist (David, Taylor, Kinon, & Breier, 2000; Knegtering et al., 2005). In a placebo-controlled RCT of patients with AD/vascular/mixed dementia and psychosis who were treated with risperidone, olanzapine, or placebo, those on risperidone had a 616% mean increase in circulating prolactin levels, compared with a 77% increase found in olanzapine-treated patients. Also, significantly more risperidone-treated patients had treatment-emergent abnormally high prolactin levels (78%) relative to olanzapine (17%) or placebo-treated patients (5%) (Deberdt et al., 2005). Many of the symptoms of hyperprolactinemia overlap with physiological changes in older adults, such as a reduction in bone mineral density, diminished ejaculate volume and gynecomastia in males, oligomenorrhea and reduced vaginal lubrication in females, and reduced libido in both sexes (Romijn, 2014), so it is more difficult to diagnose in older adults unless there is a high degree of vigilance. Use of lower doses of antipsychotics within the therapeutic range should be the first step toward reducing the risk. A reanalysis of CATIE data found that while a D_2 receptor occupancy of 65%−80% is necessary for antipsychotic effectiveness, hyperprolactinemia occurs at a lower occupancy of about 68%−70% for risperidone and only 55% for ziprasidone (Tsuboi et al., 2013). Use of adjunctive aripiprazole is another option if a prolactin elevating antipsychotic cannot be reduced or stopped. Aripiprazole 5−15 mg/day has been shown to lower prolactin levels and reduce or normalize sexual adverse effects of hyperprolactinemia in *premenopausal* women with psychosis (Kelly et al., 2018), and there is no reason to believe that the benefits will not be similar in the older population. Finally, the risk of breast cancer increases with age (Benz, 2008), and hyperprolactinemia can further increase the risk of breast cancer recurrence regardless of estrogen receptor status; even patients with carcinoma in situ are at higher risk (Rahman et al., 2014).

Tardive dyskinesia

The risk of TD appears to be much lower in older adults receiving second-generation antipsychotics. In a population of mixed-age patients (56% at or above age 65) with various psychotic disorders (21% schizophrenia, 21% mood disorders, 25% AD), the cumulative incidence of TD was 26%, 52%, and 60% after 1, 2, and 3 years of first-generation antipsychotic exposure, respectively (Jeste et al., 1995). Cumulative exposure to high-potency first-generation antipsychotics was a major risk factor for TD in multivariate analysis in the study, while age was significant only in univariate analysis, likely because its effects were secondary to other factors that were a function of age such as cumulative antipsychotic exposure. Among the second-generation antipsychotics, risperidone is the closest pharmacologically to a first-generation antipsychotic in terms of its D_2 blockade, but the risk of TD is low in older adults even with risperidone, both in primary psychotic disorders and in dementia-related psychosis. In a 1-year open-label study of 255 older institutionalized adults (mean age 82.5 years) with Alzheimer's, vascular, or mixed dementia and without dyskinesia at baseline, the cumulative incidence of persistent emergent TD on risperidone was only 2.6%. Even more surprisingly, those who had dyskinesia at baseline experienced significant reductions in the severity of dyskinesia (Jeste, Okamoto, Napolitano, Kane, & Martinez, 2000). Similarly, a one-year multicenter open-label study of risperidone in older adults with a DSM-III-R psychotic disorder (mean age 72 years) found a low rate of 4.3% for treatment-emergent TD, while preexisting dyskinesia again improved with treatment (Davidson et al., 2000).

Evidence-based drug treatment of psychotic disorders in older adults

There is no single antipsychotic drug that is ideal for use in every patient. Clinicians need to review the pharmacokinetic and pharmacodynamic properties and adverse effect profiles before matching a drug to a patient, and the information in Table 23.1 should be used in the decision-making process. Despite the paucity of drug trials in older adults with primary psychotic disorders, the few that have been done have found antipsychotics to be safe and effective. An international multisite double-blind trial compared risperidone and olanzapine in 175 relatively stable older adults over age 60 with chronic schizophrenia (DSM-IV criteria with mean duration of illness of 36.5 years) over 8 weeks and found them to be both effective and well tolerated (Jeste, Barak, Madhusoodanan, Grossman, & Gharabawi, 2003). Risperidone has been shown result in continued symptom improvement for up to one year in the treatment of DSM-III-R psychotic

disorders (schizophrenia, schizophreniform and delusional disorder) in a multicenter open-label study of older adults (mean age 72 years) with a mean dose at end-point of 3.7 mg/day (Davidson et al., 2000). A single double-blind, placebo-controlled study with 6-month open-label extension of paliperidone ER (3−12 mg/day) in older adults (mean age 70 ± 4.5 years) with schizophrenia (Tzimos et al., 2008) likewise found it to be safe and effective. Note that the mean age of onset of schizophrenia in all groups in this study was in the mid-30s, though some patients with late-onset schizophrenia were included in all groups. Perhaps the most important trial was the Antipsychotic Treatment of very Late-onset Schizophrenia-like psychosis trial (ATLAS), a single randomized, controlled, double-blind trial of low-dose amisulpride (a drug not available in the United States) in patients with very late−onset schizophrenia-like psychosis (mean age around 80 years), and it was found it to be safe and effective in treating psychotic symptoms (Howard et al., 2018). Participant-rated, subjective changes in health-related quality of life did not improve, however.

Two key issues appear to be critical for the successful treatment of the late-onset primary psychotic disorders. The first is the use of lower doses, which is supported by evidence from an open-label study that clinical stability in older adults with schizophrenia may require striatal D_2/D_3 receptor occupancy of only 50%−60% in patients on risperidone and olanzapine, compared to around 65%−80% in younger adults (Graff-Guerrero et al., 2015); it is unclear if these results can be extrapolated to other antipsychotics. Antipsychotics should be started in the lowest possible doses and titrated upward very gradually in small increments. In order to obtain lower doses, liquid preparations can be used, which may be dissolved in a beverage to improve adherence.

The second is the issue of adequate engagement of patients. In a study that looked at very late−onset schizophrenia-like psychosis patients in a mental health service that were followed for 12 months, or to the point of discharge from the service if it was before 12 months (Sin Fai Lam, Reeves, Stewart, & Howard, 2016), slightly more than one-fourth were taking antipsychotics at 12 months or at point of discharge, 55% were lost to follow-up or had not engaged with specialist services and almost 20% had engaged with services but were not receiving antipsychotic treatment, which was attributed to poor insight. This is particularly unfortunate, since hospitalized patients with very late−onset schizophrenia-like psychosis appear to have a better short-term treatment response compared to long-stay older adults with chronic schizophrenia with onset before age 40 with an acute psychotic exacerbation (Barak, Aizenberg, Mirecki, Mazeh, & Achiron, 2002). In this study, very late−onset schizophrenia-like psychosis was defined as starting at or above age 70, and the mean age of this group was 78.1 years.

Bipolar disorder in older adults

Introduction

About a quarter of all patients with bipolar disorder are 60 or older (Dols et al., 2016; Sajatovic, Blow, Ignacio, & Kales, 2005). There are no specifiers for the bipolar disorders in DSM-5 pertinent to older adults (Kaltenboeck, Winkler, & Kasper, 2016), implying that the phenomenology of bipolar disorder is similar in older and younger adults, which is largely true (Almeida & Fenner, 2002). The increased prevalence of physical illnesses is perhaps the greatest difference between younger and older adults with bipolar disorder, with 3−4 comorbid physical diseases in older patients, while psychiatric comorbidity is lower in older than in younger bipolar patients, with anxiety and substance use being the most common (Lala & Sajatovic, 2012). When older adults with earlier-onset illness are compared to those with late-onset illness, those with earlier-onset illness appear to be more ill and utilize more health services than those with new-onset illness later in life who have fewer mental health visits, likely because of a shorter duration of exposure to high-risk factors in the older-onset group (Sajatovic, Blow, et al., 2005). Similarly, a community-based study out of Australia (Almeida, Hankey, Yeap, Golledge, & Flicker, 2018) found that patients with older-onset bipolar disorder have a *lower* prevalence of cardiovascular disorders. Incidentally, renal diseases were also *not* more common in the early-onset group despite the higher risk of long-term exposure to lithium in this group. The association of lithium exposure with renal toxicity is discussed in more detail in the next section.

Risks of dementia and mortality were similar in both groups, but the causes of mortality differed according to age of onset—suicides and accidents were more common in the younger-onset group while strokes and neurodegenerative diseases were more common in the older-onset group. Strokes and neurodegenerative disorders in older adults also independently increase the risk of disinhibited and impulsive behaviors, which are often mistaken for mania or hypomania, and such patients who present with what has been called "secondary mania" (Krauthammer & Klerman, 1978) require a thorough workup, which may include neuroimaging, for diagnostic clarification. A comprehensive list of causes of secondary mania due to neurological and systemic illnesses as well as medications can be found in Van Gerpen, Johnson, & Winstead, 1999. Sustained manic-like states without grandiosity or euphoria should also raise suspicion of

behavior-variant frontotemporal dementia (bv-FTD;Wylie, Shnall, Onyike, & Huey, 2013). Conversely, euphoria is the least common neurobehavioral symptom in AD dementia (Zhao et al., 2016).

Drugs for the treatment of bipolar disorder

Drug trials of bipolar disorder in older adults are relatively few in number and have only involved the conventional mood stabilizers. While a number of second-generation antipsychotics are now FDA-approved for the treatment of bipolar disorder in older adults, either as monotherapy as an adjunct to lithium or divalproex, they have not been specifically studied in older patients (Vasudev et al., 2018), with the exception of lurasidone and asenapine. A full list of FDA-approved and Canadian Network for Mood and Anxiety Treatments (CANMAT) recommended drugs for the treatment of bipolar disorder can be found in Table 23.2.

The drugs used and the basic principles of drug treatment of bipolar disorder are essentially the same for older and younger adults, but drug doses, precautions, and adverse effects are somewhat different in older adults.

Lithium

Lithium is still the drug of choice for adults of all ages with bipolar disorder, and its use in older adults is supported by considerable evidence (Fotso Soh, Klil-Drori, & Rej, 2019). The CANMAT guidelines designate it as a first-line treatment for acute mania, for acute depression in bipolar I disorder after quetiapine and adjunctive lurasidone, and for the prevention of any mood episodes. Unfortunately, lithium monotherapy for the treatment of bipolar disorder in older adults continues to be underutilized, and in a large Canadian study (Rej et al., 2017) that looked at psychotropic medication prescribing pattern in the 30 days after discharge from a psychiatric hospital, only 1.4% of the patients were on lithium monotherapy while about 40% were on conventional antidepressant medications that are not usually indicated in bipolar disorder.

One major issue that negatively impacts the selection of lithium as the drug of choice in older adults with bipolar disorder is the uncertainty about the optimal serum level in older adults. Older adults generally require lower doses of lithium vis-à-vis younger adults to achieve the same target serum levels (Hewick, Newbury, Hopwood, Naylor, & Moody, 1977). The International Society for Bipolar Disorders (ISBD) Task Force on lithium (Nolen et al., 2019) was unable to reach a consensus about the optimal lithium level in the maintenance treatment of bipolar disorder, but the majority of the members endorsed a level between 0.40 and 0.60 mmol/L, with the option to go up to a maximum of 0.80 mmol/L at ages 65−79 years and up to 0.70 mmol/L over age 80 years. In the oldest-old and very frail individuals, even levels as low as 0.2−0.4 mmol/L may be effective and well tolerated. Older adults should be started on lithium at a dose of 150 mg/day, and the 12-hour trough lithium level 5−7 days later should be used to guide further dose changes (Fotso Soh et al., 2019). A lithium level should also be rechecked 5−7 days after starting another medication that can increase serum lithium levels. In older adults, angiotensin-converting enzyme inhibitors, diuretics (especially thiazides and osmotic diuretics), NSAIDs, and COX-2 inhibitors are the most common offending agents (Finley et al., 1995; Sajatovic, Strejilevich, et al., 2015). Giving lithium as a single bedtime daily dose is advantageous over multiple doses a day as it increases adherence, even though a single daily dosing possibly increases renal toxicity (Carter, Zolezzi, & Lewczyk, 2013) as it results in a 10%−15% higher 12 ± 1 hour trough lithium level (Amdisen, 1977).

Common adverse events reported during lithium treatment include dyspraxia, tremor, xerostomia, headache, infection, amnesia, dizziness, diarrhea, nausea, and fatigue (Sajatovic, Gyulai, et al., 2005). Major concerns include adverse effects related to the kidney, thyroid and parathyroid glands. A large retrospective analysis of lab data from the United Kingdom found that patients receiving lithium appear to develop chronic kidney disease stage III fairly quickly after treatment initiation, that high-median serum lithium levels appear to be a risk factor for the long-term adverse effects related to the kidneys, thyroid and parathyroid glands, and young women appear to be at especially high risk for renal impairment and hypothyroidism (Shine, McKnight, Leaver, & Geddes, 2015). Chronic renal failure may eventually affect about a third of patients who have been on lithium for 10−29 years, but only about 5% have severe disease (Aiff et al., 2015). Adverse effects related to the kidneys also include nephrogenic diabetes insipidus, the prevalence of which varies widely (2%−85%) in older adults, and risk factors include lithium duration, dose, level, slow-release formulation, and clinical nonresponse (Rej, Herrmann, & Shulman, 2012). Polyuria (24-hour urine volume >3 L) may be present in up to 70% of subjects, which can be highly distressing and is usually underreported (Pradhan, Chakrabarti, Irpati, & Bhardwaj, 2011).

Older age, female sex and diabetes mellitus are risk factors for lithium-induced hypothyroidism, which also appears to occur earlier in the treatment course than previously assumed (Shine et al., 2015). Lithium-induced hypercalcemia is well known but its prevalence is not (Lehmann & Lee, 2013). Older women have been found to be at highest risk of

TABLE 23.2 Medications for the treatment of bipolar disorder in the United States in 2019.

Medication (Brand name) *Available formulations*	FDA-approved indications in bipolar disorder	CANMAT 2018 recommendations
Mood stabilizers		
Lithium (Eskalith, Lithobid) *Avail as cap, tab, ER tab, solution*	Manic episodes and maintenance treatment	First-line for acute mania or bipolar depression First-line for prevention of any mood episode
Carbamazepine ER (Tegretol XR, Carbatrol ER, Equetro ER) *Avail as ER tab, ER cap*	No indication for bipolar disorder	Second-line for acute mania Second-line for prevention of any mood episode
Divalproex DR and ER (Depakote DR, Depakote ER, Depakote sprinkles) *Avail as DR tab, DR cap, ER tab*	Manic episodes	First-line for acute mania and for prevention of any mood episode Second-line for acute bipolar depression
Lamotrigine IR (Lamictal) *Avail as tab, ODT, chewable*	Maintenance treatment of bipolar I disorder	First-line for acute bipolar depression First-line for prevention of any mood episode
Second-generation antipsychotics (see Table 23.1 for brand names, available formulations and approved indications other than for bipolar disorder)		
Aripiprazole oral	Acute treatment of manic/mixed episodes in bipolar I disorder	First-line for acute mania as monotherapy or adjunct to lithium/divalproex;First-line for prevention of any mood episode as monotherapy or adjunct to lithium/divalproex
Aripiprazole IM short-acting[a]	Manic agitation	First-line for manic agitation
Aripiprazole IM long-acting	No indication in bipolar disorder	First-line for maintenance for prevention of any mood episode

Asenapine SL	Acute treatment of manic/mixed episodes in bipolar I disorder as monotherapy or adjunct to lithium/divalproex;	First-line for acute mania as monotherapy or adjunct to lithium/divalproex Second-line for manic agitation
	Maintenance treatment of bipolar I disorder as monotherapy	
Cariprazine	Acute treatment of manic or mixed episodes in bipolar I disorder	First-line for acute mania
		Second-line for acute bipolar depression
Lurasidone	Acute treatment of depressive episodes in bipolar I disorder as monotherapy or adjunct to lithium/divalproex	First-line for acute bipolar depression as monotherapy or adjunct to lithium/divalproex
		Second-line for prevention of any mood episode as adjunct to lithium/divalproex
Ziprasidone oral	Acute treatment of manic or mixed episodes in bipolar I disorder	Second-line for acute mania as monotherapy
		Second-line for prevention of any mood episode as adjunct to lithium/divalproex
Ziprasidone IM	Acute agitation in schizophrenia	Second-line for manic agitation
Olanzapine oral	Acute treatment of manic/mixed episodes in bipolar I disorder as monotherapy or adjunct to lithium/divalproex;	Second-line for acute mania as monotherapy or adjunct to lithium/divalproex
	Maintenance treatment of bipolar I disorder as monotherapy	Second-line for maintenance of any mood episode
Olanzapine IM short-acting	Manic agitation in bipolar I disorder	First-line for manic agitation
Quetiapine	Acute treatment of manic episodes in bipolar I disorder as monotherapy or adjunct to lithium/divalproex	First-line for acute mania as monotherapy or adjunct to lithium/divalproex
	Depressive episodes in bipolar disorder	First-line for acute bipolar depression
	Maintenance treatment of bipolar I disorder as adjunct to lithium/divalproex	First-line for prevention of any mood episode as monotherapy or adjunct to lithium/divalproex
Quetiapine XR	Acute treatment of manic episodes in bipolar I disorder as monotherapy or adjunct to lithium/valproate	
	Depressive episodes in bipolar disorder	
	Maintenance treatment of bipolar I disorder as adjunct to lithium/divalproex	

(*Continued*)

TABLE 23.2 (Continued)

Medication (Brand name) *Available formulations*	FDA-approved indications in bipolar disorder	CANMAT 2018 recommendations
Risperidone oral and ODT	Acute treatment of manic/mixed episodes in bipolar I disorder as monotherapy or adjunct to lithium/divalproex	Tab first-line for acute mania as monotherapy or adjunct to lithium/divalproex
		ODT second-line for manic agitation
Risperidone IM long-acting	Maintenance treatment in bipolar I disorder as monotherapy or adjunct to lithium/divalproex	Second-line for prevention of any mood episode as monotherapy or adjunct to lithium/divalproex
First-generation antipsychotics		
Chlorpromazine *Avail as tab, inj*	Mania	
Antidepressant-antipsychotic fixed-dose combination (polypill)		
Olanzapine-fluoxetine fixed-dose combination (Symbyax) *Avail as cap*	Depressive episodes in bipolar I disorder	Second-line for acute depression in bipolar I disorder

CANMAT, Canadian Network for Mood and Anxiety Treatments; *DR*, delayed release; *ER*, extended release; *XR*, extended release; *ODT*, orally dissolving tab; *IM*, intramuscular; *IR*, immediate release.
[a]*No longer available in the United States.*

developing hypercalcemia (Shine et al., 2015), but others have found low levels of hypercalcemia with high rates of intact parathyroid hormone (iPTH) and high rates of vitamin D deficiency, which can mask the hypercalcemia of lithium-induced hyperparathyroidism (van Melick, Wilting, Ziere, Kok, & Egberts, 2014). No association appears to exist between hypercalcemia and lithium dose or duration of therapy (Lehmann & Lee, 2013; van Melick et al., 2014).

Regular lab monitoring is important in older adults maintained on lithium. The ISBD task force recommends checking a lithium level and renal function tests every 3−6 months, thyroid-stimulating hormone, fasting total cholesterol, fasting glucose, triglycerides, body weight, waist circumference, and serum calcium every 6−12 months and a complete blood count every 12 months (Shulman et al., 2019). The CANMAT guidelines also recommend "routine" testing of serum calcium levels at an undefined frequency, but that may not be adequate given the high rates of Vitamin D deficiency in these patients, and iPTH and 25-hydroxy-vitamin D levels may also need to be monitored to screen for lithium-induced hyperparathyroidism.

The major drug−illness interaction in older adults involves the increased risk of lithium toxicity due to dehydration and diarrhea. In the first systematic review of lithium toxicity in older adults, the mean dose of lithium was only 675 mg/day and the most common symptoms in older adults were neurological, including mental status changes especially impaired ability to sustain and shift attention, delirium, tremor, and ataxia, and GI, including nausea and vomiting (Shulman et al., 2019). Hemodialysis is the treatment of choice for severe lithium toxicity as it completely removes lithium from the blood. Conversely, in older adults who are on hemodialysis for end-stage renal failure, a situation that is not infrequently encountered in clinical practice, lithium should be given in a low dose (300−600 mg) after dialysis, and initially, levels should be checked after each dialysis session; subsequently, levels can be checked monthly (Levy, 1990).

Divalproex

Divalproex is a mixture of valproic acid and its sodium salt in a 1:1 molar ratio. The CANMAT guidelines designate it as a first-line treatment for acute mania after lithium and quetiapine, a second-line treatment for acute depression in bipolar I disorder, and a first-line treatment for prevention of any mood episode after lithium and quetiapine. Target serum levels in older adults for the acute and maintenance phases have not been clearly defined. The CANMAT guidelines recommend a target serum level for divalproex of 50−100 mcg/mL in the acute phase, obtained 3−5 days after the most recent dose titration (Yatham et al., 2018).

Valproic acid is mainly metabolized via several UGT enzymes and mitochondrial β-oxidation (Ghodke-Puranik et al., 2013), and its clearance appears to be unchanged in older adults compared to their younger counterparts (Fattore et al., 2006), likely because the UGT enzyme system remains relatively unaffected by the aging process. As discussed in the section on pharmacokinetics, valproic acid is a highly albumin-bound capacity-limited drug with reduced hepatic clearance of the free fraction in the presence of age-related hypoalbuminemia, while the clearance of the total drug remains unchanged or even increases (Butler & Begg, 2008). Since total valproic acid concentrations are usually measured, a correction factor for hypoalbuminemia can be used to "normalize" total serum valproic acid concentrations when they are <75 μg/mL (Hermida & Tutor, 2005), but this correction may underestimate the free valproic acid fraction in up to a third of outpatients (Drisaldi et al., 2019). Protein binding also becomes highly variable in patients who are extremely sick physically, and total valproic acid concentrations cannot adequately predict the free fraction in these patients even when the correction for hypoalbuminemia is applied (Riker et al., 2017). The free valproic acid level should be preferentially utilized to guide dose titration in older adults with hypoalbuminemia or a serious physical illness, but current treatment guidelines do not address this issue.

While Depakote DR and ER are typically lumped together in guidelines, there is an important difference between them, apart from the once-daily dosing of the ER formulation. If dosed in a single bedtime daily dose, the serum level for the ER formulation should be drawn around 18−21 hours later, which is typically around 2−5 pm, which will still result in concentrations that are 3%−13% higher than true trough values (Reed & Dutta, 2006). If drawing blood later in the afternoon is not possible due to patient inconvenience or unavailability of a phlebotomist, Depakote ER should be dosed once daily in the afternoon around 2−3 pm so that a near-trough level is obtained with a morning blood draw.

While there is a perception that older adults are generally more susceptible than younger adults to the adverse effects of AEDs, including divalproex, there is little evidence to support this (Stephen, 2003). The most common side effects that adversely affect medication adherence in mixed-age adults include weight gain, hair loss, transaminitis, and GI-related side effects, which range from the relatively benign such as nausea to the serious and potentially fatal, such as pancreatitis (Murru et al., 2015). Pancreatitis typically occurs early in treatment (up to almost 70% of all cases of pancreatitis occurred within the first year in one review of patients receiving the medication to treat epilepsy), early

discontinuation of the medication is usually effective in preventing more serious reactions and a rechallenge is totally contraindicated in all such patients (Asconape, Penry, Dreifuss, Riela, & Mirza, 1993). Dose-dependent thrombocytopenia is common but usually asymptomatic (Nasreddine & Beydoun, 2008). Valproate-induced hyperammonemic encephalopathy (VHE) should be suspected in patients on divalproex who present with lethargy, GI symptoms, confusion, and an increase in seizure frequency (in those receiving divalproex for treatment of epilepsy) at any point in treatment. Risk factors among psychiatric patients include DDIs, mental retardation, carnitine deficiency, and presence of urea cycle disorders (Chopra, Kolla, Mansukhani, Netzel, & Frye, 2012). Discontinuing the offending medication is the definitive treatment, although successful treatment with carnitine supplement has been reported (Segura-Bruna, Rodriguez-Campello, Puente, & Roquer, 2006). Asymptomatic hyperammonemia is also seen in patients receiving divalproex (Carr & Shrewsbury, 2007), and stopping divalproex simply due to an increased ammonia level in the absence of VHE symptoms is usually not indicated.

Carbamazepine and oxcarbazepine

Even though carbamazepine is recommended as second-line treatment for acute mania after olanzapine and for the prevention of any mood episode after olanzapine and risperidone long-acting injections in the 2018 CANMAT guidelines, it is not FDA-approved for the treatment of bipolar disorder. Common adverse effects include neurological (ataxia, dizziness, drowsiness), GI (nausea and vomiting) and changes in visual acuity (blurred vision and diplopia) (Murru et al., 2015), which can all be very problematic in older adults. Hyponatremia is a well-known adverse effect of carbamazepine that is also more common in older adults (Berghuis et al., 2017) and is further exacerbated by concurrent use of other medications that also cause hyponatremia, such as the SSRIs and diuretics, which are commonly used in older adults. Less common side effects include leukopenia and anemia, while severe aplastic anemia, agranulocytosis, and pancytopenia are rare (Verrotti, Scaparrotta, Grosso, Chiarelli, & Coppola, 2014). The high risk of SJS and TEN in patients of Asian ancestry and DDIs involving carbamazepine have been discussed already. Since lithium and divalproex are effective drugs that are better tolerated in older adults, carbamazepine is best avoided in older adults with bipolar disorder due to its adverse effect profile and potential for multiple DDIs.

Oxcarbazepine is chemically related to carbamazepine, but differs from the latter in that it causes less hematological adverse effects and more hyponatremia (Dong, Leppik, White, & Rarick, 2005). It also induces CYP3A4 but inhibits CYP2C19 instead of being a pan-inducer of CYP enzymes. Therapeutic drug monitoring is not necessary. Hyponatremia can especially be problematic in older adults, especially in combination with other natriuretic drugs, which can lead to acute cognitive changes and even seizures. It was included as a *third-line* treatment option for acute bipolar mania and as maintenance treatment for bipolar II disorder in the 2013 CANMAT guidelines (Yatham et al., 2013), but is no longer recommended for the treatment of any phase of bipolar disorder in the 2018 CANMAT guidelines (Yatham et al., 2018), and its risk-benefit ratio does not favor the use of oxcarbazepine in older adults for the treatment of bipolar disorder.

Lamotrigine

Even though it is FDA-approved only for the maintenance treatment of bipolar disorder, the 2018 CANMAT guidelines recommend lamotrigine as first-line treatment for acute depression in bipolar I disorder after quetiapine, lurasidone, and lithium, as well as for the prevention of any mood episode after lithium, quetiapine, and divalproex. Initial evidence from a naturalistic study in mixed-age adults, at least 10% of whom were over 65 years old, indicates that lamotrigine may be even more effective in preventing relapse in bipolar II disorder to both depressive and hypomanic episodes than in bipolar I disorder (Terao, Ishida, Kimura, Yarita, & Hara, 2017). Therapeutic serum levels have not been defined and therapeutic drug monitoring is not indicated for routine clinical use. The FDA-recommended dose of lamotrigine in bipolar disorder is 200 mg/day, which is half the maximum recommended dose for the treatment of epilepsy. In older adults, the FDA recommends "starting at the lower end of the dosing range." In a reanalysis of data on older adults from two maintenance studies of bipolar I disorder in mixed-age adults, the mean age for the lamotrigine group was 62.2 ± 6.1 years and the mean lamotrigine dose was 240 mg (Sajatovic, Gyulai, et al., 2005). Given its lower recommended dose in bipolar disorder, effective doses result in much lower drug levels, for example, a mean of 3.6 mcg/mL in the Comparative Evaluation of Quetiapine-Lamotrigine (CEQUEL) study (Tunbridge et al., 2017), which was a mixed-age study where about 25% of patients with bipolar depression were above the age of 50, and a mean of 3.341 mcg/mL among patients who responded in a retrospective analysis of a large therapeutic drug monitoring database (Unholzer & Haen, 2015).

Limited data suggest that lamotrigine is generally well tolerated in older adults (Sajatovic, Ramsay, Nanry, & Thompson, 2007). When lamotrigine is given as monotherapy in older adults, its clearance is approximately 20% lower than in younger adults, and for any given serum level, older adults are twice as likely to experience significant adverse effects compared to younger adults, the most common being imbalance, drowsiness, and tremor (Arif, Svoronos, Resor, Buchsbaum, & Hirsch, 2011). Levels >10 mcg/mL lead to more adverse effects (in epilepsy patients), while levels <5 mcg/mL are well tolerated by over 90% patients, and cognitive adverse effects have been found to be minimal (in epilepsy patients) at levels below 5 mcg/mL (Hirsch et al., 2004). The most well-known adverse effect of lamotrigine is rash, which is usually benign if the FDA-recommended titration schedule is used. There is no correlation between rash and serum lamotrigine concentrations, and in one study, all those who developed a rash had levels <15 mcg/mL (Hirsch et al., 2004). In a review of 122 RCTs of lamotrigine monotherapy, 8% of patients experienced an adverse dermatologic reaction, but the incidence of SJS/TEN was only 0.04% (Bloom & Amber, 2017). A rash is not more common in older adults on lamotrigine (Sajatovic, Gyulai, et al., 2005).

Lamotrigine is metabolized by the UGT enzymes, mainly UGT1A4 and UGT2B7 (Milosheska et al., 2016). The most common pharmacokinetic DDIs involving lamotrigine are those with other AEDs. The enzyme-inducing AEDs such as carbamazepine, phenytoin, phenobarbital and its prodrug primidone induce the metabolism of lamotrigine, while valproic acid inhibits the clearance of lamotrigine (Grundmann, Koristkova, Brozmanova, & Kacirova, 2017), thus requiring a change in the titration schedule when it is used in combination with these AEDs. Three different color-coded starter packs are available, one each for monotherapy, for use in combination with enzyme-inducing AEDs and for use in combination with divalproex, but using the starter packs is much more expensive than using the regular pills for titration. A preliminary finding from the CEQUEL study was that folic acid supplementation reduces the effectiveness of lamotrigine in those patients who are carriers of the Met allele in the catechol-*O*-methyl transferase gene (Tunbridge et al., 2017), which is an interesting DDI modulated by a gene, but this awaits replication and its mechanism is unknown.

Second-generation antipsychotics

There are no RCTs in older adults of the newer antipsychotics approved for the treatment of bipolar depression (Vasudev et al., 2018), with the exception of lurasidone and asenapine. A posthoc analysis of two double-blind 6-week RCTs of lurasidone (Sajatovic et al., 2016) for the acute treatment of depression in bipolar I disorder in older adults (age 55 and above) found it to be effective and well tolerated, and the benefit was maintained over a 6-month open-label extension period with no increase in mean weight or glycemic indices and with low rates of switching to hypomania or mania. However, patients with clinically significant comorbid psychiatric and physical illnesses were excluded from the trial, so these results should be applied with caution to real-world older adults. Two open-label asenapine trials, one of asenapine as monotherapy in acute mania in patients with a mean age of 67.7 ± 6.1 years (Baruch, Tadger, Plopski, & Barak, 2013) and the other of asenapine as adjunctive treatment in patients of either polarity who had not responded to a mood stabilizer or antidepressant with a mean age of 68.6 ± 6.1 years (Sajatovic, Dines, et al., 2015), found it to be effective in the acute treatment of mania as monotherapy (dose 10 mg twice daily), as well as in the acute treatment of both mania and bipolar depression as adjunctive treatment (mean dose 11.2 ± 6.2 mg). Indirect comparisons of FDA-approved treatments for bipolar depression in younger adults suggest that the olanzapine-fluoxetine polypill, quetiapine IR and XR, and lurasidone may all be somewhat more effective than cariprazine, but weight gain and diarrhea limit the use of olanzapine-fluoxetine, while sedation and dry mouth limit the use of quetiapine (Citrome, 2019), making the relatively weight-neutral lurasidone probably the drug of choice by default for treating depression in bipolar I disorder older adults. Indeed, adjunctive lurasidone and lurasidone monotherapy are both listed as first-line agents for the treatment of acute depression in bipolar I disorder, and adjunctive lurasidone is also listed as a second-line treatment for prevention of any mood episode in the 2018 CANMAT guidelines.

Evidence-based drug treatment of bipolar disorder in older adults

The National Institute of Mental Health (NIMH)-funded multicenter Acute Pharmacotherapy of Late-Life Mania (GERI-BD) study was an RCT that compared lithium and divalproex in the acute treatment of manic, hypomanic, or mixed episodes in patients age 60 or older with bipolar I disorder over a 9-week period (Young et al., 2017); it is important to note that the study did not look at *late-onset* bipolar disorder, since the mean age of onset in the study was around 40 years. Risperidone was used as a rescue medication. Three findings from this study can be applied directly to clinical practice—the response rates did not differ significantly between the lithium and divalproex groups

(79% and 73%, respectively), the need for adjunctive risperidone was low and similar between groups (17% and 14%, respectively) and lithium was associated with a greater reduction in mania scores over the 9 weeks of the study.

There are no studies that have looked at the acute or long-term treatment of depression in bipolar I disorder in older adults, so this data have to be extrapolated from studies in younger adults. The NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (age of study participants approximately 40 ± 12 years, 68% had bipolar I disorder) did not find superiority for conventional antidepressants (paroxetine or bupropion) plus mood stabilizers over placebo plus mood stabilizers in either the acute treatment of bipolar depression or in preventing a treatment-emergent affective switch, thereby questioning the practice of adding conventional antidepressants to mood stabilizers for the acute treatment of bipolar depression. However, it should be noted that roughly a fourth of the participants in both active and placebo arms of the study did not take their mood stabilizers as per protocol (Thase, 2007). Approximately one-half who recovered from an affective episode suffered a depressive recurrence, and one quarter had a manic/hypomanic/mixed recurrence within 1 year despite ongoing treatment. Residual, subthreshold mood elevation symptoms were the single most important predictor of risk of relapse. This does not definitively negate a role for antidepressants in the treatment of depression in (mostly) bipolar I disorder, and STEP-BD certainly did not study treatment options for patients who had *breakthrough* depressive symptoms while on mood stabilizers. The most important contribution of the STEP-BD study was that it provided support for medications other than conventional antidepressants for the treatment of bipolar depression and paved the way for the FDA approval of three second-generation antipsychotics and one antipsychotic-antidepressant polypill combination for the treatment of bipolar depression, which are listed in Table 23.2.

Regarding maintenance treatment, a secondary analysis from two large, placebo-controlled trials of maintenance therapy for bipolar I disorder found that lamotrigine and lithium were effective and well tolerated in adults age 55 years and older (Sajatovic, Gyulai, et al., 2005). Lamotrigine maintenance therapy significantly delayed time-to-intervention for any mood episode as well as depression, whereas lithium maintenance therapy significantly delayed time-to-intervention for mania/hypomania/mixed episodes, but not for depression.

Most of the discussion thus far has been regarding the acute and maintenance treatment of mood episodes in bipolar I disorder. Monotherapy with a conventional antidepressant still appears to have a place in both the acute as well as maintenance treatment of depression in bipolar II disorder (Amsterdam & Shults, 2010a, 2010b). In the 2018 CANMAT guidelines, quetiapine is listed as first-line treatment for depression in bipolar II disorder, while lithium, lamotrigine, adjunctive bupropion, sertraline, and venlafaxine are all listed as second-line drugs (Yatham et al., 2018). Also, quetiapine, lithium, and lamotrigine are listed as first-line agents for the maintenance treatment of bipolar II disorder, while venlafaxine is listed as a second-line drug.

Neurostimulation strategies

Of all the available neurostimulation strategies, only electroconvulsive therapy (ECT) is recommended for the treatment of mood episodes in bipolar disorder. The CANMAT recommendations include use of ECT as second-line treatment for acute mania, as well as acute depression in bipolar I and bipolar II disorder, although data in support of its efficacy in bipolar depression are limited (Yatham et al., 2018). It is both safe and effective, and specific indications for the earlier use of ECT in bipolar disorder include intractable mania, high suicide or medical risk, and when adequate pharmacotherapy has proven to be ineffective (Sajatovic, Strejilevich, et al., 2015).

Major depressive disorder in older adults

Introduction

The prevalence and incidence of major depressive disorder in older adults are lower than in younger adults. About 8%–16% of community-dwelling older adults have clinically significant depressive symptoms (Blazer, 2003). A comprehensive review found that subsyndromal depression in community-dwelling older adults is much more common with a point prevalence of 4%–23% (median prevalence 9.8%), which was 1.1–6.9 (median 2.5) times that of the point prevalence of syndromal depression (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011), and has been reported to be as high as 50% in long-term care settings. The longitudinal risk of developing syndromal depression in patients with subsyndromal depression appears to be 8%–10% annually. The clinical presentation of major depression in older adults includes depression without sadness (Gallo & Rabins, 1999) and a considerable overlap with apathy (Lampe & Heeren, 2004). Bereavement and other losses are also common in older adults, and there are concerns that DSM-5 may have inadvertently pathologized the normative grief response by rescinding the "bereavement exclusion" from the diagnostic

criteria of major depressive disorder (Wakefield & First, 2012), leading to the potential for an increase in the diagnosis of major depressive disorder in older adults and exposing them to the risks of unnecessary treatment with antidepressants. However, clear phenomenological differences between the clinical presentation of major depression in older and younger adults have not been consistently found (Thomas, 2013), and consequently DSM-5 uses the same diagnostic criteria for major depressive disorder, regardless of age at onset.

Depressive symptoms in older adults often precede the development of a dementia and are thought to be either a risk factor for dementia or a prodrome. One of the largest studies to look at this issue followed the trajectories of depressive symptoms prior to the onset of dementia with nine assessments over 28 years (Singh-Manoux et al., 2017). This study found that only depressive symptoms in late life in the decade preceding the dementia diagnosis were associated with an increased risk of dementia, while chronic recurring midlife depressive symptoms were not, which is consistent with the hypothesis that depressive symptoms are either a dementia prodrome or the two share a common etiology, and not with the risk factor hypothesis. There was also an increase in depressive symptoms over the 10 years preceding the dementia diagnosis in this study.

Depressive symptoms are also seen in 40%–50% of patients with AD dementia, while depressive disorder is seen in 10%–20% (Wragg & Jeste, 1989). A meta-analysis (Zhao et al., 2016) looked at all published studies of neurobehavioral symptoms in AD dementia between 1964 and 2014 and found an overall pooled prevalence of 42% for depression (95% CI 37%–46%) and 39% for anxiety (95% CI 32%–46%). In a study that looked at cases with autopsy-confirmed pure AD neuropathology and age at death of 50 years or older ($N = 455$), increased odds for depression, along with agitation, anxiety, and sleep disturbances, were noted early on (Braak stage I/II) compared to controls (Ehrenberg et al., 2018).

Drugs for the treatment of major depressive disorder

Since the serendipitous discovery of the first effective antidepressant in mid-1950s, several different antidepressants have been developed. These antidepressants are classified based on their mechanism(s) of action. The "newer" antidepressants commonly used in clinical practice today are summarized in Table 23.3.

Three older classes of antidepressants will be discussed first that are not listed in Table 23.3. They are used less often now but do have great historical value. TCAs can be subdivided into the nonselective norepinephrine and serotonin reuptake inhibitors or tertiary amine TCAs, which include imipramine, amitriptyline, clomipramine, doxepin, trimipramine, and the relatively selective norepinephrine reuptake inhibitors or secondary amine TCAs, which include desipramine, nortriptyline, and protriptyline. The hepatic clearance of the TCAs is flow-limited, as noted in the section on metabolism, and their extensive first-pass metabolism is reduced in older adults resulting in higher serum concentrations of the drugs when the same doses are used in older vis-à-vis younger adults. Tertiary amine TCAs have significantly narrower therapeutic windows, poorer tolerability, and higher potential for DDIs in the presence of polypharmacy (Gillman, 2007), and they should be avoided in older adults, especially in higher doses. They also have anticholinergic, antihistaminic, α_1-receptor blocking, and membrane-stabilizing effects, all of which compromise their tolerability in older adults. The secondary amine TCAs desipramine and nortriptyline are the active metabolites of the tertiary amine TCAs imipramine and amitriptyline, respectively. Secondary amine TCAs have a lower propensity to block cholinergic, histaminergic, and α_1-receptors as compared to the tertiary amine TCAs, which translates clinically into better tolerability, especially in older adults. All TCAs slow intraventricular conduction, and this can be seen on a standard 12-lead ECG as increases in the QRS duration, PR, and QTc intervals. Overdose on TCAs can be lethal due to a complete heart block or ventricular reentry arrhythmias (Glassman & Preud'homme, 1993). Adverse effects that are clinically important in older adults include orthostatic hypotension due to α_1-blocking activity (less so with nortriptyline), a higher risk of a complete atrioventricular (AV) block due to preexisting conduction disorders (recall that first-degree AV block and bundle branch blocks are already more common in older adults), and risk of generating a cardiac arrhythmia in post-myocardial infarction patients due to the Type 1a antiarrhythmic properties of all TCAs. Both nortriptyline and desipramine are relatively "clean" drugs compared to the other TCAs as they are metabolized by just CYP2D6; they are also mild inhibitors of this enzyme, which is not clinically significant (Gillman, 2007). The relationship between plasma concentration and therapeutic response is curvilinear for nortriptyline and linear for desipramine, with a therapeutic window of 58–148 ng/mL for nortriptyline and >115 ng/mL for desipramine (Perry, Zeilmann, & Arndt, 1994). Given the low potential for adverse effects and the advantage of dosing that can be guided by therapeutic drug monitoring, these two drugs can be recommended for use in older adults as second- or third-line agents with EKG monitoring.

The MAOIs include phenelzine, tranylcypromine, and selegiline. MAOIs inhibit two enzymes, monoamine oxidase A and B (MAO-A and MAO-B), which in turn boost all the three monoamine neurotransmitters thought to be deficient

TABLE 23.3 Newer antidepressants available in the United States in 2019.

Antidepressant (Brand name) *Available formulations*	Predominant receptor activity	Metabolic pathways (major pathway(s) in bold)	Approved indications other than for the acute and maintenance treatment of major depressive disorder	Comments
Selective serotonin reuptake inhibitors (SSRIs)				
Fluoxetine (Prozac, Prozac Weekly, Sarafem) *Avail as cap, DR cap, tab, solution*	Selective serotonin reuptake inhibition	**CYP2D6**	OCD Bulimia Panic disorder Bipolar depression (with olanzapine) Treatment-resistant depression (with olanzapine)	No renal dosing necessary; lower dose or give less frequently in cirrhosis; no dose reduction necessary solely on the basis of age; higher risk of hyponatremia in older adults
Fluvoxamine (Luvox, Luvox CR) *Avail as tab, ER cap*	Selective serotonin reuptake inhibition	**CYP1A2, CYP2D6**	Approved only for OCD	No renal dosing necessary; no hepatic dosing necessary; renal clearance reduced by 50% in older patients; use lower starting dose and titrate upward slowly
Paroxetine (Paxil, Paxil CR, Pexeva) *Avail as cap, tab, ER tab*	Selective serotonin reuptake inhibition	**CYP2D6**	OCD Panic disorder Social anxiety disorder GAD PTSD PMDD Mod-severe menopausal vasomotor symptoms	Reduce initial dose, titrate slowly to a lower maximum dose in severe renal and hepatic impairment and in older adults; higher risk of hyponatremia in older adults
Sertraline (Zoloft) *Avail as tab, solution*	Selective serotonin reuptake inhibition	**CYP2C19**, CYP2B6, CYP2C9, CYP2D6, CYP3A4	OCD Panic disorder PTSD PMDD Social anxiety disorder	No renal dosing necessary; reduce dose in mild hepatic impairment and avoid in moderate–severe hepatic impairment; higher risk of hyponatremia in older adults
Citalopram (Celexa) *Avail as tab, solution*	Selective serotonin reuptake inhibition	**CYP2C19**	None	No renal dosing necessary in mild-moderate renal impairment; use caution in severe renal impairment; 20 mg/day is the maximum recommended dose for patients with hepatic impairment, for CYP2C19 poor metabolizers and in patients on a CYP2C19 inhibitor 20 mg/day is the maximum recommended dose for adults at or above age 60, higher risk of hyponatremia in older adults

Escitalopram (Lexapro) *Avail as tab, solution*	Selective serotonin reuptake inhibition S-isomer of racemic citalopram	**CYP2C19**, CYP3A4	GAD	No renal dosing necessary in mild-moderate renal impairment, use caution in severe renal impairment; 10 mg/day is the maximum recommended dose for patients with hepatic impairment; 10 mg/day is the maximum recommended dose for "most elderly patients"; higher risk of hyponatremia in older adults
Serotonin and norepinephrine reuptake inhibitors (SNRIs)				
Venlafaxine (Effexor XR) *Avail as tab, ER tab, ER cap*	Serotonin and noradrenaline reuptake inhibitor, weak inhibitor of dopamine reuptake at very high doses	**CYP2D6** converts it to active metabolite *o*-desmethylvenlafaxine	GAD Social anxiety disorder Panic disorder	Renal dosing necessary; hepatic dosing necessary, avoid in severe hepatic impairment; no dose reduction necessary solely on the basis of age; higher risk of hyponatremia in older adults
Desvenlafaxine (Pristiq, Khedezla) *Avail as ER tab*	Active metabolite of venlafaxine; Serotonin and noradrenaline reuptake inhibitor, weak inhibitor of dopamine reuptake at very high doses	**UGT isoforms**, CYP3A4	None	Renal dosing necessary; hepatic dosing necessary No dose reduction necessary solely on the basis of age; higher risk of hyponatremia and systolic orthostatic hypotension in older adults
Duloxetine (Cymbalta) *Avail as DR cap*	Serotonin and noradrenaline reuptake inhibitor, weak inhibitor of dopamine reuptake at very high doses	**CYP1A2, CYP2D6**	GAD Diabetic peripheral neuropathy Fibromyalgia Chronic musculoskeletal pain	Renal dosing necessary; avoid use in hepatic impairment; no dose reduction necessary solely on the basis of age; higher risk of hyponatremia and falls in older adults
Levomilnacipran (Fetzima) *Avail as ER cap*	Serotonin and noradrenaline reuptake inhibitor; enantiomer of the racemic milnacipran	**CYP3A4**	None	Renal dosing in moderate–severe impairment; hepatic dosing not necessary; no dose reduction necessary solely on the basis of age
Norepinephrine and dopamine reuptake inhibitors (NDRIs)				
Bupropion (Wellbutrin, Budeprion, Forfivo, Zyban) *Avail as Tab, 12 h ER tab, 24 h ER tab*	Weak inhibitor of neuronal dopamine and norepinephrine reuptake, unknown if this is its mechanism of action, no effect on serotonin or MAO	**CYP2B6**	Seasonal affective disorder Smoking cessation	Use caution in renal impairment (GFR < 90 mL/min); hepatic dosing necessary in mild-severe hepatic disease; no dose reduction necessary solely on the basis of age

(*Continued*)

TABLE 23.3 (Continued)

Antidepressant (Brand name) *Available formulations*	Predominant receptor activity	Metabolic pathways (major pathway(s) in bold)	Approved indications other than for the acute and maintenance treatment of major depressive disorder	Comments
Noradrenergic alpha$_2$ and selective serotonin antagonists (NASSAs)				
Mirtazapine (Remeron) *Avail as tab, ODT*	Potent α_2 antagonist, $5HT_2$ and $5HT_3$ antagonist, indirect $5HT_{1A}$ agonist	**CYP3A4**, CYP2D6, CYP1A2	None	Caution in renal and hepatic impairment 40% lower oral renal clearance in older males
Serotonin partial agonist and reuptake inhibitors (SPARIs)				
Vilazodone (Viibryd) *Avail as tab*	$5HT_{1A}$ partial agonist and serotonin reuptake inhibitor	**CYP3A4**	None	No renal dosing necessary; avoid in severe hepatic impairment; needs to be taken with food to ensure adequate absorption; no dose reduction necessary solely on the basis of age
Multimodal antidepressants (MMAs)				
Vortioxetine (Trintellix) *Avail as tab*	Potent serotonin reuptake inhibitor, $5HT_{1D}$, $5HT_3$, and $5HT_7$ receptor antagonist, $5HT_{1A}$ receptor agonist, and $5HT_{1B}$ receptor partial agonist	**CYP2D6**, CYP3A4, CYP2C19, CYP2C9	None	No renal dosing necessary; avoid in severe hepatic impairment; no dose reduction necessary solely on the basis of age; higher risk of hyponatremia in older adults
Glutamatergic modulators				
Esketamine (Spravato) *Avail as nasal spray*	Nonselective noncompetitive NMDA receptor antagonist	**CYP2B6, CYP3A4**, CYP2C9, CYP2C19	Only approved for treatment-resistant depression in conjunction with an oral antidepressant in adults; requires REMS certification for use	No renal dosing necessary; use caution in moderate hepatic impairment; avoid in severe hepatic impairment

ER, extended release; *DR*, delayed release; *OCD*, obsessive–compulsive disorder; *GAD*, generalized anxiety disorder; *PTSD*, posttraumatic stress disorder; *PMDD*, premenstrual dysphoric disorder; *MAO*, monoamine oxidase; *GFR*, glomerular filtration rate; *REMS*, risk evaluation and mitigation strategy; *NMDA*, *N*-methyl-D-aspartate; *5HT*, 5-hydroxytrpytamine.

in major depression—dopamine, norepinephrine (both catecholamines), and serotonin (an indoleamine). Both enzymes are found in the brain and both catabolize dopamine and tyramine. MAO-A is also present in the GI system and catabolizes all three monoamine neurotransmitters, while MAO-B is also present in platelets and catabolizes phenylethylamine. MAOIs can be nonselective (phenelzine and tranylcypromine), selective for MAO-A (moclobemide—not available in the United States) or selective for MAO-B at low doses but nonselective at high doses (selegiline). Moclobemide is a reversible inhibitor of MAO-A, which can be displaced from the enzyme by tyramine, thereby averting a tyramine reaction (Amrein, Hetzel, Stabl, & Schmid-Burgk, 1993). The tyramine reaction has already been discussed in the section on drug−food interactions. With the other available MAOIs, the enzyme inhibition is irreversible, requiring a 2-week drug-free period when switching between MAOIs and other antidepressants, including when switching to another MAOI (Jefferson, 1998), given that it takes 2 weeks to regenerate the enzyme. It appears that inhibition of MAO-A is necessary for the antidepressant effects of MAOIs, which explains why low-dose oral selegiline is ineffective as an antidepressant. High oral doses of selegiline that also inhibit MAO-A are necessary for its antidepressant effect, which necessitate dietary restrictions. MAOIs are now much less frequently used primarily due to the large number of adverse effects, including weight gain, sexual dysfunction, headache, dizziness, and insomnia, as well as large number of DDIs (Goldberg & Thase, 2013). DDIs involving the MAOIs have been discussed in the sections on DDIs.

The third older class of antidepressants is the serotonin antagonists and reuptake inhibitors (SARIs), which include trazodone and nefazodone. Trazodone is a weak SSRI that is also an antagonist at the H_1, α_1, and $5HT_{2A}$ receptors (Stahl, 2009) and is now seldom used in the treatment of depression. Its main clinical use in clinical practice today is in the treatment of agitation in dementia and as a sedative, both of which will be discussed in the sections on treatment of neurobehavioral symptoms in dementia and insomnia, respectively. Nefazodone is still available as a generic but is minimally used, if at all, after it became the only antidepressant to carry an FDA black box warning for hepatic failure. Its original manufacturers discontinued the brand-name drug in 2004 after an analysis of the WHO database of adverse drug effects found a statistically significant unexpectedly high number of reports of nefazodone-induced liver injury (Spigset, Hagg, & Bate, 2003). One psychopharmacological trivia in this context is that nefazodone is the second antidepressant to be withdrawn from many parts of the world due to hepatotoxicity, the first being the MAOI iproniazid in 1961.

SSRIs and SNRIs are the most commonly used antidepressants today and have similar indications and adverse effects. Different drugs in each class have slightly different FDA-approved indications, which is only because these were the indications submitted for approval by the manufacturers, and in most cases this does not imply that another drug from the same class will not be similarly effective for the same indication.

As with antipsychotics, an overview of the common adverse effects will be presented first in order to differentiate between the available newer antidepressants.

Suicide

Suicide is the most serious adverse outcome of major depressive disorder and the risk is particularly high in older adults, so a further increase in suicide risk with antidepressant treatment would obviously be concerning. However, in 2003 the FDA issued a Public Health Advisory about the risk of suicidality for pediatric patients taking antidepressants, which was converted to a black box warning for all antidepressants in 2005 and extended to young adults aged 18−24 years in 2007. There is evidence that antidepressants actually lower the risk of suicide in the older adult population, regardless of drug class, as seen in a meta-analysis of 372 double-blind RCTs that were submitted to the FDA (Stone et al., 2009). The effect of age was noted to be more marked on suicidal behavior than on suicidal ideation. Similarly, a meta-analysis of eight studies involving more than 200,000 patients with moderate or severe depression found a protective effect of SSRIs on completed suicides in adults aged 65 and older (OR 0.53, 95% CI 0.26−1.06) (Barbui, Esposito, & Cipriani, 2009).

Hyponatremia

Hyponatremia is typically defined as serum sodium less than 135 mmol/L, regardless of the presence or absence of clinical symptoms. Venlafaxine appears to have the highest risk among SSRIs and SNRIs. In a retrospective controlled study, about 40% of older psychiatric inpatients (mean age 74.2 years) who were treated with an SSRI or venlafaxine developed hyponatremia compared to 10% of controls (i.e., patients not prescribed an SSRI or venlafaxine), and controlling for confounders such as thiazide use did not negate the association (Kirby, Harrigan, & Ames, 2002). Mild asymptomatic hyponatremia may cause attentional deficits, gait abnormalities, and falls, while severe hyponatremia may cause seizures, coma, and respiratory arrest (Jacob & Spinler, 2006, Renneboog, Musch, Vandemergel,

Manto, & Decaux, 2006). The FDA labels caution providers about hyponatremia associated with the use of the SSRIs, SNRIs, and vortioxetine, as noted in Table 23.3. Combining these with other natriuretic medications such as thiazide diuretics, carbamazepine, and oxcarbazepine, further increases the risk, as do physical illnesses that can cause natriuresis such as hypothyroidism, congestive heart failure, and adrenal insufficiency (Verbalis et al., 2013). It may be advisable to obtain a pretreatment sodium level in such high-risk patients. Conversely, if mild-moderate asymptomatic hyponatremia is found in an older adult after starting a high-risk antidepressant, this should not be automatically attributed to the antidepressant, which may lead the patient or the provider to stop the antidepressant prematurely. Rather, the primary care provider's assistance should be enlisted in working the patient up for other common causes of hyponatremia (Greenblatt & Greenblatt, 2016). When other common causes have been ruled out, a switch to a less hyponatremia-prone antidepressant such as bupropion or mirtazapine may appear to be a logical first step, but there are no studies that support this option, and bupropion itself can increase the risk of seizures in the presence of hyponatremia which can persist for some time after initiating the switch. In severe cases, fluid restriction and very gradual infusion of hypertonic saline in a medical setting may be necessary.

Fractures and osteopenia

In a large nationwide cohort study that looked at the association between antidepressant drug use and hip fracture in older adults (mean age at index date 80.1 years) before and after initiation of treatment with antidepressants, it was found that antidepressant users sustained more than twice as many hip fractures than nonusers in the year before and the year after initiation of therapy, the odds ratio being the highest for the association 16−30 days before the prescription for the antidepressant was filled, peaking close to the index date for the fracture, and subsequently falling until 1 year thereafter (Brannstrom, Lovheim, Gustafson, & Nordstrom, 2019). There was no clear dose−response relationship. The apparent increased risk of fractures was attributed to the confounding effect of depression itself. However, antidepressants may also independently contribute to the increased risk of bone fractures. In the Fluoxetine Or Control Under Supervision (FOCUS) trial, where acute poststroke patients were randomized to receive fluoxetine 20 mg or placebo for 6 months, there was an absolute excess risk of bone fractures of 1.4% at 6 months (Martin, 2019). The mean age of patients in the fluoxetine group was 71.2 years in this study. Regardless, the risk of fractures can be reduced by using antidepressants that cause less H_1-, muscarinc, and α_1-receptor blockade, along with starting low, titrating the dose upward slowly and reviewing possible DDIs, fall prevention strategies, and need for appropriate osteoporosis management with the patient and/or surrogate decision-maker (Iaboni & Maust, 2019). The data on bone loss in older adults are similar, and depression itself appears to contribute to low bone mass and accelerated bone loss more than antidepressant use in adults aged 60 and over (Gebara et al., 2014).

Bleeding

Bleeding risk has consistently shown to be increased with the SSRIs, and a meta-analysis of observational studies found that the increase in risk of bleeding ranged from 12% to 64% across studies (Laporte et al., 2017). Risk factors include older age, chronic liver disease, concurrent administration of NSAIDs, antiplatelet therapy (aspirin, clopidogrel), or anticoagulants, in those with preexisting bleeding risk due to any cause, in those with an anticipated increase in bleeding such as following dental or other surgeries, and in those taking higher doses of OTC medications such as vitamin E or fish oil (Andrade and Sharma, 2016). In one retrospective cohort study, concurrent use of SSRIs and dual antiplatelet therapy with aspirin and clopidogrel increased the risk of bleeding by 60% over that due to over dual antiplatelet therapy alone in post-acute myocardial infarction patients (Labos, Dasgupta, Nedjar, Turecki, & Rahme, 2011). This is important, since dual antiplatelet therapy is commonly used in post-acute coronary syndrome (Levine et al., 2016) and poststroke (Ge et al., 2016) patients, and SSRIs are commonly used to treat depression in both these groups (Seligman & Nemeroff, 2015, Villa, Ferrari, & Moretti, 2018). The commonest site of bleeding is the upper GI tract, and the risk is eliminated by the use of acid suppressant drugs (Jiang et al., 2015). Omeprazole should be avoided in conjunction with clopidogrel as it inhibits CYP2C19, thereby blocking the metabolic pathway that activates the prodrug clopidogrel into its active metabolite. However, a large population-based cohort study ($N = 60746$ patients aged 65 and older with a new episode of depression) from the United Kingdom found that the increased risk of upper GI bleed was associated with use of all antidepressant classes vis-à-vis nonuse (Coupland et al., 2011). A recent nationwide cohort study from Austria that retrospectively analyzed hospital records between 2010 and 2015 of predominantly older adults (median age 76 years) also found that the increased risk of bleeding is a class effect common to all antidepressants (Sheikh Rezaei, Mittlbock, Reichardt, & Wolzt, 2019). In this study, combining SSRI as well as non-SSRI antidepressants with a novel oral anticoagulant (NOAC) increased the bleeding risk vis-à-vis combining either class of antidepressants

with a vitamin K antagonist (VKA); coadministration of SSRIs with either NOAC or VKA did not increase the risk of bleeding compared to the coadministration of other antidepressants with either anticoagulant class. The differential effects of the various drugs within the NOAC class, if any, were not identified.

Fall risk

Antidepressants increase the risk of falls in older adults, although the exact mechanisms are unknown and likely differ by medication class. A longitudinal analysis of community-dwelling older adults (mean age 73.6 years at baseline) that followed the patients from 1997 to 2004 used self-report data to identify antidepressant users to look at the risk of recurrent (defined as 2 or more) falls (Marcum et al., 2016). There was about a 20% attrition rate between year 1 and year 6 of the study. The study found a 48% greater likelihood of recurrent falls among antidepressant users compared to nonusers, even after adjusting for potential confounders. Increased likelihood of falls was noted for those taking SSRIs, those who had a short duration of use and those taking moderate doses, compared to nonuse. A meta-analysis of 22 studies also looked at the impact of medications on falls in adults 60 years and older and found an increased risk with antidepressant use, the adjusted odds ratio being 1.36 (95% CI 1.13−1.76) (Woolcott et al., 2009). There are multiple potential ways in which antidepressants can increase the risk of falls, including cardiovascular side effects, insomnia, excessive daytime drowsiness, and orthostatic hypotension (Darowski, Chambers, & Chambers, 2009). However, as pointed out in a meta-analysis (Gebara et al., 2015), all the studies that show an association between SSRI use and falls in older adults are observational only, and that the direction of the association remains undetermined. Therefore, while every effort should be made to select an antidepressant that has the fewest adverse effects associated with falls, stopping or reducing one or more carefully selected antidepressant medication(s) simply to avoid the risk of falls may not be justified due to the increased morbidity and patient and caregiver distress related to untreated depression or anxiety.

Cardiac adverse effects

On August 22, 2011, the FDA issued an advisory recommending that patients above the age of 60 should not receive more than 20 mg/day of citalopram due to the dose-dependent risk of QTc prolongation; however, the FDA did not update the product labeling until March 28, 2012, which has since stated that citalopram be avoided in patients with congenital long QT syndrome, bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure. Escitalopram likely also prolongs the QT interval (Girardin et al., 2013) and Health Canada and the European Medicines Agency (but not the FDA) have issued warnings regarding dose-dependent QT prolongation with escitalopram (Do et al., 2016). However, the FDA did issue a safety warning for fluoxetine in 2013, citing postmarketing reports of QT prolongation and ventricular arrhythmias. A comprehensive review of cardiovascular adverse effects of newer antidepressants also found a small but definite risk of tachycardia, hypertension, and orthostatic hypotension with use of the SNRIs (Mago, Tripathi, & Andrade, 2014).

Evidence-based drug treatment of depressive disorders in older adults

The choice of an appropriate SSRI or SNRI should be based on the elimination half-life and potential for DDIs. Fluoxetine has the longest elimination half-life by far. The elimination half-life of fluoxetine is 1−3 days after acute administration, which increases to 4−6 days after chronic administration, while its active metabolite, norfluoxetine, has an elimination half-life of 4−16 days after acute and chronic administration. This has both advantages and disadvantages. It allows for once a week dosing (Prozac Weekly), and occasional missed doses do not affect serum concentrations much. It also results in few, if any, withdrawal symptoms upon discontinuation. However, such a long elimination half-life also means that it takes 5 or more weeks for the drug and its active metabolite to completely wash out, so any adverse effects or DDIs involving fluoxetine can persist up to 5 weeks after the medication is stopped. It also makes a long 5-week drug washout period imperative when switching from fluoxetine to an MAOI. Venlafaxine immediate-release has the shortest half-life of only about 5 hours and has to be dosed three times a day, followed closely by duloxetine which is about 8−12 hours, which is why venlafaxine extended-release and duloxetine delayed-release were formulated. Pharmacokinetic DDIs involving the SSRIs have already been discussed in the drug interactions section.

A basic tenet of antidepressant dosing in older adults is use of lower starting doses and gradual dose titration. A study that looked at serum concentrations from a routine therapeutic drug monitoring database ($N = 17{,}930$ patients) found that the dose-adjusted serum concentrations were elevated twofold for citalopram, escitalopram, fluvoxamine, nortriptyline, and paroxetine and 1.5-fold for amitriptyline, clomipramine, duloxetine, mianserin, mirtazapine, sertraline, and venlafaxine in adults over the age of 65, compared to those younger than 40, and were higher for women than men (Waade, Molden, Refsum, & Hermann, 2012).

There is some evidence from a recent meta-analysis of 19 RCTs and two observational studies that SSRIs are better tolerated than SNRIs for the acute treatment (<12 weeks) of major depressive disorder in adults 65 years and older (Sobieraj et al., 2019). Citalopram or escitalopram should be tried first due to the low risk of DDIs, but cardiotoxicity remains a concern with both these medications, as noted above. The dose−response curve of the SSRIs remains relatively flat once a minimal effective dose is reached, which results in 70% serotonin reuptake inhibition. A meta-analysis of studies in mixed-age patients found that slightly higher doses of SSRIs do appear to be more effective which plateaus at around 250 mg of imipramine equivalents or 50 mg of fluoxetine, but the slightly increased benefit is offset by reduced tolerability (Jakubovski, Varigonda, Freemantle, Taylor, & Bloch, 2016).

In the presence of a nonresponse or partial response to the first drug, switching to another antidepressant or augmentation should be considered. Use of supratherapeutic doses of antidepressants has never been well studied, but there is some evidence from studies in mixed-age adults supporting higher than recommended doses of venlafaxine and perhaps tranylcypromine to treat drug-resistant depression (Adli, Baethge, Heinz, Langlitz, & Bauer, 2005). Switching strategies are also not well studied in older adults, but data from a meta-analysis of four clinical trials in mixed-age adults suggests that there may be a modest advantage to switching patients with SSRI-resistant depression to a non-SSRI antidepressant, including an SNRI, rather than switching within class (Papakostas, Fava, & Thase, 2008).

Treatment-resistant depression in older adults

Treatment-resistant depression in older adults (TRDOA) is a common and vexing problem, and most studies define TRDOA as nonresponse to just one adequate antidepressant trial. Augmentation with aripiprazole, bupropion, and lithium are commonly used strategies (Arandjelovic, Eyre, & Lavretsky, 2016). A detailed discussion of all of these is beyond the scope of this chapter, but the most widely used augmentation strategy for treatment-resistant depression in clinical practice today is the use of second-generation antipsychotics, several of which are approved for this indication based on studies in mixed-age patients, including quetiapine, aripiprazole, and brexpiprazole as adjunctive treatment, and the olanzapine-fluoxetine polypill as monotherapy, as noted in Table 23.1. Risperidone, ziprasidone, and cariprazine also have data supporting adjunctive use, but do not have an FDA-approved indication for the treatment of major depressive disorder so far (Durgam et al., 2016; Nelson & Papakostas, 2009; Papakostas et al., 2015). A meta-analysis of placebo-controlled randomized trials indicates that all second-generation antipsychotics are similarly effective augmentation agents in major depressive disorder (Nelson & Papakostas, 2009). In the absence of head-to-head comparisons, a network meta-analysis provides some guidance regarding choosing between four augmentation strategies—aripiprazole, quetiapine, risperidone, and the olanzapine-fluoxetine polypill—in treatment-resistant depression, albeit in mixed-age adults. While all antipsychotics provide benefit in standard, but not low, doses, risperidone and aripiprazole in standard doses were more beneficial than placebo in terms of improving quality of life and functioning, and risperidone was better tolerated than the others (Zhou et al., 2015). Adverse effects that have been most notable in augmentation studies include akathisia with aripiprazole; sedation with quetiapine; weight gain with olanzapine; somnolence and akathisia with ziprasidone; headache, sedation, and dry mouth with risperidone; and akathisia, insomnia, and nausea with cariprazine. The low but definite risk of TD should be discussed with the patient if longer-term treatment is being considered (Thase, 2016).

Specific studies in TRDOA are few in number. In a double-blind RCT of aripiprazole (maximum 15 mg/day) versus placebo augmentation of venlafaxine XR (range 150−300 mg/day) in older adults aged 60 or above, 12 weeks of sustained remission was noted in almost 50% the participants in the intervention group (Lenze et al., 2015). Akathisia and drug-induced parkinsonism were the most common adverse effects in the aripiprazole group, which is consistent with its known adverse effect profile. The US Department of Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study compared three alternative treatment options for TRDOA (defined in the study as suboptimal response to adequate treatment with an SSRI, SNRI, or mirtazapine) in a predominantly male middle-aged veteran study population (mean age 54.4 years) for a 12-week acute treatment phase, followed by a 24-week continuation phase (Mohamed et al., 2017). The three treatment options were switching to bupropion, augmenting current antidepressant with bupropion, or augmenting current antidepressant with aripiprazole. At the end of the 12-week trial, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission compared with switching to bupropion monotherapy, but it resulted in higher response rates than both the bupropion groups. There was no statistically significant difference between the two bupropion groups on either remission or response rates. There were also no significant differences in the secondary outcome of cumulative relapse between the three groups among those who achieved remission in the acute treatment phase. Treatment-emergent anxiety was the most common adverse effect in both the bupropion groups, while somnolence, extrapyramidal effects including akathisia, and weight gain were the most common adverse effects in the aripiprazole augmentation group.

Lithium has been found to be effective for augmenting antidepressant treatment in older adults with major depression in a single open RCT with a 2-year follow-up, with tremor as the main side effect which did not significantly increase the number of drop-outs (Kok, Vink, Heeren, & Nolen, 2007). Adjunctive intravenous ketamine has been shown to be effective in younger adults with treatment-resistant depression (Fava et al., 2018), and studies are under way to evaluate its role in TRDOA (O'Brien et al., 2019). The Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Participants with Treatment-Resistant Depression (TRANSFORM-3) was a 4-week phase III double-blind placebo-controlled augmentation trial of esketamine nasal spray in patients aged 65 or older who failed two or more adequate antidepressant trials. There was no statistically significant benefit for the antidepressant-esketamine group over the antidepressant-placebo group in the primary efficacy analysis (Ochs-Ross et al., 2019), but there was between treatment−group difference in favor of esketamine augmentation in the 65- to 74-year age group and in patients with onset of depression before age 55, so esketamine augmentation may be a viable option specifically for treating resistant early-onset depression in the young-old population. At the time this chapter was being prepared, the Optimizing Outcomes of Treatment-Resistant Depression in Older Adults (OPTIMUM) trial was still enrolling patients (Cristancho et al., 2019), which will compare five different treatment strategies for TRDOA. Treatment resistance is defined in this study as failure to respond to two adequate antidepressant trials.

The use of methylphenidate in older adults with major depressive disorder appears to be safe and effective based on a randomized placebo-controlled RCT of augmentation of citalopram with methylphenidate in geriatric major depressive disorder (mean age of the sample 69.7 years $\pm$ 7.3) (Lavretsky et al., 2015). Note that the patients included in the study did not have treatment-resistant depression, acute suicidality, or violent behaviors and were psychotropic medication-free for 2 weeks before starting the trial. The mean dose of citalopram was 32 mg (range 20−60 mg) in this study, which is higher than what is recommended for patients aged 60 and above by the FDA, while the mean dose of methylphenidate was 16 mg (range 5−40 mg). All three groups (citalopram + placebo, methylphenidaye + placebo, and citalopram + methylphenidate) improved over the 16 weeks of the study. The improvement in depression severity and clinical global impression was most prominent in the citalopram + methylphenidate group, and it occurred at a faster rate for the first 4 weeks of the trial. There were no between-group differences in cognitive improvement which occurred in all groups or in side effects.

Cognitive symptoms in depressive disorder in older adults

Cognitive symptoms often accompany depressive symptoms in older adults, and 30%−40% older adults with depression without a dementia have evidence of executive dysfunction on cognitive assessment (Lockwood, Alexopoulos, & van Gorp, 2002). Cognitive and depressive symptoms appear to have a tight temporal relationship in older adults with major depressive disorder, as higher levels of chronic depressive symptoms are related to lower cognitive functioning (Dzierzewski et al., 2015). The temporal order of symptom onset is important, and such patients should not be confused with new onset of depressive symptoms in patients with known dementia. In some patients with a depressive disorder, the cognitive symptoms are severe enough to reach the severity of a dementia, which is typically reversible ("depressive pseudodementia"). They usually remit with treatment in the short term, but eventually often goes on to become an irreversible dementia. In a study that followed 57 older adults consecutively hospitalized for the treatment of major depressive disorder, the group with a reversible dementia at baseline was 4.69 times more likely to develop irreversible dementia over a follow-up period of almost 34 months compared to the group with no dementia at baseline, and no clinical characteristic was found to discriminate between the two groups (Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993). There is some evidence that older adults with cognitive symptoms in the context of a depressive disorder may benefit from SSRIs, but the improvement was limited to attention and executive function only in one study of sertraline which was seen in only those whose depression improved, and there was little overall cognitive improvement (Devanand et al., 2003).

Other studies have found that a depression-executive dysfunction syndrome is not only a predictor of poor treatment response, but also a risk factor for progression to a dementia (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). Executive functions include several cognitive skills, not all of which are predictors of response to treatment in depression. In the Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GREY) RCT (Kaneriya et al., 2016), 181 patients with TRDOA (mean age 68 years), defined as failing to remit with venlafaxine monotherapy up to 300 mg/day times 12 weeks in open treatment, were randomly assigned to either augmentation with aripiprazole (starting dose 2 mg and titrated as tolerated to a maximum of 15 mg/day) or placebo for an additional 12 weeks, while maintaining the last dose of venlafaxine. Better pretreatment performance on set-shifting as assessed by the Trail Making Test score increased the odds of remission with only with adjunctive aripiprazole and not with placebo, with a

number-needed-to-treat of 4. On the other hand, response inhibition, as assessed by the Color-Word Interference Task, did not affect the odds of remission. Greater severity of anxiety at baseline did not moderate the response to treatment and predicted a lower remission rate in both the aripiprazole and placebo groups. Baseline physical comorbidity did not predict remission have a significant interaction with the active treatment arm.

The non-DSM-5 diagnosis of MBI applies to older adults with late-onset depressive symptoms who are retrospectively identified as having a dementia prodrome. The provisional research diagnostic criteria for MBI proposed by the AA-ISTAART (Ismail et al., 2016) lists *affective dysregulation* as one of the five proposed MBI subtypes, and longitudinal studies have found that over half of individuals who go on to develop a dementia or MCI develop neurobehavioral symptoms *before* the cognitive disorder, with depression and irritability being the most common symptoms (Wise et al., 2019). These are likely the same patients who are prospectively identified as having "depressive pseudodementia." What is the impact of treatment on the long-term progression of such patients to dementia? In general, antidepressant treatment does not appear to reduce the progression to MCI and dementia in the long-term, and indeed, in a meta-analysis of 18 longitudinal studies (mean age in the trials ranged from 55 to 81 years, follow-up duration ranged from 1.7 to 20 years), antidepressant use did not protect against the development of MCI and dementia (Chan, Yiu, Kwok, Wong, & Tsoi, 2019). All antidepressant classes were similar in this regard, but this meta-analysis did not look at the differential impact of antidepressants in those with and without "depressive pseudodementia". Long-term SSRI treatment may *delay* the progression to dementia in short-term responders. Ongoing long-term SSRI treatment (>4 years) in patients with MCI and a history of depression with onset at any age but without active depressive symptoms for at least 1 year (i.e., responders), did *delay* progression to AD dementia by about 3 years compared to shorter-term treatment, treatment with other antidepressants, or no treatment at all (Bartels, Wagner, Wolfsgruber, Ehrenreich, & Schneider, 2018). Presence or absence of prior "depressive pseudodementia" in these responders was not reported in the study.

While memantine *monotherapy* has not been found to improve *neurobehavioral symptoms* (including depression) in mild or moderate AD *dementia* as measured by the Neuropsychiatric Inventory (NPI) (Schneider, Dagerman, Higgins, & McShane, 2011), and memantine augmentation of antidepressant therapy does not improve depression in major depressive disorder in mixed-age (Kishi, Matsunaga, & Iwata, 2017) or older adults (Omranifard, Shirzadi, Samandari, Afshar, & Maracy, 2014) in the absence of cognitive symptoms, adjunctive treatment with memantine has been found to provide short-term benefit in patients with depression and cognitive symptoms. In an open-label pilot study, the escitalopram-memantine combination was effective in improving depression and cognition (memory, category fluency, and language domains only) over the 48-week study period, but the mean dose of escitalopram used (18.62 ± 5.15 mg) was higher than what is recommended for older adults (Pelton et al., 2016). A placebo-controlled RCT compared an escitalopram-memantine combination with escitalopram-placebo in depressed older adults (average age 71.9 years) with subjective memory complaints over a 6-month study period, followed by a 60-month naturalistic follow-up period (Lavretsky et al., 2020), and found depression to be significantly improved in both groups; the escitalopram-memantine group showed a significantly greater improvement in delayed recall, executive functioning, and global performance at 12 months. Both medications were well tolerated, and the mean doses of both medications were within or close to the recommended dose ranges for older adults (escitalopram 11.1 ± 3.7 mg and memantine 19.3 ± 2.6 mg). The longer-term impact of this combination on the progression to MCI and eventually to dementia is unknown and was not the focus of these studies.

Contrary to the experience with memantine, adding a cholinesterase inhibitor to antidepressant treatment in older adults with depression and cognitive impairment has yielded mixed results. In a randomized control pilot trial, donepezil augmentation of antidepressant therapy was effective in improving memory for the 12-week duration of the trial as well as the 8-month open extension phase, but no noncognitive benefits were seen (Pelton et al., 2008). In a double-blind RCT where older patients (65 and older) with or without MCI who had responded to an open phase of antidepressant treatment were randomly assigned to maintenance antidepressant treatment plus either donepezil or placebo, a temporary positive effect on global cognition in the antidepressant + donepezil group was overshadowed by paradoxically higher rates of recurrent depression in the MCI group, while cognitively intact individuals demonstrated no benefits and no increase in the recurrence of depression on donepezil (Reynolds et al., 2011). Thus, the evidence indicates that augmentation of antidepressant treatment with a cholinesterase inhibitor in older adults with cognitive deficits related to major depressive disorder is not beneficial and should not be recommended.

Of the newer antidepressant medications, vortioxetine has considerable data supporting its pro-cognitive benefits in major depressive disorder. Head-to-head comparisons are lacking, but a network meta-analysis that looked at the effects of antidepressants on the digit symbol substitution test (Baune, Brignone, & Larsen, 2018) across 12 RCTs found that vortioxetine was the only antidepressant that improved performance on the test, which is known to be sensitive to

change but has low specificity as it measures skills across a number of cognitive domains (Jaeger, 2018). The cognitive benefit of vortioxetine does not appear to be secondary to improvement in depressive symptoms, but rather a direct treatment effect (Mahableshwarkar, Zajecka, Jacobson, Chen, & Keefe, 2015). It is available as a brand-name drug only for now, and whether its use for this indication is cost-effective should be established on a case-by-case basis collaboratively between the patient and the provider.

Neurostimulation strategies

TRDOA not only affects quality of life but also increases the cost burden and stress level for family and providers. Neurostimulation offers an effective tool to manage TRDOA with better tolerability and safety as compared to antidepressants. Although there are a growing number of neurostimulation techniques available, ECT remains the gold standard due to its more effective and faster onset of antidepressant response in older than in younger subjects. The major recent advancement in ECT delivery has come from the use of an ultra-brief pulse (0.3 ms), which has been found to be effective while reducing adverse cognitive effects (Sackeim et al., 2008), and is therefore ideal for older adults.

The best evidence supporting ECT use in TRDOA comes from the Prolonging Remission in Depressed Elderly (PRIDE) study. In phase I of the study, right unilateral ultra-brief pulse ECT along with venlafaxine was found to be a rapidly acting, highly effective, and well-tolerated treatment for depressed older patients (Kellner et al., 2016a). The average number of ECT treatments was about 7, and the remission and the response rates were about 62% and 70%, respectively, with a low dropout rate. The 24-week phase II of this study revealed that maintenance ECT in addition to medications (lithium and venlafaxine) was more effective than, and as safe as, maintenance medications without ECT after an acute response to ECT (Kellner et al., 2016b). A comprehensive review of ECT studies in the treatment of TRDOA concluded that right unilateral ultra-brief ECT was as effective as brief-pulse ECT during acute as well as maintenance treatment, with fewer adverse effects (Geduldig & Kellner, 2016).

Although efficacy data are not as impressive for the other neurostimulation strategies, such as repetitive transcranial magnetic stimulation (rTMS), there is general perception that rTMS may be a safe intervention in geriatric depression. Unique characteristics of older adults, including cortical atrophy, reduction in functional hemispheric asymmetry, and increased cerebral white matter disease limit the use of rTMS in older adults, and widely accepted age-appropriate protocols for treating depression in older adults are not yet in place (Iriarte & George, 2018). Older subjects may also require higher rTMS intensity and longer treatment for the optimal effects. Overall, response rates in depression in older adults have generally been reported to be in the 20%−50% range with rTMS (Galvez et al., 2015), which are much lower than those reported for ECT.

There are currently no data from studies in older adults to support the use of other neurostimulation modalities in older adults, such as vagus nerve stimulation, transcranial direct current stimulation, deep brain stimulation, and magnetic seizure therapy (Galvez et al., 2015).

The dementias in older adults

Introduction

DSM-5 replaced the conventional term *dementia* with the new term *neurocognitive disorder* (American Psychiatric Association DSM-5 Task Force and American Psychiatric Association, 2013). The DSM-5 text indicates that neurocognitive disorder is a broader construct than dementia and recommends restricting the use of the latter term only for neurodegenerative dementias in older adults where there is substantial decline in at least two cognitive domains, one of which may or may not be memory. Dropping the requirement that memory must be one of the affected cognitive domains in order to diagnose dementia is a major change in DSM-5. DSM-5 also distinguishes between Major and Mild Neurocognitive disorder. Mild neurocognitive disorder differs from major neurocognitive disorder in that the cognitive impairment in mild neurocognitive disorder does not interfere with capacity for independence in everyday activities with or without the use of compensatory strategies or accommodation, and the word *mild* was borrowed from the voluminous literature on MCI. This chapter will forgo the use of the new DSM-5 terminology in the interest of continuity, as stated in the overview, since the older terms dementia and MCI continue to be used in research in general and specifically in the studies reviewed here.

The prevalence of dementia increases with age, with rates typically around 1%−2% at age 65 and as high as 30% by age 85 (American Psychiatric Association et al., 2013), of which AD dementia is the most common, its prevalence ranging from 60% to 90% depending upon the setting. The nosology of the dementias is confusing. They can be classified in several ways, such as based on underlying etiology (e.g., neurodegenerative, vascular, infectious, and metabolic),

based the predominant cognitive domain(s) affected in the initial stages (usually amnestic or non-amnestic, involving single or multiple domains), based on reversibility with treatment or lack thereof, and based on age at onset (usually an arbitrary age cutoff of 65 years is used to distinguish between early-onset and late-onset dementias). Neurodegenerative dementias can be further classified based on the underlying proteinopathy, for example synucleinopathy, tauopathy, amyloidopathy, TDP-43-opathy, etc. The neurocognitive disorders in DSM-5 are classified based on a combination of several different schemes. Thus, a diagnosis of neurocognitive disorder due to AD is based on presumed underlying proteinopathy (amyloidopathy with tauopathy), while a diagnosis of frontotemporal neurocognitive disorder is based on the topographic distribution of cerebral atrophy (frontal, temporal, or both) seen on structural imaging. AD dementia refers to the clinical syndrome of a predominantly amnestic dementia, while the term AD itself refers to the underlying neuropathology. Similarly, the term frontotemporal lobar degeneration (FTLD) refers to the neuropathology underlying FTD and several other related clinical syndromes. To make matters more confusing, clinicopathological correlation in the frontotemporal neurocognitive disorder subtypes is poor, especially in the FTD subtypes. A simplified classification scheme based on the predominant cognitive deficit in the initial stages, rather than based on neuropathology, has more clinical value, as patients with cognitive impairment typically present with a constellation of cognitive and neurobehavioral symptoms rather than with known neuropathology or neuroimaging findings. This scheme certainly has some drawbacks as well. It artificially splits some dementias with the same underlying neuropathology into different diagnostic categories and lumps together other dementias with disparate neuropathologies. Table 23.4 summarizes this proposed unified scheme for classifying the common neurodegenerative and vascular dementias. The lack of one-to-one clinicopathological correlation in the dementias is clearly evident from the way the cells are staggered across the columns in the table. Further discussion of this vast topic is beyond the scope of this chapter.

Drugs for the treatment of cognitive symptoms in the dementias

Four medications are currently FDA-approved for the treatment of the various dementias, and these belong to two-drug classes: acetylcholinesterase inhibitors (also called cholinesterase inhibitors, ChEIs or AChEIs) and NMDA receptor antagonists. There are several differences between the antidementia drugs, which are summarized in Table 23.5.

Other clinically pertinent facts about the drugs are as follows. Donepezil is highly protein-bound. Both donepezil and memantine have long elimination half-lives; donepezil is dosed once daily and a switch to once-daily dosage has been shown to be well tolerated for memantine (Ott, Blake, Kagan, & Resnick, 2007). Switching to Namenda XR at the same daily dose of the standard-release memantine formulation results in higher steady-state levels. Namenda XR 28 mg daily yields a 45% greater steady-state plasma peak and 36% greater trough levels than 10 mg twice daily of the standard formulation, while standard-release tablets given as 20 mg once daily or XR 21 mg once daily yield levels similar to 10 mg of the standard-release tablet given twice daily (Lam, Smith, & Gomolin, 2015). Rivastigmine and memantine are unique as they do not undergo hepatic metabolism and therefore are not affected by CYP450 inhibitors and inducers. All four antidementia medications are now available as generics in the United States. Rivastigmine is the only cholinesterase inhibitor available as a skin patch, which is also available as a generic now. Long-acting preparations of galantamine (Razadyne ER) and memantine (Namenda XR) are still available as brand name only.

The Namzaric polypill is not shown in Table 23.4. It contains memantine ER and donepezil in two fixed-dose combinations of 14/10 mg and 28/10 mg, respectively. Patients should be stabilized on memantine (5 or 10 mg BID) or memantine ER (at least 14 mg daily) and donepezil (not less than 10 mg daily) before starting the polypill. Its place in clinical practice remains unclear, except perhaps in improving adherence in patients who are averse to taking too many pills daily. Even in such patients, it may not prove to be cost-effective as it is currently available as brand name only.

Given their differing mechanisms of action, it is not surprising that the adverse-effect profiles of the two antidementia drug classes are different. Overactive bladder is a vexing problem in older adults with dementia, which can be exacerbated by the cholinesterase inhibitors. Scheduled toileting and prompted voiding are preferable to using bladder antispasmodics in these patients. CNS-active bladder antispasmodics such as oxybutynin and tolterodine should be avoided as they are highly anticholinergic. GI-related side effects due to their pro-cholinergic activity are common with all cholinesterase inhibitors, and cholinesterase inhibitor-induced weight loss can be especially concerning (Sheffrin, Miao, Boscardin, & Steinman, 2015). Constipation, dizziness, headache, hypertension, and somnolence are the most common side effects of memantine, and none of these are very common (Jones, 2010). Pharmacodynamic DDIs resulting from the use of antidementia drugs have already been discussed in the section on DDIs.

Evidence-based drug treatment of cognitive symptoms in the dementias in older adults

Donepezil is FDA-approved for the entire spectrum of AD dementia, from mild to severe disease. The recommended dose for mild-to-moderate disease is 5−10 mg/day, and for moderate to severe disease is 10−23 mg/day. Galantamine

TABLE 23.4 A unified classification scheme for the common dementias.

Cognitive domain(s) predominantly affected in initial stages	Commonly used terminology	DSM-5 classification	Terminology based on most recent non-DSM-5 classifications	Underlying proteinopathy/ pathology
Amnestic deficit	Alzheimer's disease dementia	Major or mild neurocognitive disorder due to Alzheimer's disease	Alzheimer's clinical syndrome[a]	Amyloidopathy with tauopathy
Isolated executive function deficit			Frontal-executive variant of Alzheimer's disease[b]	
Language deficits (agrammatism/apraxia of speech/impaired object naming and single word comprehension/impaired word retrieval with intact grammar, comprehension, and motor components of speech)	Primary progressive aphasia (PPA)	Major or mild frontotemporal neurocognitive disorder, language variant	Nonfluent/agrammatic-variant PPA (nfv-PPA or PPA-G)[c]	Tauopathy or TDP-43-opathy (Type A)[d]
			Logopenic-variant PPA (lv-PPA or PPA-L)[c]	Amyloidopathy with tauopathy
			Semantic-variant PPA (sv-PPA or PPA-S)[c]	TDP-43-opathy (Type C)[d]
Agnosia (prosopagnosia)			Right temporal variant-FTD[e]	
Visuospatial deficits	Lewy body dementia	Major or mild neurocognitive disorder with Lewy bodies	Dementia with Lewy bodies[f]	Synucleinopathy
		Major or mild neurocognitive disorder due to Parkinson's disease	Parkinson's disease dementia[g]	Synucleinopathy
Agnosia (simultanagnosia)	Visual variant of Alzheimer's disease	Major or mild neurocognitive disorder due to Alzheimer's disease	Posterior cortical atrophy[h]	Amyloidopathy with tauopathy
Oro-buccal or limb apraxia (with asymmetric limb rigidity/bradykinesia/ dystonia/myoclonus)	Corticobasal syndrome[i]	Major or mild neurocognitive disorder due to another medical condition	Probable or possible corticobasal syndrome	Corticobasal degeneration (tauopathy)
		Major or mild neurocognitive disorder due to Alzheimer's disease	Alzheimer's disease—corticobasal syndrome[j]	Amyloidopathy with tauopathy

(*Continued*)

TABLE 23.4 (Continued)

Cognitive domain(s) predominantly affected in initial stages	Commonly used terminology	DSM-5 classification	Terminology based on most recent non-DSM-5 classifications	Underlying proteinopathy/ pathology
Deficits in social cognition	Behavioral-variant frontotemporal dementia (bv-FTD)	Major or mild frontotemporal neurocognitive disorder, behavioral variant	bv-FTD[k]	Tauopathy or TDP-43-opathy (Type A or B)[d]
Mixed clinical presentations, usually involving deficits in attention, processing speed, and executive function, but can involve other domains as well	Vascular dementia	Major or mild vascular neurocognitive disorder	Vascular cognitive impairment[l]	Poststroke dementia
				Mixed dementias
				Subcortical ischemic vascular dementia
				Multiinfarct (cortical) dementia

[a] *2018 National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework (Jack et al., 2018).*
[b] *The behavioral/ dysexecutive variant of Alzheimer's disease (Ossenkoppele et al., 2015).*
[c] *Classification of primary progressive aphasia (Gorno-Tempini et al., 2011).*
[d] *Transactive response DNA-binding protein-43 kD.*
[e] *Clinical profile of right temporal lobe atrophy (Chan et al., 2009).*
[f] *Fourth Consensus Report of the DLB Consortium (McKeith et al., 2017).*
[g] *Clinical diagnostic criteria for Parkinson's disease dementia (Emre et al., 2007).*
[h] *Consensus classification of posterior cortical atrophy (Crutch et al., 2017).*
[i] *Criteria for the diagnosis of corticobasal degeneration (Armstrong et al., 2013).*
[j] *Alzheimer's disease presenting as corticobasal syndrome (Sakae et al., 2019).*
[k] *Revised diagnostic criteria for the behavioral variant of frontotemporal dementia (Rascovsky et al., 2011).*
[l] *Guidelines from the Vascular Impairment of Cognition Classification Consensus Study—VICCCS2 (Skrobot et al., 2018).*

TABLE 23.5 Antidementia drugs available in the United States in 2019.

Antidementia drug (Brand name) *Available formulations*	Elimination half-life	Metabolic pathway (major pathway (s) in bold)	Comments
Donepezil (Aricept) *Avail as tab, ODT*	70 h	**CYP3A4**, CYP2D6	No renal dosing necessary
Rivastigmine (Exelon) *Avail as cap, patch*	1.5 h; nonlinear PK above 3 mg BID dose	**Cholinesterases**	Reduce dosage in mild-moderate hepatic impairment; no data in severe hepatic impairment; reduce dosage in moderate–severe renal impairment
Galantamine (Razadyne) *Avail as tab, solution, ER cap*	7 h	**CYP2D6, CYP3A4**	Reduce dosage in moderate–severe hepatic impairment; reduce dosage in moderate–severe renal impairment
Memantine (Namenda) *Avail as tab, solution, ER cap*	60–80 h	Does not involve the CYP450 system, almost 50% excreted unchanged in urine	Use with caution in severe hepatic impairment; reduce dosage in severe renal impairment

ODT, orally dissolving tab; *PK*, pharmacokinetics; *ER*, extended release.

and rivastigmine are FDA-approved to treat only mild-to-moderate AD dementia, but there is no reason to believe that they are not effective for severe disease as well. Memantine is effective for and FDA-approved for the treatment of only moderate to severe AD dementia (Kishi et al., 2017; Kishi, Matsunaga, Oya et al., 2017). In contrast to the cholinesterase inhibitors, there is research to show that memantine is *not* effective for mild AD dementia (Schneider et al., 2011), and its use in mild cases is not recommended. Whether memantine is best used as monotherapy or as adjunct to a cholinesterase inhibitor in moderate to severe AD dementia has been the subject of debate ever since memantine was first marketed. Long-term continuation of donepezil therapy appeared to confer cognitive and functional benefits in moderate to severe AD that were not exceeded by adding memantine in the 52-week donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO) trial (Howard et al., 2012). European guidelines recommend the use of the combination "based on weak evidence" (Schmidt et al., 2015), and a meta-analysis also supports the use of combination therapy in moderate to severe AD dementia, as combination of donepezil and memantine led to greater improvement in cognitive functions, neurobehavioral symptoms, and global functions than did donepezil monotherapy (Matsunaga, Kishi, & Iwata, 2014).

No medication is currently approved for the treatment of cognitive symptoms in vascular dementia, which is a highly heterogeneous category as is evident from Table 23.4. The clinical benefit of cholinesterase inhibitors and memantine in vascular dementia is questionable, which may be because loss of cholinergic function is present only in patients with co-occurring AD dementia, also called mixed dementia (Sharp et al., 2009). Their widespread use in vascular dementia is not recommended, but they may benefit select patients. Presence of hippocampal atrophy at baseline may improve the response to donepezil in vascular dementia, but whether such atrophy is an imaging biomarker for co-occurring AD could not be ascertained in the study (Roman et al., 2010). Similarly, there is some evidence in support of a differential benefit of memantine in patients with more severe vascular dementia, and in vascular dementia due to small vessel disease rather than due to large vessel strokes (Mobius & Stoffler, 2003). A meta-analysis that included all studies (of 6-months duration each) that compared the cholinesterase inhibitors and memantine with placebo (Kavirajan & Schneider, 2007) concluded that all active drugs produced small benefits in cognition and no benefits in behavior or functioning in patients with mild-to-moderate vascular dementia. Adverse effects were common with the cholinesterase inhibitors (anorexia, nausea, vomiting, diarrhea, and insomnia) but not with memantine. In a single double-blind RCT of donepezil for the treatment of cognitive symptoms in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is the most common hereditary stroke disorder, there was evidence that the active drug improved the three main "vascular" cognitive symptoms—executive function, processing speed, and attention—in this relatively "pure" vascular dementia sample (Dichgans et al., 2008), which has not yet been replicated.

Cholinesterase inhibitors are indicated for the treatment of both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). No medication has an FDA-approved indication for the treatment of DLB, although improvements in cognition and behaviors have been found with the cholinesterase inhibitors including in cognitive fluctuations, but not in the activities of daily living (Noufi, Khoury, Jeyakumar, & Grossberg, 2019). In a large placebo-controlled RCT from Europe and the United Kingdom, rivastigmine was found to be effective in treating cognition and behaviors in DLB in the short term, but the benefits did not persist upon drug discontinuation as would be expected with a symptomatic treatment (McKeith et al., 2000). Another small 96-week open trial also found that the benefits did not persist beyond 36 weeks (Grace et al., 2001). Donepezil has similarly been found to be effective in the treatment of DLB for at least up to 52 weeks (16-week RCT and 36-week open-label extension), and patients who did not respond to the 5-mg dose responded to the 10-mg dose without any worsening in parkinsonism (Mori, Ikeda, Nagai et al., 2015; Mori, Ikeda, Nakagawa et al., 2015).

Rivastigmine (oral and patch) is the only cholinesterase inhibitor that has an FDA-approved indication for the treatment of PDD, based on a 24-week EXelon in PaRkinson's disEaSe dementia Study (EXPRESS) with a 48-week open-label extension that found oral rivastigmine effective in treating cognition, behavior, and activities of daily living (Emre et al., 2004; Poewe et al., 2006). Almost a third of patients experienced nausea, while vomiting and tremor were other common adverse effects in the RCT and its open-label extension. There is a suggestion from open-label and open-controlled trials (Aarsland, Hutchinson, & Larsen, 2003; Litvinenko, Odinak, Mogil'naya, & Emelin, 2008) that galantamine has a larger treatment effect on hallucinations and even on parkinsonism, gait, and falls in PDD, but it has a distinct adverse effect profile (drooling, postural hypotension, nausea, dysuria in a third of patients). Its place in the treatment of PDD vis-à-vis rivastigmine is unclear in the absence of head-to-head comparisons of the two drugs in PDD.

Memantine appears to have a differential treatment effect in the Lewy body dementias, leading to global and behavioral improvement in DLB but not in PDD patients in a large placebo-controlled RCT, with no significant worsening of parkinsonism (Emre et al., 2010).

In summary, the cholinesterase inhibitors should be tried for the treatment of cognitive symptoms in the Lewy body dementias, with oral rivastigmine being the drug of choice, and the patch should be tried instead if the oral drug is not tolerated due to nausea and vomiting. Donepezil should be considered next for the treatment of DLB, and galantamine for the treatment of PDD. In addition to cognition, cholinesterase inhibitors may improve behavior in both DLB and PDD, as well as cognitive fluctuations in DLB. Memantine should be tried in DLB but avoided in PDD patients.

No treatments are approved by the FDA for bv-FTD. Cholinesterase inhibitors have not been shown to be effective in treatment of bv-FTD and may even worsen cognition and behaviors (Noufi et al., 2019). Memantine alone had no benefit and led to cognitive worsening in patients with clinically and radiologically confirmed bv-FTD and semantic-variant primary progressive aphasia in a large, multicenter RCT (Boxer et al., 2013). A single double-blind RCT of trazodone in FTD diagnosed by the 1994 Lund and Manchester criteria (Lebert, Stekke, Hasenbroekx, & Pasquier, 2004) found improvement in irritability, agitation, depressive symptoms, and eating disorders, and it was well tolerated, but this has not been replicated using the current 2011 Roscovsky bv-FTD diagnostic criteria. Also, 11 of 26 patients reported a treatment-emergent adverse event on trazodone, including fatigue, dizziness, hypotension, and cold extremities. Lack of insight is particularly problematic for patients with bv-FTD, and they are unwilling to accept a medication that is dosed 2−3 times daily. A long-acting formulation of trazodone (Oleptro) was briefly available in the United States, which may have been more acceptable to such patients due to its once-daily dosing, but it has since been withdrawn from the market.

Neurobehavioral symptoms in the dementias in older adults

Introduction

Neurobehavioral symptoms, also referred to as *behavioral disturbance* in DSM-5 and as *neuropsychiatric symptoms of dementia* or *behavioral and psychological symptoms of dementia* in research studies, occur to a greater or lesser extent in all dementias and lead to a worse prognosis, greater functional decline, increased caregiver distress, increased mortality risk, and higher cost of care. Agitation and psychosis result in increased caregiver distress and burnout (Hiyoshi-Taniguchi, Becker, & Kinoshita, 2018), which in turn leads to more emergency room visits and hospitalizations (Maust et al., 2017). Psychosis is also a well-known predictor of institutionalization (Connors, Ames, Woodward, & Brodaty, 2018). Apathy has been shown to be significantly associated with impairment of both basic and instrumental activities of daily living in AD dementia, accounting for 27% of the variance in instrumental and 15% of the variance in basic activities of daily living, over and above that due to executive dysfunction deficits alone (Boyle et al., 2003). Like other neurobehavioral symptoms, apathy is also associated with a faster rate of cognitive and functional decline in AD dementia.

Across the dementias, greater baseline neurobehavioral symptoms have been associated with male sex, severity of the dementia, and a diagnosis of bv-FTD, while AD dementia is associated with lower levels of neurobehavioral symptoms at baseline compared to other types of dementia (Brodaty, Connors, Xu, Woodward, & Ames, 2015). Prevalence studies generally indicate that apathy is the most common neurobehavioral symptom, followed by depression in AD and vascular dementias, and agitation in DLB and bv-FTD (Benalfew Legesse, Baktash Babadi, & Brent Forester, 2017). However, mixed pathologies are seen in 10%−74% of aging brains with a higher prevalence in those who have dementia (Rahimi & Kovacs, 2014), and epidemiological studies that lack histopathological confirmation run the risk of conflating dementia patients with AD and other co-occurring neuropathology. In autopsy-confirmed AD cases where all non-AD pathology was excluded, higher odds vis-à-vis healthy controls were reported for agitation, anxiety, depression, and sleep disturbances in Braak stages I/II, with the higher odds for agitation continuing into Braak stages III/IV. Braak stages V/VI was associated with a higher odds for delusions (Ehrenberg et al., 2018), while apathy was not common. Radiologically defined white matter hyperintensities in the deep fronto-subcortical regions in patients with AD/vascular/mixed dementia are thought to be a marker for small vessel disease in the brain and have been shown to be independently related to apathy and mental slowness (Jonsson et al., 2010). Cerebrovascular pathology is more common on autopsy in AD than in other neurodegenerative dementias, and some degree of vascular pathology has been reported in up to 80% of all AD cases on autopsy, which was thought to be severe enough to contribute to clinical symptoms in a third of all AD cases (Toledo et al., 2013). More recent work has found that brain network disruption seen on diffusion tensor tractography underlies apathy, while the radiological markers of white matter hyperintensities and lacunar infarcts only partially mediated the relationship between apathy and the brain network measures (Tay et al., 2019).

The prevalence of neurobehavioral symptoms increases with progression of the dementia. The Cache County study revealed found a trend for the point prevalence of nearly all neurobehavioral symptoms to increase over a 5-year period

in incident dementia (Steinberg et al., 2008). Over the 5-year period of the study, 97% of those with incident dementia experienced at least one neurobehavioral symptom. Five-year period prevalence was greatest for depression (77%), apathy (71%), and anxiety (62%), while it was the lowest for elation (6%). However, not all neurobehavioral symptoms increase as the dementia progresses. In a clinic-based study from Australia that followed dementia patients over a 3-year period, the 12-item NPI symptoms that progressively increased were delusions, hallucinations, agitation, anxiety, apathy, disinhibition, irritability, and aberrant motor behavior, while neurobehavioral symptoms that did not increase over time were depression, euphoria, nighttime behaviors, and appetite (Brodaty et al., 2015). All patients had baseline and five follow-up assessments, and at each assessment, approximately 90% of the sample had one or more NPI symptoms, over 50% of the sample had one or more clinically significant symptoms, and around had 80% multiple symptoms, which again speaks to how ubiquitous neurobehavioral symptoms are in the dementias.

Before embarking on a plan of treatment, it is important to clearly define some neurobehavioral symptom(s). Psychosis and agitation in dementia are usually considered together but there are important differences between the two. The International Psychogeriatric Association Agitation Definition Work Group developed a provisional consensus definition of agitation that applies to all patients with cognitive impairment or dementia syndrome (Cummings et al., 2015). Behaviors included are excessive motor activity, verbal or physical aggression severe enough to cause disability in excess of that due to the cognitive impairment itself, which are persistent or frequently recurrent for a minimum of 2 weeks, represents a change from the patient's usual behavior, and are not due to another psychiatric disorder, medical condition, or substance use.

Psychosis has been defined in AD dementia to differentiate it from primary psychotic disorders (Jeste & Finkel, 2000). The diagnostic criteria for psychosis of dementia indicate that, in a patient who has never met the criteria for a primary psychotic disorder or mood disorder with psychotic features, the onset of hallucinations (visual and/or auditory) and/or delusions must follow the onset of AD dementia, be present continuously or intermittently for at least 1 month and cause some impairment of functioning for the patient and/or caregivers, not occur exclusively during a delirium, and is not better explained by a medication, substance use, or another medical condition. The text clarifies that the criteria "may apply to a similar psychotic syndrome associated with other dementias such as Lewy body dementia, vascular dementia, and mixed dementia." The phenomenology of persisting schizophrenia in older adults is distinct from that of psychosis in dementia in that the former presents with bizarre or complex delusions, auditory hallucinations, Schneiderian first-rank symptoms, and a prior history of psychosis (Jeste & Finkel, 2000), while the phenomenology of psychosis of dementia differs according to the type of dementia. In psychosis of AD, simple persecutory delusions (theft) are the most common (about 50% of all delusions), visual hallucinations (median 19%) are twice as common as auditory (median 9%), and a median of around 25% of patients have uncategorized psychotic symptoms, mostly misidentification symptoms (Ropacki & Jeste, 2005). Cooccurring Lewy body pathology, advanced small vessel disease, and cerebral amyloid angiopathy, which is often a comorbid condition in AD that presents as cerebral microbleeds ("blooming artifacts") on MRI, can all result in an increased risk of psychosis in AD dementia (Fischer et al., 2016; Vik-Mo, Bencze, Ballard, Hortobagyi, & Aarsland, 2019). Prevalence rates and phenomenology of psychosis in vascular and mixed dementias approximates that in age-matched AD dementia when autopsy confirmation of the diagnosis is obtained (Echavarri et al., 2013), although the heterogeneity inherent in the vascular dementia diagnosis makes it difficult to make accurate estimates. The discrepant finding of a higher prevalence of psychosis in studies of vascular dementia in community-dwelling adults aged 85 and above vis-à-vis AD dementia (Ostling, Gustafson, Blennow, Borjesson-Hanson, & Waern, 2011) may be explained by the increased prevalence of mixed pathologies in the oldest-old.

In psychosis of DLB, recurrent well-formed visual hallucinations are seen in 80% of patients (McKeith et al., 2017), which are typically complex, often involving people, children, or animals, and may be accompanied by typical parkinsonian presence and passage hallucinations, as well as illusions. Pareidolias are complex visual hallucinations involving ambiguous stimuli that are perceived as meaningful objects (e.g., seeing a face in a piece of toast) and are common in patients with DLB, with or without true visual hallucinations (Uchiyama et al., 2012). Delusional misidentification and related symptoms are also common in DLB. A study that looked at all patients who had received a diagnosis of Capgras syndrome at the Mayo Clinic from 1996 to 2006 found that about 80% of patients had a neurodegenerative disorder, of which DLB was the most common (68%), all of whom had visual hallucinations (Josephs, 2007).

As already noted, apathy and depression are also common neurobehavioral symptoms in the dementias. The Association Française de Psychiatrie Biologique and the European Psychiatric Association Task Force developed criteria for apathy in AD and other neuropsychiatric disorders in 2009, which were revised in 2018 (Robert et al., 2018). Criterion A in the revised criteria includes "presence of quantitative reduction of goal-directed activity either in the behavioral, cognitive, emotional, or social dimension in comparison to the patient's previous level of functioning."

Criterion B distinguishes apathy from transient or intermittent states by specifying a minimum duration of 4 weeks, and symptoms need to present in at least two out of the following three dimensions: behavior and cognition, emotion, and social interaction. Criterion C refers to functional impairment due to the above symptoms, and criterion D excludes symptoms "not exclusively explained or due to major changes in the patient's environment." The provisional NIMH definition of depression of AD was borrowed from the categorical approach of DSM-IV-TR with modifications to accommodate lack of verbal expression in patients with AD (Olin et al., 2002). Only three or more symptoms are required, as opposed to five for diagnosing major depressive disorder, to be present in the same 2-week period as opposed to nearly every day, and must represent a change from previous functioning, at least one of which is either depressed mood or decreased positive affect/pleasure. New criteria for the presence of irritability and social isolation/withdrawal were added. Footnotes were provided to indicate that information should be obtained from informants, and that social withdrawal and isolation as well as psychomotor retardation and agitation can also occur due to AD itself, and clinical judgment should be exercised in differentiating between the two. It was also noted that suicidal ideations are less commonly observed in depression of AD than in major depressive disorder, but when they do occur, they are likely specific for depression. The patient should meet all criteria for a diagnosis of AD dementia, the symptoms should cause clinically significant disruption in functioning or distress, and should not occur exclusively during a delirium or be accounted for by substance use, other primary psychiatric disorders, or bereavement. Criterion validity for these criteria has been established (Sepehry et al., 2017).

Drugs for the treatment of neurobehavioral symptoms in the dementias

Nonpharmacological interventions should be tried first in treating all neurobehavioral symptoms (Cohen-Mansfield & Mintzer, 2005; Reus et al., 2016). However, these interventions are time- and resource-intensive, and in the current era of rapid staff turnover in residential settings, trained individuals are increasingly difficult to hire and retain. These interventions will not be covered here in any detail as the focus here is on psychopharmacological interventions, but a practical review of nonpharmacological approaches can be found here in Caspar, Davis, Douziech, & Scott, 2018.

Prior to deciding on an appropriate pharmacological treatment, a standard approach to evaluating neurobehavioral symptoms in dementia is critical. A complete dementia evaluation should be carried out to determine underlying etiology as much as possible, including neuroimaging in all patients and functional imaging and/or cerebrospinal fluid biomarker studies when indicated. The neurobehavioral symptoms should be clearly identified, and use of standard definitions and an assessment tool, such as the 12-item NPI (Cummings, 1997), at least once during the initial evaluation is strongly recommended.

Once the presence of both the dementia and the neurobehavioral symptoms has been established, use of the DICE approach to decision-making is recommended. DICE is comprised of four steps, namely Describe, Investigate, Create, and Evaluate (Kales, Gitlin, & Lyketsos, 2014), and is supported by CMS. The DICE approach identifies three situations where there are concerns about imminent dangerousness—major depression with or without suicidal ideations, psychosis causing harm or with great potential of harm, and aggression causing risk to self or others. In each of these cases, the time-limited use of psychotropic medications is recommended with close follow-up to monitor for any adverse effects after a thorough evaluation of the risk/benefit ratio. A similar approach is supported by the 2016 American Psychiatric Association (APA) Practice Guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia in statement 5 (Reus et al., 2016). Also, while the large CATIE-AD study (Schneider et al., 2006) found that the modest improvement in psychosis was offset by the high rate of adverse effects, a reanalysis of the data subsequently found antipsychotics to be particularly effective in treating the target symptoms of anger, aggression, and paranoid ideations (Sultzer et al., 2008).

The careful use of select antipsychotics in treating psychosis of dementia, mostly AD dementia, is supported across clinical guidelines (Azermai et al., 2012), although the effect size varies across studies and there are considerable differences between available antipsychotics, both in terms of benefits as well as adverse effects. In 2005, the FDA issued a black box advisory after an analysis of 17 controlled studies of elderly demented patients found that patients treated with these drugs were 1.6−1.7 times more likely to die than patients given placebo. Specifically, the FDA found that patients taking olanzapine, aripiprazole, risperidone, or quetiapine had a 4.5% risk of dying, while the risk in those taking placebo was 2.6%. The advisory was expanded to include all antipsychotics in 2008 (Kuehn, 2008). Since then, antipsychotic-associated mortality in dementia has been assumed to be a class effect and all antipsychotics, whether first or second generation, have carried the black box warning, including the novel antipsychotic pimavanserin. Unfortunately, while the black box warnings have led to a reduction in antipsychotic use in the dementias, an unintended consequence has been the increase in use of nonantipsychotic medications, including a threefold increase in the

use of benzodiazepines (Singh & Nayak, 2016), which carry their own risks that will be discussed later in the section on treatment of anxiety.

Four second-generation antipsychotics, risperidone, olanzapine, quetiapine, and aripiprazole, have been studied the most for the treatment of psychosis and agitation/aggression in AD dementia, but there is little consensus about which antipsychotic is the most effective. In the CATIE-AD trial, the median time-to-discontinuation due to lack of efficacy favored olanzapine and risperidone, while quetiapine did not differ significantly from placebo (Schneider et al., 2006). A meta-analysis looked at benefits and adverse effects of these four atypical antipsychotics in patients with dementia (Schneider, Dagerman, & Insel, 2006) and found significant improvement with aripiprazole and risperidone with small but statistically significant effect sizes, while for olanzapine, the benefits did not reach statistical significance. While data from three quetiapine trials could not be pooled, none of the trials individually showed improvement. A 2006 Cochrane collaboration review found efficacy for risperidone and olanzapine for the treatment of both aggression and psychosis in AD dementia, but recommended against their routine use because "both are associated with serious adverse cerebrovascular events and extrapyramidal symptoms" (Ballard & Waite, 2006). In a review of available meta-analyses (Tampi, Tampi, Balachandran, & Srinivasan, 2016), the first-generation antipsychotics were found to have modest efficacy when used in individuals with dementia with no superiority for any particular medication in this drug class, and three second-generation antipsychotic medications (risperidone, olanzapine, and aripiprazole) were also found to have modest efficacy, while quetiapine was found to have limited efficacy. The 2016 APA practice guidelines do not recommend use of any one antipsychotic as a first-line agent (Reus et al., 2016). The Canadian Consensus Conference (Herrmann, Lanctot, & Hogan, 2013) noted "insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression, and psychosis associated with dementia", and recommended that "risperidone, olanzapine, and aripiprazole be used for severe agitation, aggression, and psychosis associated with dementia where there is risk of harm to the patient and/or others."

Since psychosis does not persist for very long in most patients with dementia, a "short" antipsychotic trial is typically recommended. How short is "short"? The recommended length ranges from a 3-month trial (Ballard et al., 2009) to a 4-month trial in the APA guideline (Reus et al., 2016) to a 3- to 6-month trial in the 2004 Expert Consensus Guidelines (Alexopoulos, Streim, Carpenter, & Docherty, 2004) once there is an adequate initial response. Unfortunately, this does not reduce the risk of mortality. Many, but not all, studies found that the mortality risk is front-loaded (Ballard et al., 2009; Ralph & Espinet, 2018), and in the subsequent weeks to months after starting an antipsychotic, the risk of mortality likely drops but not all the way down to zero. Early identification of non-response to an antipsychotic medication therefore becomes important, so that the drug is not unnecessarily continued for several additional weeks. The CATIE-AD study found that a 5% reduction in the Brief Psychiatric Rating Scale score at week 2 provided about 70% accuracy in predicting the treatment response to antipsychotics by week 8 (Yoshida et al., 2017). This suggests that a lack of response at the end of week 2 should prompt the clinician to consider switching antipsychotics, rather than wait another few weeks. In a reanalysis of the CATIE-AD data (Nagata et al., 2017), better treatment response was predicted by "a lower Mini-Mental State Examination score, treatment with risperidone (vs olanzapine and quetiapine), history of diabetes mellitus, healthier physical status, and more severe initial psychotic symptoms" at baseline.

Apart from increased mortality, most of the adverse effects of antipsychotics are essentially the same as those seen with their use in the treatment of schizophrenia in older adults, with some exceptions. Risk of cerebrovascular events (strokes) appears to be higher with antipsychotic use in dementia, especially for first-generation antipsychotics and within the first 30 days (Kleijer et al., 2009; Sacchetti, Turrina, Cesana, & Mazzaglia, 2010; Sacchetti, Turrina, & Valsecchi, 2010). Placebo-controlled clinical trials are mostly short-term studies, and the difference in the cerebrovascular risk between active and placebo groups is maximized when the risk is assumed to remain stable over the course of longer-term treatment (Sacchetti et al., 2010; Sacchetti, Turrina, Cesana, et al., 2010). Population studies cover longer periods of time, which explains why the slightly increased risk of cerebrovascular adverse events found in short-term RCTs with the use of risperidone and olanzapine has not been seen in longer-term observational studies in real-world patients (Herrmann & Lanctot, 2005). Antipsychotics also appear to increase the risk of venous thromboembolism in older patients in general (Lacut et al., 2007), and the risk may increase further in dementia patients who are even more frail and sedentary than nondemented older adults.

Alternatives to antipsychotic use for the treatment of neurobehavioral symptoms in dementia have been well studied, and two classes of drugs deserve mention, the antidementia drugs and the SSRIs. Use of cholinesterase inhibitors and memantine increased twofold after the first FDA antipsychotic advisory was issued in 2005 (Singh & Nayak, 2016). Antidementia medications have an antipsychotic-sparing effect, which has been found for both cholinesterase inhibitors and memantine in several, but not all, studies (Martinez, Jones, & Rietbrock, 2013; Suh et al., 2004). Cholinesterase

inhibitors are better tolerated than antipsychotics, but their overall clinical benefit in treating neurobehavioral symptoms is small and any improvement in symptoms may take weeks to months, which is why short-duration studies fail to find benefit (Passmore, Gardner, Polak, & Rabheru, 2008). They are best used as an adjunct to antipsychotics and not as monotherapy for treating neurobehavioral symptoms.

The Citalopram for Agitation in Alzheimer's Disease (CitAD) trial has greatly contributed to the preexisting evidence base supporting the use of SSRIs in the treatment of agitation in AD dementia, which appears to be a class effect (Aga, 2019). In the CitAD trial (Porsteinsson et al., 2014), 186 patients clinically diagnosed with AD dementia were randomized to receive a psychosocial intervention plus either citalopram ($n = 94$) or placebo ($n = 92$) for 9 weeks. By the end of the 9-week study, about 80% subjects remained on treatment, indicating a low dropout rate, but 78% of the sample were receiving 30 mg citalopram daily, which is more than the FDA-recommended maximum of 20 mg for patients above 60 years. There was an advantage for citalopram over placebo in the treatment of agitation and caregiver distress, which was not solely a function of citalopram-induced sedation (Newell et al., 2016). A reanalysis of the CitAD data found the following predictors of response (Schneider et al., 2016): outpatients, those with milder cognitive impairment, those with moderate agitation, and those who were within the middle age range (76–82 years).

Other drugs that have been studied for the treatment of psychosis or agitation in the dementias are summarized in Table 23.6. None is recommended for the first- or second-line treatment of neurobehavioral symptoms in dementia, but since there are not many pharmacological options, the use of carbamazepine, gabapentin, trazodone, and cannabinoids may be justified in special situations on a case-by-case basis and only after a thorough risk-benefit analysis that is carried out collaboratively with the patient or surrogate decision-maker that should be documented. Optimal doses are unknown for these medications for the treatment of neurobehavioral symptoms in dementia; as a general rule, providers must start low and titrate the dose slowly once it is decided to use one of these medications.

Evidence-based drug treatment of neurobehavioral symptoms in the dementias in older adults

Many algorithmic approaches have been recommended for the treatment of agitation and psychosis in the dementias, and a recent sequential algorithm for use in patients with AD or mixed dementia has practical value (Davies et al., 2018). The following recommendations build upon this algorithm, with a few modifications based on the discussion in the previous section:

1. Screening for cardiac risk should be completed prior to starting the medications below, which should include a cardiac history, checking baseline electrolyte levels and a baseline EKG in all patients.
2. A cholinesterase inhibitor should be started as first-line agents for the treatment of neurobehavioral symptoms in all patients with AD/vascular/mixed/Lewy body dementias.
3. Instead of using antipsychotics and citalopram sequentially as recommended in the Davies algorithm, the next step should be to decide on the presence and severity of psychosis versus nonpsychotic agitation:
   a. Agitation/aggression with low-grade/no psychosis—In these patients, citalopram or escitalopram should be considered as a second-line agent, with as-needed antipsychotic use only as rescue medications for the first several weeks that it takes for citalopram (or escitalopram) to become effective.
   b. Frank psychosis and/or imminent risk of physical aggression—In these patients, antipsychotics should be considered next. Risk-benefit analysis should be discussed with patients/caregivers/surrogate decision-makers, including the FDA black box warnings, and informed consent should be clearly documented.
4. Risperidone should be considered as the first-line antipsychotic for treatment of severe agitation, aggression, and frank psychosis in AD/vascular/mixed dementia, and olanzapine and aripiprazole should be considered as second-line antipsychotics.
5. Quetiapine and clozapine should be considered first in the Lewy body dementias. Use of risperidone, olanzapine and aripiprazole should be avoided as they can worsen parkinsonism.
6. Use of adjunctive carbamazepine or gabapentin should be considered on a case-by-case basis based on the underlying etiology. Monitoring for hyponatremia and DDIs and testing for HLA B*1502 in Asian patients (see section on drug–gene interactions) when using carbamazepine is critical for a successful trial. Gabapentin use is best avoided in DLB, as marked worsening of neurobehavioral symptoms, especially hallucinations, has been reported (Rossi, Serrao, & Pozzessere, 2002).
7. Cannabinoids have a role as add-on treatment for severe agitation/aggression in hospitalized patients with severe AD dementia.

TABLE 23.6 Nonantipsychotic medications for the treatment of psychosis and agitation in the dementias.

Medication (Brand name)	Risks and benefits	Comments
Antiepileptic drugs		
Divalproex sodium (Depakote) Valproic acid (Depakene)	Poorly tolerated (sedation, risk of urinary tract infections, falls, infection, GI disorders); accelerates brain volume loss in AD dementia; mortality risk likely no different from risperidone and olanzapine	Avoid
Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Epitol, Equetro)	Evidence from RCTs supports its use for the treatment of hostility and aggression, especially in patients with AD dementia; considerable risk of hyponatremia, DDIs, ataxia, diplopia, and blood dyscrasias; may take up to 12 weeks to be effective	May consider using as *third-line* drug in treatment of hostility/aggression/agitation in moderate to severe AD/vascular/mixed dementia after a thorough risk-benefit analysis; optimal dose unknown, but modal dose used in two large studies was only 300 mg/day; no therapeutic blood level is known
Oxcarbazepine (Trileptal)	One negative RCT in AD/mixed/vascular dementia; risk of severe hyponatremia	Avoid
Gabapentin (Neurontin)	Non-RCT evidence supports its use; higher doses can be sedating; renal dosing essential in older adults	Non-RCT evidence base supports use in low doses as *fourth-line* drug in AD/vascular/mixed dementia; optimal dose unknown
Levetiracetam (Keppra)	Open-label studies support use for mania but not agitation in dementia; very preliminary evidence of improvement in memory tasks in amnestic MCI in tiny doses; high rates of psychiatric and behavioral side effects, which occur in more than 20% of patients with epilepsy	Avoid due to behavioral side effects
Topiramate (Topamax)	One RCT that compared it to risperidone in AD dementia lacked a placebo group; loss of appetite and weight can occur, especially if used concurrently with cholinesterase inhibitors	Avoid due to risk of weight loss
Lamotrigine (Lamictal)	Minimal non-RCT evidence supports use in treatment of mania-like symptoms and agitation in AD dementia; slow dose titration makes it a poor choice for acute treatment	Avoid in the absence of known bipolar disorder at baseline
Nonantiepileptic mood stabilizers		
Lithium (Eskalith, Lithobid)	Non-RCT evidence supports use in low doses to treat anxiety, psychosis, and aggression in AD and FTD; increased risk of toxicity in presence of dehydration; high potential for DDIs in older adults (e.g., with thiazides, ACEIs, ARBs, NSAIDs)	Avoid in the absence of known bipolar disorder at baseline

Antidepressants		
Trazodone (Desyrel)	In one RCT in FTD, trazodone improved irritability, agitation, depressive symptoms, and eating disorders; higher risk of falls and sedation; most guidelines recommend against its use	Best avoided, except for treating neurobehavioral symptoms in FTD; optimal dose unknown − in the FTD study, patients received a dose of 150−300 mg/day
Cannabinoids		
Dronabinol (Marinol) Nabilone (Cesamet)	Modest evidence to support the use of dronabinol as add-on therapy to antipsychotics for agitation/aggression in severe dementia (mostly AD/VaD/mixed pathology), based on a retrospective chart review; a 14-week placebo cross-over RCT of nabilone as an add-on to antidementia and psychotropic medications for treatment of agitation in AD was positive without any cognitive worsening; both can cause sedation and delirium; both are controlled substances; insurance coverage for this indication may be difficult to obtain	*Fourth-line* use as adjunct to antipsychotics for the treatment of agitation/ aggression in severe AD/mixed dementia; optimal dose of both is unknown—in the dronabinol study, the mean daily dose was 7.03 mg/day, and in the nabilone RCT, patients received 0.25−2 mg/day

GI, gastrointestinal; *AD*, Alzheimer's disease; *VaD*, vascular dementia; *DDIs*, drug−drug interactions; *RCT*, randomized control trial; *FTD*, frontotemporal dementia; *ACEIs*, angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin receptor blockers; *NSAIDs*, nonsteroidal antiinflammatory drugs; *MCI*, mild cognitive impairment.

8. Psychotic symptoms in AD/vascular/mixed dementia are usually short-lasting. After 3–6 months of treatment, a first attempt should be made to wean the patient off the antipsychotic medication. The optimal length of treatment with antipsychotics in the Lewy body dementias is unknown.

Finally, antidepressants are the obvious choice for treating depression in dementia, and indeed, in a Finnish nationwide register study, antidepressant use was three times more prevalent among persons with AD dementia (mean age 80.0 ± 6.8 years) compared to individuals without AD dementia who were matched for age, sex, and region of residence (Laitinen et al., 2015), with the prevalence of antidepressant use increasing with the duration of AD dementia. As depression is more common in the prodrome and during the early stage of AD dementia but psychosis more common later in the disease, the pattern of increasing use implies that antidepressants were being used to treat both early depression and later psychosis. However, antidepressants have been found to have weak to no efficacy in treating depression in AD dementia (Farina, Morrell, & Banerjee, 2017; Nelson & Devanand, 2011). A meta-analysis of seven double-blind RCTs that compared antidepressants with placebo for the treatment for depression in AD dementia found no statistically significant difference between the two groups for depressive symptoms and rated the quality of evidence as moderate (Orgeta, Tabet, Nilforooshan, & Howard, 2017). A systematic review and meta-analysis from the Cochrane collaboration similarly found weak evidence that antidepressants are effective for the treatment of depression in any type of dementia, especially beyond 12 weeks, with high-quality evidence showing little or no effect on depression rating scale scores; furthermore, patients on antidepressants were more likely than those on placebo to drop out of treatment (Dudas, Malouf, McCleery, & Dening, 2018). Antidepressants also did not lead to any improvement in the patient's ability is to manage activities of daily living and had little or no effect on cognitive functioning. This study did not report on any differences between the various dementias, the different classes of antidepressants, or the different subtypes of depression. Augmentation strategies for the treatment of depression in dementia have not been systematically studied, and a 2011 review of augmentation strategies for TRDOA (Cooper et al., 2011) did not specifically address strategies for the treatment of depression in dementia.

Anxiety in older adults

Introduction

Older people often have much to worry about: illness, physical and financial security, social isolation, safety, accidents, and the approach of disability, dependence, dementia and ultimately, death. As a psychiatric diagnostic category, age-appropriate worry can progress to a clinical diagnosis of anxiety and eventually to a syndromal diagnosis of generalized anxiety disorder (GAD) if it is long-lasting. Furthermore, advanced age is not a barrier to the experience of the spectrum of anxiety disorders, including social anxiety, panic, and phobias. However, these spectrum disorders are less common in the elderly, so this section will be devoted to the treatment of acute anxiety and the more chronic GAD (Salzman, 2005).

Anxiety in older people is characterized by cognitive, emotional, and physical symptoms. Decreased concentration, attention, and memory are common, as are disturbed sleep, fluctuating GI and urinary symptoms, and a variety of aches and pains. Distinguishing between anxiety as a diagnostic category worthy of psychiatric treatment and "worry," a normal mood state that does not necessarily require pharmacological treatment, is important. There is an effect of age on worry, with younger adults worrying more about work and interpersonal relationships and older adults worrying more about health and welfare of loved ones (Goncalves & Byrne, 2013).

Anxiety disorders are quite prevalent in older adults, with a 12-month prevalence of around 10% and lifetime prevalence of around 15% (Beekman et al., 1998). They result in increased use of health care services, greater disability, and a lower health-related quality of life (Porensky et al., 2009). GAD is the most common anxiety disorder. About 50% of older adults with GAD have onset after age 50, and late-onset GAD differs from early-onset GAD by a more frequent association with the presence of hypertension and a poorer health-related quality of life (Chou, 2009), while those with early-onset GAD appear to have a more severe course with higher rates of psychiatric comorbidity and psychotropic medication use (Le Roux, Gatz, & Wetherell, 2005).

Drugs for the treatment of anxiety

When anxiety and anxiety disorders require psychotropic drug treatment, several classes of medications are available for prescription. These are listed in Table 23.7.

Regardless of drug chosen, general geriatric prescribing principles apply, and these are listed in Table 23.8.

Drugs commonly used for the treatment of anxiety include the benzodiazepines, buspirone, and the antidepressants.

TABLE 23.7 Drugs for the treatment of anxiety and anxiety disorders.

Drugs	Use	Comments	FDA approval
Benzodiazepine (short half-life)	For immediate relief	Safe and effective; side effects may limit long-term use	Alprazolam, oxazepam, and lorazepam for "anxiety"
Buspirone	Long-term use GAD	Less reliable efficacy	Approved for "anxiety"
Antidepressants (SSRIs, SNRIs, TCAs)	Long-term use GAD Other anxiety disorders	Effective; side effects and DDIs may limit use; may need additional benzodiazepines	Paroxetine, escitalopram, venlafaxine, and duloxetine for GAD
			Paroxetine, fluoxetine, fluvoxamine, sertraline, and clomipramine for OCD
			Paroxetine and sertraline for PTSD
			Paroxetine, fluoxetine, sertraline, venlafaxine, clomipramine, and imipramine for panic disorder
			Paroxetine, fluvoxamine, sertraline, and venlafaxine for seasonal affective disorder
			Doxepin for "anxiety"
Gabapentin	Less effective	Side effects limit use	Not approved
Pregabalin			
Antihistamines	Available OTC as sleep aid	Avoid	Hydroxyzine for "anxiety"

SSRI, selective serotonin reuptake inhibitor; *SNRI*, serotonin and norepinephrine reuptake inhibitor; *TCA*, tricyclic antidepressant; *DDI*, drug–drug interaction; *OTC*, over the counter; *GAD*, generalized anxiety disorder; *OCD*, obsessive–compulsive disorder; *PTSD*, posttraumatic stress disorder.

TABLE 23.8 General prescribing guidelines for the treatment of anxiety and anxiety-spectrum disorders.

Use very low doses
Start low and titrate doses gradually
Use short half-life medications
Caution regarding DDIs and drug–disease interactions
Caution regarding OTC supplement use
Caution regarding alcohol and substance use and withdrawal
Monitor side effects closely

DDIs, drug–drug interaction; *OTC*, over the counter.

Benzodiazepines

Benzodiazepines bind to the $GABA_A$ receptor at the benzodiazepine site, which is at the junction of the α- and γ-subunits. Although benzodiazepines are among the safest psychotropic drugs given to elderly individuals, controversy has accompanied their use and is especially active with regard to potential side effects in the elderly (Salzman, 2005). Benzodiazepine usage rates are higher for older patients than for younger adults, and the elderly constitute the largest group of long-term users. Extensive clinical experience suggests, however, that when the drugs are used in low therapeutic doses, the side effects, when present, are mild and reversible when the drugs are discontinued (see side effects below).

Three benzodiazepines are well suited for use in older adults. Lorazepam has a half-life of 12 hours and has a rapid onset, and the 0.25 mg dose is commonly used. Oxazepam has a half-life of 8 hours, a slow onset, and therefore little abuse potential. The 15 mg dose is commonly used. Temazepam has a half-life of 10 hours and is used primarily for sleep. Long-acting benzodiazepines that are FDA-approved for the treatment of anxiety and spectrum disorders (chlordiazepoxide and diazepam for "anxiety", and clonazepam for panic disorder) have not been included in Table 23.7 and are best avoided in older adults.

Benzodiazepines have several common side effects. Sedation is the most common side effect and can lead to falls and confusion. In addition, benzodiazepines may also interact with other sedating medications. Short half-life benzodiazepines can contribute to unsteadiness and falls, especially at night, which may lead to fractures and physical decline. Interestingly, one study found that the benzodiazepine-related fall risk is significantly modified by CYP2C9 genotype, and an increased risk of falls was associated with at least two CYP2C9 reduced enzyme activity alleles (Ham et al., 2017). The mechanism of this drug−gene interaction has yet to be elucidated. Benzodiazepines cause psychomotor impairment, and diminished speed and accuracy may limit automobile driving. Recent recall is commonly impaired and is usually reversible, but benzodiazepine use does not cause irreversible dementia (Salzman & Shader, 2015). Finally, mild dependence is common, and withdrawal can be limited by a very slow drug dose taper. Given the widespread and often appropriate use of benzodiazepines for the older anxious individual, it is important to alert the older individual (and family members if available) to these side effects. Doses should be kept low in order to avoid or minimize these side effects. Clinical experience suggests that the older individual is willing to experience mild side effects, such as diminished recent recall, in order to achieve the calming relief that a low dose achieves. It is only when the doses are inappropriately high and side effects produce functional impairments that alternatives to benzodiazepines should be considered along with lowering the dose.

All benzodiazepines are metabolized via CYP3A4 with a few exceptions. Lorazepam, oxazepam, and temazepam do not undergo phase I metabolism, which makes them less susceptible to the effects of aging, liver disease, and CYP450 interactions, while the metabolism of diazepam involves an additional pathway via CYP2C19 that makes it less susceptible to DDIs involving CYP3A4. As discussed in the section on pharmacokinetics, diazepam, temazepam, and lorazepam are all highly protein-bound drugs with capacity-limited hepatic clearance, leading to higher free fractions at equivalent doses in older than in younger adults. However, there is no role for therapeutic drug monitoring of benzodiazepines in routine clinical practice.

Buspirone

Buspirone is a nonbenzodiazepine anxiolytic drug that lacks sedative properties and dependence (Napoliello & Domantay, 1991). The anxiolytic activity of buspirone seems to be related to its agonist activity at the presynaptic $5HT_{1A}$ receptor, although it also demonstrates some affinity to the D_2 receptor (Tunnicliff, 1991). Its mechanism of action is distinct from that of the $GABA_A$ agonists as it demonstrates no effect on GABAergic neurotransmission. It is metabolized by CYP3A4. No reduction in dose is recommended solely based upon age, but its use is to be avoided in severe renal and hepatic impairment. It is approved for the short-term treatment of anxiety in mixed-age adults, and there are no RCTs lasting more than 4 weeks. It appears to be less effective than benzodiazepines but has a role in the treatment of GAD in benzodiazepine-naive patients (Chessick et al., 2006). In an 8-week randomized, single-blind trial (Mokhber, Azarpazhooh, Khajehdaluee, Velayati, & Hopwood, 2010) that compared sertraline and buspirone for the treatment of late-life (not late-onset) GAD (the age of patients at inclusion in the study was >60 years), both sertraline and buspirone were found to be efficacious and well tolerated. There was also a signal that the anxiolytic response to buspirone started earlier than with sertraline, but sertraline eventually caught up by the end of the trial period.

Antidepressants

Two classes of antidepressants, SSRIs and TCAs, have established antianxiety effect in long-term use for GAD and other anxiety-spectrum disorders, but they are not used for the acute treatment of anxiety. Treatment with these drugs requires low starting doses with monitoring for DDIs and drug−disease interaction, as discussed in the section on major depressive disorder. Phenelzine, an MAOI, is also FDA-approved for the treatment of panic disorder, but MAOIs have significant adverse effects in older adults and are best avoided as first- or second-line agents due to the availability of better-tolerated alternatives. Bupropion paradoxically increases anxiety as well as the potential for DDIs via CYP2D6 inhibition and is not recommended for the treatment of anxiety disorders, while mirtazapine is sedating and causes weight gain. The is insufficient experience with treating anxiety disorders in older adults with newer antidepressants such as vilazodone and vortioxetine to make recommendations for their use in this population.

Pregabalin

Pregabalin reduces the synaptic release of several neurotransmitters, apparently by binding to α_2-delta subunits of the voltage-gated calcium channels (Taylor, Angelotti, & Fauman, 2007). It has been shown to be effective in the treatment of GAD in mixed-age adults, and its short half-life, absence of active metabolites, and no interactions with the CYP450 enzymes make it a viable alternative for the treatment of GAD patients (Buoli, Caldiroli, & Serati, 2017), but due to its narrow therapeutic window (Eppenga et al., 2016), strict renal dosing is required, which can be an impediment to its use in older adults.

Evidence-based drug treatment of anxiety in older adults

The decision to treat the anxious older patient with psychotropic drugs depends on the severity and duration of symptoms and the degree to which they impair function and quality of life. As a general principle, psychotropic treatment should not be undertaken without a thorough medical and psychological appraisal of the symptoms has been conducted. A thorough listing of *all* medications, supplements, and OTC remedies is mandatory, since some of these drugs can cause or worsen anxiety. Providers should also attempt to attain an accurate record of alcohol or substance use that may be understated by the patient (Salzman, 2005). Anxiety symptoms may occur as part of physical illness or its drug treatment, as well as alcohol and substance use, especially during withdrawal.

All patients should be offered psychological therapies, including relaxation training and cognitive behavioral therapy. The choice of medication should be made based on adverse effect profile and potential for DDIs. SSRIs are commonly the first choice for a chronically anxious older person. These drugs can be effective after a lag period, but they have no acute therapeutic effect. Benzodiazepines are often prescribed along with an SSRI to assist in acute daytime anxiety and sleep onset. Citalopram and escitalopram have no clinically significant DDIs, which makes them the SSRIs of choice in older adults where polypharmacy is common. TCAs are less commonly used for treatment of chronic anxiety states because of their side effects, as discussed in the section on major depressive disorder. While clomipramine, imipramine, and doxepin are TCAs that are FDA-approved for the treatment of anxiety disorders, use of nortriptyline and desipramine is preferable, since therapeutic drug monitoring can be used to guide dosing and EKGs can monitor potential cardiac (widening QTc interval) toxicity. Nortriptyline produces slightly less orthostatic hypotension, while desipramine produces slightly less anticholinergic side effects.

Guidelines for the use of SSRIs and TCAs in treating anxiety in older adults are summarized in Table 23.9.

Insomnia in older adults

Introduction

Insomnia disorder is defined as follows in DSM-5: symptoms must include difficulty initiating or maintaining sleep or early-morning awakening with inability to return to sleep, must cause clinically significant functional distress or impairment, must be present for at least three nights per week for at least 3 months, and must not be better explained by another sleep, medical, or mental disorder (American Psychiatric Association, 2013). Other common sleep disorders

TABLE 23.9 Guidelines for the use of SSRIs and TCAs in the treatment of anxiety in older adults.

Drug	Recommended dose	Comments
Selective serotonin reuptake inhibitors		
Citalopram	5–20 mg/day	Higher doses may cause cardiac side effects
Escitalopram	5–10 mg/day	Commonly used and well tolerated, but higher doses may cause cardiac side effects
Tricyclic antidepressants		
Nortriptyline	10–100 mg/day	Titrate dose based on therapeutic drug monitoring, use EKG to monitor for cardiotoxicity
Desipramine	10–100 mg/day	May be activating, titrate dose based on therapeutic drug monitoring, use EKG to monitor for cardiotoxicity

EKG, electrocardiogram.

in older adults include obstructive sleep apnea-hypopnea, which is classified as a breathing-related sleep disorder in DSM-5, and rapid eye movement (REM) sleep behavior disorder, which is classified as a Parasomnia in DSM-5; these will not be considered further except for a brief note on the drug treatment of the latter condition.

Sleep problems are common in older adults, and of the three DSM-5 specifiers for Insomnia disorder, the one that applies most commonly to older adults is "with other medical comorbidity." In an epidemiological study of three cohorts in the United States with more than 9000 participants aged 65 years and older, less than 20% of the participants in each community rarely or never had any complaints related to sleep (Foley et al., 1995). Furthermore, in multivariate analyses, sleep complaints were associated with an increasing number of concurrent physical illnesses, including respiratory symptoms, physical disabilities, nonprescription medication use, depressive symptoms, and poorer self-perceived health, which illustrates the effect of sleep problems on multiple body systems as well as on general well-being. In another epidemiological study of 6899 men and women aged 65 years and older, the annual incidence of insomnia was calculated at about 5%, with a higher incidence in those with physical diseases such as heart disease, stroke, and diabetes; almost 95% of those with incident insomnia had one or more risk factors, such as depressed mood, respiratory symptoms, fair-to-poor perceived health, physical disability, and sedative use (Foley, Monjan, Simonsick, Wallace, & Blazer, 1999).

Drugs for the treatment of insomnia

The American Academy of Sleep Medicine (AASM) issued a clinical practice guideline in 2017 for the treatment of chronic insomnia in mixed-age adults (Sateia, Buysse, Krystal, Neubauer, & Heald, 2017), and made recommendations for the use of several drugs based on available evidence. These drugs, along with their pharmacokinetic information, are summarized in Table 23.10.

Dual orexin receptor antagonists

Suvorexant is currently the only dual orexin receptor antagonist (DORA) approved in the United States. It blocks binding of wakefulness-promoting neuropeptides orexin (OX) A and OXB to receptors OX1R and OX2R, hence the term *dual receptor* (Yang, 2014). It is approved for both sleep-onset and sleep-maintenance insomnia, but its effects are more pronounced on sleep-maintenance than sleep-onset, hence the AASM recommendation diverges from the FDA-approved indication. The effects of suvorexant in adults 65 years or older with insomnia were studied in a subgroup analysis of pooled 3-month data from two efficacy and three safety RCTs (Herring et al., 2017). Since antagonism of the OX receptors could lead to a narcolepsy-like condition with cataplexy resulting in falls, suvorexant is not indicated for use in patients with narcolepsy, and narcolepsy was an exclusion criterion for its phase III trials. Mild-to-moderate somnolence was the most common adverse effect in older adults, while severe excessive daytime somnolence leading to impairment was dose-related and rare ($<1\%$) at both the 15 and 30 mg doses. Falls did not occur significantly more often in older adults with no history of narcolepsy than on placebo. Both doses did not impair on-the-road driving the morning after bedtime use in healthy older adults (Vermeeren et al., 2016).

H_1-receptor antagonists

Doxepin is a secondary amine TCA that selectively blocks H_1-receptors in low doses and is marketed for sleep-maintenance insomnia as a new brand-name drug. However, generic doxepin is available as a 10 mg/mL liquid and can be used in lower doses with the help of a 1 mL dosing syringe at a fraction of the cost. Three RCTs in older adults have found it to be effective in treating sleep-maintenance insomnia in both the 3 and 6 mg doses, and it was well tolerated with no complex sleep behaviors (Abad & Guilleminault, 2018). Complex sleep behaviors are described below in the section on Nonbenzodiazepine $GABA_A$ receptor agonists. Most drugs approved for the treatment of insomnia are metabolized partially or completely via CYP3A4, as can be seen in Table 23.10, but doxepin is one exception as it is primarily metabolized via CYP2C19 and CYP2D6 (Gillman, 2007), which has important implications for DDIs.

Two H_1-blockers that are commonly used as sedatives in older adults but are *not* recommended for such use are diphenhydramine and hydroxyzine. Diphenhydramine is commonly marketed as an OTC "sleep aid." Both drugs are listed in the Beers criteria as drugs to avoid due to their high anticholinergic activity and their reduced renal clearance in older adults, but there are important differences between them. The anticholinergic activity of hydroxyzine is much lower than that of diphenhydramine (Orzechowski, Currie, & Valancius, 2005) and it is more selective for histamine receptors than for muscarinic receptors (Liu & Farley, 2005), but oral hydroxyzine also has better bioavailability and a longer elimination half-life than diphenhydramine, so more hydroxyzine is absorbed per unit dose, which then takes longer to be eliminated. Most importantly, these drugs are likely not more effective than placebo for the treatment of

TABLE 23.10 Drugs for the treatment of insomnia in mixed-age adults.

Drug (Brand name) *Available formulations*	Metabolic pathway (major pathway(s) in bold)	AASM recommendation for sleep-onset insomnia	AASM recommendation for sleep-maintenance insomnia	FDA-approved indication(s)
Dual orexin receptor antagonists (DORA)				
Suvorexant (Belsomra) *Avail as tab*	**CYP3A4**, CYP2C19	−	+	O, M
H_1-receptor antagonists				
Doxepin (Silenor) *Avail as tab*	**CYP2C19, CYP2D6**, CYP1A2, CYP2C9	−	+	M
Nonbenzodiazepine $GABA_A$ receptor agonists				
Eszopiclone (Lunesta) *Avail as tab*	**CYP3A4**	+	+	O, M
Zaleplon (Sonata) *Avail as cap*	**Aldehyde oxidase**, CYP3A4	+	−	O
Zolpidem IR (Ambien) *Avail as tab, ODT*	**CYP3A4**	+	−	O
Zolpidem CR (Ambien CR) *Avail as tab*	**CYP3A4**	+	+	O, M
Benzodiazepine $GABA_A$ receptor agonists				
Triazolam (Halcion) *Avail as tab*	**CYP3A4**	+	−	Short-term use

(*Continued*)

TABLE 23.10 (Continued)

Drug (Brand name) *Available formulations*	Metabolic pathway (major pathway(s) in bold)	AASM recommendation for sleep-onset insomnia	AASM recommendation for sleep-maintenance insomnia	FDA-approved indication(s)
Temazepam (Restoril) *Avail as cap*	None	+	+	Short-term use
Flurazepam (Dalmane) *Avail as cap*	CYP3A4	−	−	Short-term use
Quazepam (Doral) *Avail as tab*	CYP3A4	−	−	Short-term use
Estazolam (Prosom) *Avail as tab*	**CYP3A4**	−	−	Short-term use
Melatonin receptor agonists				
Ramelteon (Rozerem) *Avail as tab*	**CYP1A2**, CYP3A4, CYP2C9/19	+	−	O

AASM, American Academy of Sleep Medicine; *CYP, cytochrome P450;H*, histamine; *GABA*, Gamma-aminobutyric acid; *O*, sleep-onset insomnia; *M*, sleep-maintenance insomnia; *ODT*, orally dissolving tab; *IR*, immediate release; *CR*, controlled release.

insomnia in older adults. In a 2-week RCT comparing temazepam 15 mg, diphenhydramine 50 mg, and placebo in older adults (mean age 73.9 years), diphenhydramine did not separate from placebo on any of the sleep measures except for the improvement in the number of awakenings (Glass, Sproule, Herrmann, & Busto, 2008).

Nonbenzodiazepine $GABA_A$ receptor agonists

This class of "Z-drugs" includes the multiple formulations of zolpidem, along with zaleplon and eszopiclone. Zolpidem is now available as an immediate-release tab, a controlled-release tab, an oral spray (brand-name Zolpimist), a sublingual tab for initial insomnia (brand-name Edluar), and a sublingual tab for middle-of-the-night insomnia (brand-name Intermezzo) (Monti, Spence, Buttoo, & Pandi-Perumal, 2017). The racemic drug zopiclone is not available in the United States but is available in Europe, Canada, and Latin America. Eszopiclone is the s-isomer of zopiclone and is available in the United States as Lunesta. Z-drugs compare favorably to the benzodiazepine $GABA_A$ receptor agonists due to the lower incidence of retrograde amnesia, daytime sleepiness, respiratory depression, and orthostatic hypotension, but they are not completely risk-free. The $GABA_A$ receptor contains binding sites for the endogenous ligand GABA and for benzodiazepines. Nonbenzodiazepine $GABA_A$ receptor agonists selectively bind to sites on the $GABA_A$ receptor other than these two sites, and the differences in binding sites and pharmacokinetics differentiate the Z-drugs from each other. Zaleplon is unique among the Z-drugs, in that it is primarily metabolized by aldehyde oxidase while CYP3A4 is a secondary metabolic pathway, while all other Z-drugs are primarily metabolized via CYP3A4 (Dolder, Nelson, & McKinsey, 2007).

In addition to the indications for the Z-drugs noted in Table 23.10, zaleplon and sublingual zolpidem 1.75 or 3 mg (brand-name Intermezzo) can be used for middle-of-the-night insomnia, as long as the individual can spend at least 4 hours in bed after taking the medication, as driving performance remains unimpaired if these medications are taken more than 4 hours before driving (Verster et al., 2002).

Lower doses should be used in older adults for all Z-drugs. All Z-drugs may cause adverse effects that are dose-related, including headache, dizziness, falls, and residual effects the morning after leading to driving impairment, with the exceptions noted above. All Z-drugs now carry a black box warning in the United States for "complex sleep behaviors" such as sleep-eating, sleep-sex, and sleep-driving, but these have been mostly reported with zolpidem and occasionally with racemic zopiclone (Chen et al., 2013). Dependence remains a concern with these medications, none of which should be combined with alcohol or other CNS depressants. Zaleplon has higher abuse potential than other Z-drugs due to its shorter half-life and the fact that it can be insufflated to produce a high (Abad & Guilleminault, 2018).

Benzodiazepines

FDA-approved benzodiazepines for the treatment of short-term insomnia include triazolam, estazolam, temazepam, flurazepam, and quazepam. Of these, only temazepam and triazolam are approved by the AASM for treatment of insomnia. Of the five FDA-approved agents, triazolam has the shortest half-life followed by temazepam, while half-lives of quazepam and especially flurazepam are much longer. Flurazepam is the one approved benzodiazepine that should *never* be used in older adults due to the excessively long half-life of its active metabolite. In addition, the latter two drugs also have active metabolites that accumulate with repeated dosing. Triazolam and temazepam are both effective for both sleep-onset and sleep-maintenance insomnia (Abad & Guilleminault, 2018), but the use of triazolam is best avoided due to amnesia, confusion, disorientation, and even hallucinations and delusions that can persist through the next day (Bixler et al., 1991). The Beers criteria strongly recommends against using benzodiazepines in elderly patients due to increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes, and all benzodiazepines carry a black box warning in the United States regarding risk of profound sedation, respiratory depression, coma, and death when used concurrently with opioids.

Clonazepam is an effective (off-label) treatment for REM-sleep behavior disorder, but its long half-life can result in excessive daytime drowsiness, and it can worsen sleep-disordered breathing (de Almeida, Pachito, Sobreira-Neto, Tumas, & Eckeli, 2018).

Melatonin and melatonin receptor agonists

Melatonin (MT) is a natural hormone that is available as a dietary supplement in the United States. There are major quality control issues and tremendous variability in MT content, as well as the presence of unexpected contaminants (Erland & Saxena, 2017). This greatly limits its use, despite the fact that it does not produce dependence and there is weak evidence of efficacy in improving sleep-onset insomnia, including in older adults (Abad & Guilleminault, 2018). Furthermore, the optimal dose in older adults remains undefined, and doses used in various studies vary 20-fold, which

undoubtedly affects the outcome data (Pierce, Linnebur, Pearson, & Fixen, 2019). Like clonazepam, MT is also an effective medication for the treatment of REM-sleep behavior disorder, with less propensity to cause excessive daytime drowsiness and worsen sleep-disordered breathing than clonazepam (de Almeida et al., 2018), and is therefore preferred over clonazepam to treat this condition in older adults.

Ramelteon is a highly selective MT receptor (MT1 and MT2) agonist that is FDA-approved for the treatment of sleep-onset and sleep-maintenance insomnia, and is available in a single dose of 8 mg. There is weak evidence in support of its use in older adults (Wilt et al., 2016), but it may be safer to use in patients with chronic respiratory problems and balance/falls problems, based on data from studies in mixed-age adults (Abad & Guilleminault, 2018). It is another drug approved for the treatment of insomnia that is not metabolized via CYP3A4. Its main metabolic pathway involves CYP1A2, and the potent CYP1A2 inhibitor fluvoxamine has been shown to result in a 190-fold increase in the serum concentration of ramelteon (McGechan & Wellington, 2005). Another advantage is that ramelteon is not a controlled substance and has no known tendency to produce dependence.

Tasimelteon is a new MT receptor agonist that is more selective for MT2 than MT1 receptors (Lavedan, Forsberg, & Gentile, 2015). It was approved in 2016 by the FDA only for the treatment of non-24-hour sleep-wake disorder in blind adults, and is the first drug approved for the treatment of any circadian rhythm disorder that resets the circadian pacemaker itself (Keating, 2016).

Trazodone

There is weak evidence to support the off-label use of trazodone for the treatment of insomnia, increased risk of dizziness, and orthostatic hypotension leading to falls (Abad & Guilleminault, 2018). A Cochrane collaboration review found the studies of trazodone in the treatment of insomnia to be of low-to-moderate quality, and pooled data found a moderate improvement in subjective sleep outcomes over placebo, but objective polysomnographic data did not find any improvement in sleep efficiency (Everitt et al., 2018). Similarly, the extensive review by the AASM task force (Sateia et al., 2017) found no evidence favoring the use of trazodone for the treatment of insomnia, but did note that its use for this indication will likely continue due to the perception of trazodone as a "safer" sleep-promoting agent by many physicians. Indeed, clinical experience suggests that low doses of trazodone can be effective in treating insomnia in mixed-age adults. However, safety concerns have been reported in older adults, and a particularly compelling nursing home–based study of adults 66 and older found that starting low-dose trazodone (defined as 150 mg/day or lower) was no safer with respect to risk of a fall-related injury than new use of benzodiazepines (Bronskill et al., 2018). This could not be attributed to high initial doses of trazodone, since the median dose of trazodone in this study was 50 mg/day, the interquartile range was 25.0–51.7 mg/day, and the 95th percentile was only 107.1 mg/day.

Evidence-based drug treatment of insomnia in older adults

Psychological treatments should always be tried first for insomnia, and low-moderate quality evidence exists to support using cognitive behavior therapy for insomnia (CBT-I), brief behavior therapy, and stimulus control in improving one or more aspects of insomnia in older adults (Qaseem, Kansagara, Forciea, Cooke, & Denberg, 2016). Unfortunately, their use is limited due to poor access to trained therapists, leading to an increase in Internet-based alternatives (Seyffert et al., 2016). The American College of Physicians (ACP) 2016 clinical practice guideline for the management of chronic insomnia disorder in adults recommended that all adult patients receive CBT-I as the initial treatment for chronic insomnia disorder (Qaseem et al., 2016).

A shared decision-making approach is necessary in all cases when discussing the benefits and harms of adjunctive pharmacotherapy (Qaseem et al., 2016). Head-to-head comparisons of two or more of these agents in older adults are lacking, and therefore selection of a particular drug to alleviate sleep problems should be guided by the drug's pharmacokinetic properties, its side-effect profile, cooccurring psychiatric and physical illnesses, the patient's history of prior sedative-hypnotic use, and cost, with older drugs and generics being much cheaper than brand-name drugs. Drugs should be used in the lowest possible doses for the shortest period of time. The ACP 2016 guideline recommended "short-term use of medications" only for those "in whom CBT-I alone was unsuccessful." Studies supporting longer-term use have not been done, with one notable exception. Zaleplon (both 5 and 10 mg doses) has been studied in a 1-year open-label extension of two randomized, double-blind trials in older adults with insomnia (mean age 73.3 ± 5.3 years) (Ancoli-Israel et al., 2005). The findings were reassuring, as zaleplon maintained its efficacy over the 12-month study period, and discontinuation over a 7-day run-out period did not result in rebound insomnia. The AASM guideline recommended *not* using trazodone, tiagabine, diphenhydramine, MT, tryptophan, and valerian for chronic sleep-onset or sleep-maintenance insomnia, as evidence for or against their use in mixed-age adults is weak or completely lacking.

If benzodiazepines are to be used for the treatment of insomnia in older adults, the lowest possible doses should be used, and drugs with short elimination half-lives (temazepam) and those with minimal risk of pharmacokinetic DDIs (temazepam, off-label use of lorazepam) should be preferred.

Summary and conclusions

Regardless of the symptoms being treated or the class of drug used, psychopharmacological treatment in older adults should be guided by the basic principles summarized in the initial sections of this chapter. A careful review of the patient's current physical illness, possible substance use, and current medication regimen is mandatory before initiating treatment planning. Coadministration of medications for physical illnesses is common in this age group, which may interact adversely with psychotropic drugs. Older adults are more likely to develop toxic effects from psychotropic drugs, often at doses and blood levels usually considered to be within the therapeutic range in younger adults. The older adult's greater sensitivity to psychotropic drug effects is related to several factors, including age-related changes in neurotransmitters and their receptors, and the tendency of psychotropic drugs to exert greater effect for longer periods of time due to age-related changes that alter drug disposition. Deprescribing, rather than prescribing new medication(s), is often indicated as the first step in treatment. Close professional contact with the older patient is recommended in the initial phase of treatment in order to assure optimal adherence and to monitor both response and adverse effects. The provider should guard against both underdosing and overdosing due to dependence on treatment guidelines that are primarily for a young adult population.

However, none of the above should deter the provider from providing adequate psychopharmacological treatment to the older adult. The geriatric psychopharmacology dictum "Start low, go slow" should always be kept in mind, to which most experienced geriatric providers add, "but do go." If the principles outlined in this chapter are followed, psychopharmacological treatment of some of the most vulnerable patients in society is more likely to be successful.

References

Aarsland, D., Hutchinson, M., & Larsen, J. P. (2003). Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. *International Journal of Geriatric Psychiatry*, *18*(10), 937–941.

Abad, V. C., & Guilleminault, C. (2018). Insomnia in elderly patients: Recommendations for pharmacological management. *Drugs & Aging*, *35*(9), 791–817.

Aboukarr, A., & Giudice, M. (2018). Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Canadian Journal of Hospital Pharmacy*, *71*(3), 196–207.

Adams, C. E., Bergman, H., Irving, C. B., & Lawrie, S. (2013). Haloperidol versus placebo for schizophrenia. *The Cochrane Database of Systematic Reviews* (11), Cd003082.

Adli, M., Baethge, C., Heinz, A., Langlitz, N., & Bauer, M. (2005). Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *European Archives of Psychiatry and Clinical Neuroscience*, *255*(6), 387–400.

Aga, V. M. (2018). Structural and functional imaging. In R. R. Tampi, D. J. Tampi, & L. L. Boyle (Eds.), *Psychiatric disorders late in life: A comprehensive review* (pp. 103–136). Cham: Springer International Publishing.

Aga, V. M. (2019). When and how to treat agitation in Alzheimer's disease dementia with citalopram and escitalopram. *The American Journal of Geriatric Psychiatry*, *27*(10), 1099–1107.

Aga, V. M., Barklage, N. E., & Jefferson, J. W. (2003). Linezolid, a monoamine oxidase inhibiting antibiotic, and antidepressants. *The Journal of Clinical Psychiatry*, *64*(5), 609–611.

Agbabiaka, T. B., Wider, B., Watson, L. K., & Goodman, C. (2017). Concurrent use of prescription drugs and herbal medicinal products in older adults: A systematic review. *Drugs & Aging*, *34*(12), 891–905.

Aiff, H., Attman, P. O., Aurell, M., Bendz, H., Ramsauer, B., Schon, S., & Svedlund, J. (2015). Effects of 10 to 30 years of lithium treatment on kidney function. *Journal of Psychopharmacology*, *29*(5), 608–614.

Akner, G. (2009). Analysis of multimorbidity in individual elderly nursing home residents. Development of a multimorbidity matrix. *Archives of Gerontology and Geriatrics*, *49*(3), 413–419.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Mattis, S., & Kakuma, T. (1993). The course of geriatric depression with "reversible dementia": A controlled study. *The American Journal of Psychiatry*, *150*(11), 1693–1699.

Alexopoulos, G. S., Kiosses, D. N., Klimstra, S., Kalayam, B., & Bruce, M. L. (2002). Clinical presentation of the "depression-executive dysfunction syndrome" of late life. *The American Journal of Geriatric Psychiatry*, *10*(1), 98–106.

Alexopoulos, G. S., Streim, J., Carpenter, D., & Docherty, J. P. (2004). Using antipsychotic agents in older patients. *The Journal of Clinical Psychiatry*, *65*(Suppl. 2), 5–99, discussion 100-102; quiz 103-104.

Almeida, O. P., & Fenner, S. (2002). Bipolar disorder: Similarities and differences between patients with illness onset before and after 65 years of age. *International Psychogeriatrics*, *14*(3), 311–322.

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2018). Older men with bipolar disorder: Clinical associations with early and late onset illness. *International Journal of Geriatric Psychiatry*, *33*(12), 1613−1619.

Almeida, O. P., Ford, A. H., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2019). Risk of dementia associated with psychotic disorders in later life: The health in men study (HIMS). *Psychological Medicine*, *49*(2), 232−242.

Amdisen, A. (1977). Serum level monitoring and clinical pharmacokinetics of lithium. *Clinical Pharmacokinetics*, *2*(2), 73−92.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: American Psychiatric Association.

American Psychiatric Association DSM-5 Task Force., & American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: American Psychiatric Association.

Amrein, R., Hetzel, W., Stabl, M., & Schmid-Burgk, W. (1993). RIMA—A new concept in the treatment of depression with moclobemide. *International Clinical Psychopharmacology*, *7*(3−4), 123−132.

Amsterdam, J. D., & Shults, J. (2010a). Efficacy and mood conversion rate of short-term fluoxetine monotherapy of bipolar II major depressive episode. *Journal of Clinical Psychopharmacology*, *30*(3), 306−311.

Amsterdam, J. D., & Shults, J. (2010b). Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: A randomized, double-blind, placebo-substitution study. *The American Journal of Psychiatry*, *167*(7), 792−800.

Ancoli-Israel, S., Richardson, G. S., Mangano, R. M., Jenkins, L., Hall, P., & Jones, W. S. (2005). Long-term use of sedative hypnotics in older patients with insomnia. *Sleep Medicine*, *6*(2), 107−113.

Anderson, G. D., & Chan, L. N. (2016). Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clinical Pharmacokinetics*, *55*(11), 1353−1368.

Andrade, C. (2013). Drug interactions in the treatment of depression in patients receiving beta-blocker drugs. *The Journal of Clinical Psychiatry*, *74*(1), e75−e78.

Andrade, C., & Sharma, E. (2016). Serotonin reuptake inhibitors and risk of abnormal bleeding. *Psychiatr Clin North Am*, *39*(3), 413−426.

Antoniou, T., & Juurlink, D. N. (2014). Synthetic cannabinoids. *CMAJ: Canadian Medical Association Journal*, *186*(3), 210-210.

Arandjelovic, K., Eyre, H. A., & Lavretsky, H. (2016). Clinicians' views on treatment-resistant depression: 2016 survey reports. *The American Journal of Geriatric Psychiatry*, *24*(10), 913−917.

Arif, H., Svoronos, A., Resor, S. R., Jr., Buchsbaum, R., & Hirsch, L. J. (2011). The effect of age and comedication on lamotrigine clearance, tolerability, and efficacy. *Epilepsia*, *52*(10), 1905−1913.

Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., & Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology*, *80*(5), 496−503.

Asconape, J. J., Penry, J. K., Dreifuss, F. E., Riela, A., & Mirza, W. (1993). Valproate-associated pancreatitis. *Epilepsia*, *34*(1), 177−183.

Azermai, M., Petrovic, M., Elseviers, M. M., Bourgeois, J., Van Bortel, L. M., & Vander Stichele, R. H. (2012). Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. *Ageing Research Reviews*, *11*(1), 78−86.

Bailey, D. G., Dresser, G., & Arnold, J. M. O. (2013). Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? *CMAJ: Canadian Medical Association Journal*, *185*(4), 309−316.

Bajaj, N., Hauser, R. A., & Grachev, I. D. (2013). Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(11), 1288−1295.

Ball, S. E., Ahern, D., Scatina, J., & Kao, J. (1997). Venlafaxine: In vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *British Journal of Clinical Pharmacology*, *43*(6), 619−626.

Ballard, C., & Howard, R. (2006). Neuroleptic drugs in dementia: Benefits and harm. *Nature Reviews Neuroscience*, *7*(6), 492−500.

Ballard, C., & Waite, J. (2006). The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *The Cochrane Database of Systematic Reviews* (1), Cd003476.

Ballard, C., Hanney, M. L., Theodoulou, M., Douglas, S., McShane, R., Kossakowski, K., . . . Jacoby, R. (2009). The dementia antipsychotic withdrawal trial (DART-AD): Long-term follow-up of a randomised placebo-controlled trial. *The Lancet Neurology*, *8*(2), 151−157.

Barak, Y. (2002). No weight gain among elderly schizophrenia patients after 1 year of risperidone treatment. *The Journal of Clinical Psychiatry*, *63*(2), 117−119.

Barak, Y., Aizenberg, D., Mirecki, I., Mazeh, D., & Achiron, A. (2002). Very late-onset schizophrenia-like psychosis: Clinical and imaging characteristics in comparison with elderly patients with schizophrenia. *The Journal of Nervous and Mental Disease*, *190*(11), 733−736.

Barbui, C., Esposito, E., & Cipriani, A. (2009). Selective serotonin reuptake inhibitors and risk of suicide: A systematic review of observational studies. *CMAJ: Canadian Medical Association Journal*, *180*(3), 291−297.

Bartels, C., Wagner, M., Wolfsgruber, S., Ehrenreich, H., & Schneider, A. (2018). Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. *The American Journal of Psychiatry*, *175*(3), 232−241.

Baruch, Y., Tadger, S., Plopski, I., & Barak, Y. (2013). Asenapine for elderly bipolar manic patients. *Journal of Affective Disorders*, *145*(1), 130−132.

Baune, B. T., Brignone, M., & Larsen, K. G. (2018). A network meta-analysis comparing effects of various antidepressant classes on the digit symbol substitution test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder. *The International Journal of Neuropsychopharmacology*, *21*(2), 97−107.

Beekman, A. T., Bremmer, M. A., Deeg, D. J., van Balkom, A. J., Smit, J. H., de Beurs, E., . . . van Tilburg, W. (1998). Anxiety disorders in later life: A report from the Longitudinal Aging Study Amsterdam. *International Journal of Geriatric Psychiatry*, *13*(10), 717−726.

Beers, M. H. (1997). Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Archives of Internal Medicine*, *157*(14), 1531–1536.

Beers, M. H., Ouslander, J. G., Rollingher, I., Reuben, D. B., Brooks, J., & Beck, J. C. (1991). Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Archives of Internal Medicine*, *151*(9), 1825–1832.

Benalfew, L., Baktash, B., & Brent, F. (2017). Management of neuropsychiatric symptoms in neurocognitive disorders. *FOCUS*, *15*(1), 18–25.

Benet, L. Z., & Cummins, C. L. (2001). The drug efflux-metabolism alliance: Biochemical aspects. *Advanced Drug Delivery Reviews*, *50*(Suppl. 1), S3–S11.

Benz, C. C. (2008). Impact of aging on the biology of breast cancer. *Critical Reviews in Oncology/Hematology*, *66*(1), 65–74.

Berghuis, B., van der Palen, J., de Haan, G. J., Lindhout, D., Koeleman, B. P. C., & Sander, J. W. (2017). Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. *Epilepsia*, *58*(7), 1227–1233.

Bishara, D., & Taylor, D. (2014). Adverse effects of clozapine in older patients: Epidemiology, prevention and management. *Drugs & Aging*, *31*(1), 11–20.

Bixler, E. O., Kales, A., Manfredi, R. L., Vgontzas, A. N., Tyson, K. L., & Kales, J. D. (1991). Next-day memory impairment with triazolam use. *Lancet*, *337*(8745), 827–831.

Blazer, D. G. (2003). Depression in late life: Review and commentary. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(3), 249–265.

Bloom, R., & Amber, K. T. (2017). Identifying the incidence of rash, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients taking lamotrigine: A systematic review of 122 randomized controlled trials. *Anais Brasileiros de Dermatologia*, *92*(1), 139–141.

Bonetto, N., Santelli, L., Battistin, L., & Cagnin, A. (2007). Serotonin syndrome and rhabdomyolysis induced by concomitant use of triptans, fluoxetine and hypericum. *Cephalalgia*, *27*(12), 1421–1423.

Boxer, A. L., Knopman, D. S., Kaufer, D. I., Grossman, M., Onyike, C., Graf-Radford, N., ... Miller, B. L. (2013). Memantine in patients with frontotemporal lobar degeneration: A multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, *12*(2), 149–156.

Boyle, P. A., Malloy, P. F., Salloway, S., Cahn-Weiner, D. A., Cohen, R., & Cummings, J. L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *11*(2), 214–221.

Brannstrom, J., Lovheim, H., Gustafson, Y., & Nordstrom, P. (2019). Association between antidepressant drug use and hip fracture in older people before and after treatment initiation. *JAMA Psychiatry*, *76*(2), 172–179.

Brodaty, H., Connors, M. H., Xu, J., Woodward, M., & Ames, D. (2015). The course of neuropsychiatric symptoms in dementia: A 3-year longitudinal study. *Journal of the American Medical Directors Association*, *16*(5), 380–387.

Bronskill, S. E., Campitelli, M. A., Iaboni, A., Herrmann, N., Guan, J., Maclagan, L. C., ... Maxwell, C. J. (2018). Low-dose trazodone, benzodiazepines, and fall-related injuries in nursing homes: A matched-cohort study. *Journal of the American Geriatrics Society*, *66*(10), 1963–1971.

Budnitz, D. S., Lovegrove, M. C., Shehab, N., & Richards, C. L. (2011). Emergency hospitalizations for adverse drug events in older Americans. *The New England Journal of Medicine*, *365*(21), 2002–2012.

Buoli, M., Caldiroli, A., & Serati, M. (2017). Pharmacokinetic evaluation of pregabalin for the treatment of generalized anxiety disorder. *Expert Opinion on Drug Metabolism and Toxicology*, *13*(3), 351–359.

Butler, J. M., & Begg, E. J. (2008). Free drug metabolic clearance in elderly people. *Clinical Pharmacokinetics*, *47*(5), 297–321.

Camm, A. J., Karayal, O. N., Meltzer, H., Kolluri, S., O'Gorman, C., Miceli, J., ... Kane, J. M. (2012). Ziprasidone and the corrected QT interval: A comprehensive summary of clinical data. *CNS Drugs*, *26*(4), 351–365.

Campbell, N., Boustani, M., Limbil, T., Ott, C., Fox, C., Maidment, I., ... Gulati, R. (2009). The cognitive impact of anticholinergics: A clinical review. *Clinical Interventions in Aging*, *4*, 225–233.

Carr, R. B., & Shrewsbury, K. (2007). Hyperammonemia due to valproic acid in the psychiatric setting. *The American Journal of Psychiatry*, *164*(7), 1020–1027.

Carrillo, J. A., & Benitez, J. (2000). Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clinical Pharmacokinetics*, *39*(2), 127–153.

Carter, L., Zolezzi, M., & Lewczyk, A. (2013). An updated review of the optimal lithium dosage regimen for renal protection. *The Canadian Journal of Psychiatry*, *58*(10), 595–600.

Cartet-Farnier, E., Goutelle-Audibert, L., Maire, P., De la Gastine, B., & Goutelle, S. (2017). Implications of using the MDRD or CKD-EPI equation instead of the Cockcroft-Gault equation for estimating renal function and drug dosage adjustment in elderly patients. *Fundamental & Clinical Pharmacology*, *31*(1), 110–119.

Caspar, S., Davis, E. D., Douziech, A., & Scott, D. R. (2018). Nonpharmacological management of behavioral and psychological symptoms of dementia: What works, in what circumstances, and why? *Innovation in Aging*, *2*(1), igy001.

Catterson, M. L., Preskorn, S. H., & Martin, R. L. (1997). Pharmacodynamic and pharmacokinetic considerations in geriatric psychopharmacology. *The Psychiatric Clinics of North America*, *20*(1), 205–218.

Chan, D., Anderson, V., Pijnenburg, Y., Whitwell, J., Barnes, J., Scahill, R., & Fox, N. C. (2009). The clinical profile of right temporal lobe atrophy. *Brain: A Journal of Neurology*, *132*(Pt 5), 1287–1298.

Chan, J. Y. C., Yiu, K. K. L., Kwok, T. C. Y., Wong, S. Y. S., & Tsoi, K. K. F. (2019). Depression and antidepressants as potential risk factors in dementia: A systematic review and meta-analysis of 18 longitudinal studies. *Journal of the American Medical Directors Association*, *20*(3), 279–286, e271.

Chen, L. F., Lin, C. E., Chou, Y. C., Mao, W. C., Chen, Y. C., & Tzeng, N. S. (2013). A comparison of complex sleep behaviors with two short-acting Z-hypnosedative drugs in nonpsychotic patients. *Neuropsychiatric Disease and Treatment*, *9*, 1159–1162.

Chessick, C. A., Allen, M. H., Thase, M. E., Batista Miralha da Cunha, A., Kapczinski, F., Silva de Lima, M., & dos Santos Souza, J. (2006). Azapirones for generalized anxiety disorder. *Cochrane Database of Systematic Reviews* (3).

Chhatre, S., Cook, R., Mallik, E., & Jayadevappa, R. (2017). Trends in substance use admissions among older adults. *BMC Health Services Research*, *17*(1), 584.

Chopra, A., Kolla, B. P., Mansukhani, M. P., Netzel, P., & Frye, M. A. (2012). Valproate-induced hyperammonemic encephalopathy: An update on risk factors, clinical correlates and management. *General Hospital Psychiatry*, *34*(3), 290−298.

Chou, K. L. (2009). Age at onset of generalized anxiety disorder in older adults. *The American Journal of Geriatric Psychiatry*, *17*(6), 455−464.

Citrome, L. (2019). Cariprazine for bipolar depression: What is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *International Journal of Clinical Practice*, *73*(10), e13397.

Clark, S. R., Warren, N. S., Kim, G., Jankowiak, D., Schubert, K. O., Kisely, S., … Siskind, D. J. (2018). Elevated clozapine levels associated with infection: A systematic review. *Schizophrenia Research*, *192*, 50−56.

Cockcroft, D. W., & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, *16*(1), 31−41.

Cohen-Mansfield, J., & Mintzer, J. E. (2005). Time for change: The role of nonpharmacological interventions in treating behavior problems in nursing home residents with dementia. *Alzheimer Disease and Associated Disorders*, *19*(1), 37−40.

Colliver, J. D., Compton, W. M., Gfroerer, J. C., & Condon, T. (2006). Projecting drug use among aging baby boomers in 2020. *Annals of Epidemiology*, *16*(4), 257−265.

Connors, M. H., Ames, D., Woodward, M., & Brodaty, H. (2018). Psychosis and clinical outcomes in Alzheimer disease: A longitudinal study. *The American Journal of Geriatric Psychiatry*, *26*(3), 304−313.

Cooper, C., Katona, C., Lyketsos, K., Blazer, D., Brodaty, H., Rabins, P., … Livingston, G. (2011). A systematic review of treatments for refractory depression in older people. *The American Journal of Psychiatry*, *168*(7), 681−688.

Coryell, W., Miller, D. D., & Perry, P. J. (1998). Haloperidol plasma levels and dose optimization. *The American Journal of Psychiatry*, *155*(1), 48−53.

Cosgrove, L., Cristea, I. A., Shaughnessy, A. F., Mintzes, B., & Naudet, F. (2019). Digital aripiprazole or digital evergreening? A systematic review of the evidence and its dissemination in the scientific literature and in the media. *BMJ Evidence-Based Medicine*, *24*(6), 231−238.

Coupland, C., Dhiman, P., Morriss, R., Arthur, A., Barton, G., & Hippisley-Cox, J. (2011). Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. *BMJ*, *343*, d4551.

Crass, R. L., & Pai, M. P. (2019). Estimating renal function in drug development: Time to take the fork in the road. *The Journal of Clinical Pharmacology*, *59*(2), 159−167.

Cristancho, P., Lenard, E., Lenze, E. J., Miller, J. P., Brown, P. J., Roose, S. P., … Karp, J. F. (2019). Optimizing outcomes of treatment-resistant depression in older adults (OPTIMUM): Study design and treatment characteristics of the first 396 participants randomized. *The American Journal of Geriatric Psychiatry*, *27*(10), 1138−1152.

Crome, P., Lally, F., Cherubini, A., Oristrell, J., Beswick, A. D., Clarfield, A. M., … Mills, G. (2011). Exclusion of older people from clinical trials: Professional views from nine European countries participating in the PREDICT study. *Drugs & Aging*, *28*(8), 667−677.

Crutch, S. J., Schott, J. M., Rabinovici, G. D., Murray, M., Snowden, J. S., van der Flier, W. M., … Fox, N. C. (2017). Consensus classification of posterior cortical atrophy. *Alzheimer's & Dementia*, *13*(8), 870−884.

Cullinan, S., O'Mahony, D., O'Sullivan, D., & Byrne, S. (2016). Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. *Age Ageing*, *45*(1), 115−120.

Cummings, J. L. (1997). The neuropsychiatric inventory: Assessing psychopathology in dementia patients. *Neurology*, *48*(5 Suppl. 6), S10−S16.

Cummings, J., Mintzer, J., Brodaty, H., Sano, M., Banerjee, S., Devanand, D. P., … Zhong, K. (2015). Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics*, *27*(1), 7−17.

Curtin, D., Dukelow, T., James, K., O'Donnell, D., O'Mahony, D., & Gallagher, P. (2019). Deprescribing in multi-morbid older people with polypharmacy: Agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases. *European Journal of Clinical Pharmacology*, *75*(3), 427−432.

Darling, P., & Huthwaite, M. A. (2011). Infection-associated clozapine toxicity. *Clinical Schizophrenia & Related Psychoses*, *5*(3), 159−160.

Darowski, A., Chambers, S. A., & Chambers, D. J. (2009). Antidepressants and falls in the elderly. *Drugs & Aging*, *26*(5), 381−394.

David, S. R., Taylor, C. C., Kinon, B. J., & Breier, A. (2000). The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clinical Therapeutics*, *22*(9), 1085−1096.

Davidson, M., Harvey, P. D., Vervarcke, J., Gagiano, C. A., De Hooge, J. D., Bray, G., … Haushofer, M. (2000). A long-term, multicenter, open-label study of risperidone in elderly patients with psychosis. On behalf of the Risperidone Working Group. *International Journal of Geriatric Psychiatry*, *15*(6), 506−514.

Davies, S. J., Burhan, A. M., Kim, D., Gerretsen, P., Graff-Guerrero, A., Woo, V. L., … Rajji, T. K. (2018). Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. *Journal of Psychopharmacology*, *32*(5), 509−523.

de Almeida, C. M. O., Pachito, D. V., Sobreira-Neto, M. A., Tumas, V., & Eckeli, A. L. (2018). Pharmacological treatment for REM sleep behavior disorder in Parkinson disease and related conditions: A scoping review. *Journal of the Neurological Sciences*, *393*, 63−68.

De Freitas, B., & Schwartz, G. (1979). Effects of caffeine in chronic psychiatric patients. *The American Journal of Psychiatry*, *136*(10), 1337−1338.

Deberdt, W. G., Dysken, M. W., Rappaport, S. A., Feldman, P. D., Young, C. A., Hay, D. P., … Breier, A. (2005). Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. *The American Journal of Geriatric Psychiatry*, *13*(8), 722−730.

Decker, M. W. (1987). The effects of aging on hippocampal and cortical projections of the forebrain cholinergic system. *Brain Research Reviews*, *12*(4), 423–438.

Devanand, D. P., Pelton, G. H., Marston, K., Camacho, Y., Roose, S. P., Stern, Y., & Sackeim, H. A. (2003). Sertraline treatment of elderly patients with depression and cognitive impairment. *International Journal of Geriatric Psychiatry*, *18*(2), 123–130.

Di Marzo, V., & Piscitelli, F. (2015). The endocannabinoid system and its modulation by phytocannabinoids. *Neurotherapeutics*, *12*(4), 692–698.

Dichgans, M., Markus, H. S., Salloway, S., Verkkoniemi, A., Moline, M., Wang, Q., … Chabriat, H. S. (2008). Donepezil in patients with subcortical vascular cognitive impairment: A randomised double-blind trial in CADASIL. *The Lancet Neurology*, *7*(4), 310–318.

Do, A., Noohi, S., Elie, D., Mahdanian, A. A., Yu, C., Segal, M., … Rej, S. (2016). Health Canada warning on citalopram and escitalopram—Its effects on prescribing in consultation-liaison Psychiatry. *Psychosomatics*, *57*(1), 57–63.

Dolder, C., Nelson, M., & McKinsey, J. (2007). Use of non-benzodiazepine hypnotics in the elderly: Are all agents the same? *CNS Drugs*, *21*(5), 389–405.

Dols, A., Kessing, L. V., Strejilevich, S. A., Rej, S., Tsai, S. Y., Gildengers, A. G., … Sajatovic, M. (2016). Do current national and international guidelines have specific recommendations for older adults with bipolar disorder? A brief report. *International Journal of Geriatric Psychiatry*, *31*(12), 1295–1300.

Dong, X., Leppik, I. E., White, J., & Rarick, J. (2005). Hyponatremia from oxcarbazepine and carbamazepine. *Neurology*, *65*(12), 1976–1978.

Donnelly, L., Rathbone, J., & Adams, C. E. (2013). Haloperidol dose for the acute phase of schizophrenia. *The Cochrane Database of Systematic Reviews* (8), Cd001951.

Dowling, T. C., Wang, E. S., Ferrucci, L., & Sorkin, J. D. (2013). Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: Impact on renal drug dosing. *Pharmacotherapy*, *33*(9), 912–921.

Döring, B., & Petzinger, E. (2014). Phase 0 and phase III transport in various organs: Combined concept of phases in xenobiotic transport and metabolism. *Drug Metabolism Reviews*, *46*(3), 261–282.

Drisaldi, A., Weeda, E., Neyens, R., Orvin, N., Bonilha, L., Campbell, Z., & Bohm, N. (2019). Accuracy of valproic acid concentration correction based on serum albumin. *Neurocrit Care*, *30*(2), 301–306.

Dudas, R., Malouf, R., McCleery, J., & Dening, T. (2018). Antidepressants for treating depression in dementia. *The Cochrane Database of Systematic Reviews*, *8*, Cd003944.

Durgam, S., Earley, W., Guo, H., Li, D., Nemeth, G., Laszlovszky, I., … Montgomery, S. A. (2016). Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: A randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. *The Journal of Clinical Psychiatry*, *77*(3), 371–378.

Dzierzewski, J. M., Potter, G. G., Jones, R. N., Rostant, O. S., Ayotte, B., Yang, F. M., … Steffens, D. C. (2015). Cognitive functioning throughout the treatment history of clinical late-life depression. *International Journal of Geriatric Psychiatry*, *30*(10), 1076–1084.

Echavarri, C., Burgmans, S., Uylings, H., Cuesta, M. J., Peralta, V., Kamphorst, W., … Verhey, F. R. (2013). Neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. *Journal of Alzheimer's Disease*, *33*(3), 715–721.

Ehrenberg, A. J., Suemoto, C. K., Franca Resende, E. P., Petersen, C., Leite, R. E. P., Rodriguez, R. D., … Grinberg, L. T. (2018). Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *Journal of Alzheimer's Disease*, *66*(1), 115–126.

Eiermann, B., Engel, G., Johansson, I., Zanger, U. M., & Bertilsson, L. (1997). The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. *British Journal of Clinical Pharmacology*, *44*(5), 439–446.

Elliott, R. A., & Marriott, J. L. (2009). Standardised assessment of patients' capacity to manage medications: A systematic review of published instruments. *BMC Geriatrics*, *9*, 27.

Elliott, R. A., Goeman, D., Beanland, C., & Koch, S. (2015). Ability of older people with dementia or cognitive impairment to manage medicine regimens: A narrative review. *Current Clinical Pharmacology*, *10*(3), 213–221.

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., & Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*, *22*(12), 1689–1707, quiz 1837.

Emre, M., Aarsland, D., Albanese, A., Byrne, E. J., Deuschl, G., De Deyn, P. P., … Lane, R. (2004). Rivastigmine for dementia associated with Parkinson's disease. *The New England Journal of Medicine*, *351*(24), 2509–2518.

Emre, M., Tsolaki, M., Bonuccelli, U., Destee, A., Tolosa, E., Kutzelnigg, A., … Jones, R. (2010). Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: A randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, *9*(10), 969–977.

Eppenga, W. L., Kramers, C., Derijks, H. J., Wensing, M., Wetzels, J. F., & De Smet, P. A. (2016). Drug therapy management in patients with renal impairment: How to use creatinine-based formulas in clinical practice. *European Journal of Clinical Pharmacology*, *72*(12), 1433–1439.

Erdő, F., & Krajcsi, P. (2019). Age-related functional and expressional changes in efflux pathways at the blood-brain barrier. *Frontiers in Aging Neuroscience*, *11*, 196-196.

Erland, L. A., & Saxena, P. K. (2017). Melatonin natural health products and supplements: Presence of serotonin and significant variability of melatonin content. *Journal of Clinical Sleep Medicine*, *13*(2), 275–281.

Everitt, H., Baldwin, D. S., Stuart, B., Lipinska, G., Mayers, A., Malizia, A. L., … Wilson, S. (2018). Antidepressants for insomnia in adults. *Cochrane Database of Systematic Reviews* (5).

Faber, M. S., & Fuhr, U. (2004). Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clinical Pharmacology & Therapeutics*, *76*(2), 178–184.

Farina, N., Morrell, L., & Banerjee, S. (2017). What is the therapeutic value of antidepressants in dementia? A narrative review. *International Journal of Geriatric Psychiatry*, *32*(1), 32–49.

Fattore, C., Messina, S., Battino, D., Croci, D., Mamoli, D., & Perucca, E. (2006). The influence of old age and enzyme inducing comedication on the pharmacokinetics of valproic acid at steady-state: A case-matched evaluation based on therapeutic drug monitoring data. *Epilepsy Research*, *70* (2−3), 153−160.

Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., … Papakostas, G. I. (2018). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry*.

Ferrell, P. B., Jr., & McLeod, H. L. (2008). Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics*, *9*(10), 1543−1546.

Fick, D. M., Cooper, J. W., Wade, W. E., Waller, J. L., Maclean, J. R., & Beers, M. H. (2003). Updating the Beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. *Archives of Internal Medicine*, *163*(22), 2716−2724.

Finley, P. R., Warner, M. D., & Peabody, C. A. (1995). Clinical relevance of drug interactions with lithium. *Clinical Pharmacokinetics*, *29*(3), 172−191.

Fischer, C. E., Qian, W., Schweizer, T. A., Millikin, C. P., Ismail, Z., Smith, E. E., … Munoz, D. G. (2016). Lewy bodies, vascular risk factors, and subcortical arteriosclerotic leukoencephalopathy, but not Alzheimer pathology, are associated with development of psychosis in Alzheimer's disease. *Journal of Alzheimer's Disease*, *50*(1), 283−295.

Foebel, A. D., Hirdes, J. P., & Heckman, G. A. (2012). Caregiver status affects medication adherence among older home care clients with heart failure. *Aging Clinical and Experimental Research*, *24*(6), 718−721.

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep*, *18*(6), 425−432.

Foley, D. J., Monjan, A., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1999). Incidence and remission of insomnia among elderly adults: An epidemiologic study of 6,800 persons over three years. *Sleep*, *22*(Suppl. 2), S366−S372.

Fotso Soh, J., Klil-Drori, S., & Rej, S. (2019). Using lithium in older age bipolar disorder: Special considerations. *Drugs & Aging*, *36*(2), 147−154.

Friedman, J. H., Berman, R. M., Goetz, C. G., Factor, S. A., Ondo, W. G., Wojcieszek, J., … Marcus, R. N. (2006). Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. *Movement Disorders*, *21*(12), 2078−2081.

Gallo, J. J., & Rabins, P. V. (1999). Depression without sadness: Alternative presentations of depression in late life. *American Family Physician*, *60* (3), 820−826.

Galvez, V., Ho, K. A., Alonzo, A., Martin, D., George, D., & Loo, C. K. (2015). Neuromodulation therapies for geriatric depression. *Current Psychiatry Reports*, *17*(7), 59.

Gandhi, T. K., Weingart, S. N., Borus, J., Seger, A. C., Peterson, J., Burdick, E., … Bates, D. W. (2003). Adverse drug events in ambulatory care. *The New England Journal of Medicine*, *348*(16), 1556−1564.

Ge, F., Lin, H., Liu, Y., Li, M., Guo, R., Ruan, Z., & Chang, T. (2016). Dual antiplatelet therapy after stroke or transient ischaemic attack—How long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischaemic attack: A systematic review and meta-analysis. *European Journal of Neurology*, *23*(6), 1051−1057.

Gebara, M. A., Shea, M. L., Lipsey, K. L., Teitelbaum, S. L., Civitelli, R., Muller, D. J., … Lenze, E. J. (2014). Depression, antidepressants, and bone health in older adults: A systematic review. *Journal of the American Geriatrics Society*, *62*(8), 1434−1441.

Gebara, M. A., Lipsey, K. L., Karp, J. F., Nash, M. C., Iaboni, A., & Lenze, E. J. (2015). Cause or effect? Selective serotonin reuptake inhibitors and falls in older adults: A systematic review. *The American Journal of Geriatric Psychiatry*, *23*(10), 1016−1028.

Geduldig, E. T., & Kellner, C. H. (2016). Electroconvulsive therapy in the elderly: New findings in geriatric depression. *Current Psychiatry Reports*, *18*(4), 40.

Ghodke-Puranik, Y., Thorn, C. F., Lamba, J. K., Leeder, J. S., Song, W., Birnbaum, A. K., … Klein, T. E. (2013). Valproic acid pathway: Pharmacokinetics and pharmacodynamics. *Pharmacogenetics and Genomics*, *23*(4), 236−241.

Gill, S. S., Mamdani, M., Naglie, G., Streiner, D. L., Bronskill, S. E., Kopp, A., … Rochon, P. A. (2005). A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Archives of Internal Medicine*, *165*(7), 808−813.

Gillman, P. K. (2005). Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *British Journal of Anaesthesia*, *95*(4), 434−441.

Gillman, K. (2007). Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British Journal of Pharmacology*, *151*, 737−748.

Girardin, F. R., Gex-Fabry, M., Berney, P., Shah, D., Gaspoz, J. M., & Dayer, P. (2013). Drug-induced long QT in adult psychiatric inpatients: The 5-year cross-sectional ECG screening outcome in psychiatry study. *The American Journal of Psychiatry*, *170*(12), 1468−1476.

Glass, J. R., Sproule, B. A., Herrmann, N., & Busto, U. E. (2008). Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: A randomized, placebo-controlled trial. *Journal of Clinical Psychopharmacology*, *28*(2), 182−188.

Glassman, A. H., & Preud'homme, X. A. (1993). Review of the cardiovascular effects of heterocyclic antidepressants. *The Journal of Clinical Psychiatry*, *54*(Suppl.), 16−22.

Glassock, R. J., & Winearls, C. (2009a). Ageing and the glomerular filtration rate: Truths and consequences. *Transactions of the American Clinical and Climatological Association*, *120*, 419−428.

Glassock, R. J., & Winearls, C. G. (2009b). eGFR: Readjusting its rating. *Clinical Journal of the American Society of Nephrology*, *4*(5), 867−869.

Goetz, C. G., Blasucci, L. M., Leurgans, S., & Pappert, E. J. (2000). Olanzapine and clozapine: Comparative effects on motor function in hallucinating PD patients. *Neurology*, *55*(6), 789−794.

Goh, A. M., Westphal, A., Daws, T., Gascoigne-Cohen, S., Hamilton, B., & Lautenschlager, N. T. (2016). A retrospective study of medical comorbidities in psychogeriatric patients. *Psychogeriatrics*, *16*(1), 12–19.

Goldberg, J. F. (2017). Do you order pharmacogenetic testing? Why? *The Journal of Clinical Psychiatry*, *78*(8), 1155–1156.

Goldberg, J. F., & Thase, M. E. (2013). Monoamine oxidase inhibitors revisited: What you should know. *The Journal of Clinical Psychiatry*, *74*(2), 189–191.

Goncalves, D. C., & Byrne, G. J. (2013). Who worries most? Worry prevalence and patterns across the lifespan. *International Journal of Geriatric Psychiatry*, *28*(1), 41–49.

Goodnick, P. J. (2007). Seligiline transdermal system in depression. *Expert Opinion on Pharmacotherapy*, *8*(1), 59–64.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., ... Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006–1014.

Grace, J., Daniel, S., Stevens, T., Shankar, K. K., Walker, Z., Byrne, E. J., ... McKeith, I. G. (2001). Long-term use of rivastigmine in patients with dementia with Lewy bodies: An open-label trial. *International Psychogeriatrics*, *13*(2), 199–205.

Graff-Guerrero, A., Rajji, T. K., Mulsant, B. H., Nakajima, S., Caravaggio, F., Suzuki, T., ... Mamo, D. C. (2015). Evaluation of antipsychotic dose reduction in late-life schizophrenia: A prospective dopamine D2/3 receptor occupancy study. *JAMA Psychiatry*, *72*(9), 927–934.

Gram, L. F., Hansen, M. G., Sindrup, S. H., Brosen, K., Poulsen, J. H., Aaes-Jorgensen, T., & Overo, K. F. (1993). Citalopram: Interaction studies with levomepromazine, imipramine, and lithium. *Therapeutic Drug Monitoring*, *15*(1), 18–24.

Grandison, M. K., & Boudinot, F. D. (2000). Age-related changes in protein binding of drugs: Implications for therapy. *Clinical Pharmacokinetics*, *38*(3), 271–290.

Greenblatt, H. K., & Greenblatt, D. J. (2016). Antidepressant-associated hyponatremia in the elderly. *Journal of Clinical Psychopharmacology*, *36*(6), 545–549.

Gross, B. W., Gillio, M., Rinehart, C. D., Lynch, C. A., & Rogers, F. B. (2017). Omega-3 fatty acid supplementation and warfarin: A lethal combination in traumatic brain injury. *Journal of Trauma Nursing*, *24*(1), 15–18.

Grundmann, M., Koristkova, B., Brozmanova, H., & Kacirova, I. (2017). Lamotrigine drug interactions in combination therapy and the influence of therapeutic drug monitoring on clinical outcomes of adult patients. *Therapeutic Drug Monitoring*, *39*(5), 543–549.

Gu, L., Gonzalez, F. J., Kalow, W., & Tang, B. K. (1992). Biotransformation of caffeine, paraxanthine, theobromine and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. *Pharmacogenetics*, *2*(2), 73–77.

Ham, A. C., Ziere, G., Broer, L., Swart, K. M., Enneman, A. W., van Dijk, S. C., ... van der Velde, N. (2017). CYP2C9 genotypes modify benzodiazepine-related fall risk: Original results from three studies with meta-analysis. *Journal of the American Medical Directors Association*, *18*(1), 88.e81–88.e15.

Han, B. H., Moore, A. A., Ferris, R., & Palamar, J. J. (2019). Binge drinking among older adults in the United States, 2015 to 2017. *Journal of the American Geriatrics Society*, *67*(10), 2139–2144.

Hanlon, J. T., Schmader, K. E., Koronkowski, M. J., Weinberger, M., Landsman, P. B., Samsa, G. P., & Lewis, I. K. (1997). Adverse drug events in high risk older outpatients. *Journal of the American Geriatrics Society*, *45*(8), 945–948.

Harris, M. J., & Jeste, D. V. (1988). Late-onset schizophrenia: An overview. *Schizophrenia Bulletin*, *14*(1), 39–55.

Harvey, A. T., & Preskorn, S. H. (1996). Cytochrome P450 enzymes: Interpretation of their interactions with selective serotonin reuptake inhibitors. Part I. *Journal of Clinical Psychopharmacology*, *16*(4), 273–285.

He, Z. X., Chen, X. W., Zhou, Z. W., & Zhou, S. F. (2015). Impact of physiological, pathological and environmental factors on the expression and activity of human cytochrome P450 2D6 and implications in precision medicine. *Drug Metabolism Reviews*, *47*(4), 470–519.

Hermida, J., & Tutor, J. C. (2005). A theoretical method for normalizing total serum valproic acid concentration in hypoalbuminemic patients. *Journal of Pharmacological Sciences*, *97*(4), 489–493.

Herring, W. J., Connor, K. M., Snyder, E., Snavely, D. B., Zhang, Y., Hutzelmann, J., ... Michelson, D. (2017). Suvorexant in elderly patients with insomnia: Pooled analyses of data from phase III randomized controlled clinical trials. *The American Journal of Geriatric Psychiatry*, *25*(7), 791–802.

Herrmann, N., & Lanctot, K. L. (2005). Do atypical antipsychotics cause stroke? *CNS Drugs*, *19*(2), 91–103.

Herrmann, N., Lanctot, K. L., & Hogan, D. B. (2013). Pharmacological recommendations for the symptomatic treatment of dementia: The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. *Alzheimer's Research & Therapy*, *5*(Suppl. 1), S5.

Hewick, D. S., Newbury, P., Hopwood, S., Naylor, G., & Moody, J. (1977). Age as a factor affecting lithium therapy. *British Journal of Clinical Pharmacology*, *4*(2), 201–205.

Hilmer, S. N., Shenfield, G. M., & Le Couteur, D. G. (2005). Clinical implications of changes in hepatic drug metabolism in older people. *Therapeutics and Clinical Risk Management*, *1*(2), 151–156.

Hirsch, L. J., Weintraub, D., Du, Y., Buchsbaum, R., Spencer, H. T., Hager, M., ... Morrell, M. J. (2004). Correlating lamotrigine serum concentrations with tolerability in patients with epilepsy. *Neurology*, *63*(6), 1022–1026.

Hiyoshi-Taniguchi, K., Becker, C. B., & Kinoshita, A. (2018). What behavioral and psychological symptoms of dementia affect caregiver burnout? *Clinical Gerontologist*, *41*(3), 249–254.

Holton, A. E., Gallagher, P., Fahey, T., & Cousins, G. (2017). Concurrent use of alcohol interactive medications and alcohol in older adults: A systematic review of prevalence and associated adverse outcomes. *BMC Geriatrics*, *17*(1), 148.

Howard, R., Rabins, P. V., Seeman, M. V., & Jeste, D. V. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. The International Late-Onset Schizophrenia Group. *The American Journal of Psychiatry*, *157*(2), 172–178.

Howard, R., McShane, R., Lindesay, J., Ritchie, C., Baldwin, A., Barber, R., … Phillips, P. (2012). Donepezil and memantine for moderate-to-severe Alzheimer's disease. *The New England Journal of Medicine*, *366*(10), 893–903.

Howard, R., Cort, E., Bradley, R., Harper, E., Kelly, L., Bentham, P., … Gray, R. (2018). Antipsychotic treatment of very late-onset schizophrenia-like psychosis (ATLAS): A randomised, controlled, double-blind trial. *Lancet Psychiatry*, *5*(7), 553–563.

Hsu, Y. H., Huang, C. F., Tu, M. C., & Hua, M. S. (2015). Prospective memory in subjective cognitive decline: A preliminary study on the role of early cognitive marker in dementia. *Alzheimer Disease and Associated Disorders*, *29*(3), 229–235.

Hudson, J. Q., & Nolin, T. D. (2018). Pragmatic use of kidney function estimates for drug dosing: The tide is turning. *Advances in Chronic Kidney Disease*, *25*(1), 14–20.

Iaboni, A., & Maust, D. T. (2019). A status update on the association between antidepressants and fractures: Breaking up? *JAMA Psychiatry*, *76*(2), 113–114.

Iriarte, I. G., & George, M. S. (2018). Transcranial magnetic stimulation (TMS) in the elderly. *Current Psychiatry Reports*, *20*(1), 6.

Isik, A. T., Soysal, P., Stubbs, B., Solmi, M., Basso, C., Maggi, S., … Mueller, C. (2018). Cardiovascular outcomes of cholinesterase inhibitors in individuals with dementia: A meta-analysis and systematic review. *Journal of the American Geriatrics Society*, *66*(9), 1805–1811.

Ismail, Z., Smith, E. E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., … Lyketsos, C. G. (2016). Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia*, *12*(2), 195–202.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., … Sperling, R. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535–562.

Jacob, S., & Spinler, S. A. (2006). Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Annals of Pharmacotherapy*, *40*(9), 1618–1622.

Jaeger, J. (2018). Digit symbol substitution test: The case for sensitivity over specificity in neuropsychological testing. *Journal of Clinical Psychopharmacology*, *38*(5), 513–519.

Jakubovski, E., Varigonda, A. L., Freemantle, N., Taylor, M. J., & Bloch, M. H. (2016). Systematic review and meta-analysis: Dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. *The American Journal of Psychiatry*, *173*(2), 174–183.

Jancova, P., Anzenbacher, P., & Anzenbacherova, E. (2010). Phase II drug metabolizing enzymes. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, *154*(2), 103–116.

Jankowska-Polanska, B., Zameta, K., Uchmanowicz, I., Szymanska-Chabowska, A., Morisky, D., & Mazur, G. (2018). Adherence to pharmacological and non-pharmacological treatment of frail hypertensive patients. *Journal of Geriatric Cardiology*, *15*(2), 153–161.

Jefferson, J. W. (1998). Problems with switching rapidly from one MAOI to another. *The Journal of Clinical Psychiatry*, *59*(2), 87.

Jeste, D. V., & Finkel, S. I. (2000). Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *The American Journal of Geriatric Psychiatry*, *8*(1), 29–34.

Jeste, D. V., Caligiuri, M. P., Paulsen, J. S., Heaton, R. K., Lacro, J. P., Harris, M. J., … McAdams, L. A. (1995). Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Archives of General Psychiatry*, *52*(9), 756–765.

Jeste, D. V., Okamoto, A., Napolitano, J., Kane, J. M., & Martinez, R. A. (2000). Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. *The American Journal of Psychiatry*, *157*(7), 1150–1155.

Jeste, D. V., Barak, Y., Madhusoodanan, S., Grossman, F., & Gharabawi, G. (2003). International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. *The American Journal of Geriatric Psychiatry*, *11*(6), 638–647.

Jiang, R., Yamaori, S., Okamoto, Y., Yamamoto, I., & Watanabe, K. (2013). Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metabolism and Pharmacokinetics*, *28*(4), 332–338.

Jiang, H. Y., Chen, H. Z., Hu, X. J., Yu, Z. H., Yang, W., Deng, M., … Ruan, B. (2015). Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: A systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*, *13*(1), 42–50, e43.

Jones, R. W. (2010). A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors. *International Journal of Geriatric Psychiatry*, *25*(6), 547–553.

Jonsson, M., Edman, A., Lind, K., Rolstad, S., Sjogren, M., & Wallin, A. (2010). Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia. *International Journal of Geriatric Psychiatry*, *25*(6), 588–595.

Josephs, K. A. (2007). Capgras syndrome and its relationship to neurodegenerative disease. *Archives of Neurology*, *64*(12), 1762–1766.

Junghanns, K., Graf, I., Pfluger, J., Wetterling, G., Ziems, C., Ehrenthal, D., … Wurst, F. M. (2009). Urinary ethyl glucuronide (EtG) and ethyl sulphate (EtS) assessment: Valuable tools to improve verification of abstention in alcohol-dependent patients during in-patient treatment and at follow-ups. *Addiction*, *104*(6), 921–926.

Kahn, R. S., Fleischhacker, W. W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I. P., … Grobbee, D. E. (2008). Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: An open randomised clinical trial. *Lancet*, *371*(9618), 1085–1097.

Kales, H. C., Gitlin, L. N., & Lyketsos, C. G. (2014). Management of neuropsychiatric symptoms of dementia in clinical settings: Recommendations from a multidisciplinary expert panel. *Journal of the American Geriatrics Society*, *62*(4), 762–769.

Kaltenboeck, A., Winkler, D., & Kasper, S. (2016). Bipolar and related disorders in DSM-5 and ICD-10. *CNS Spectrums*, *21*(4), 318–323.

Kane, J. M. (2018). Comments on abilify MyCite. *Clinical Schizophrenia & Related Psychoses*, *11*(4), 205–206.

Kaneriya, S. H., Robbins-Welty, G. A., Smagula, S. F., Karp, J. F., Butters, M. A., Lenze, E. J., … Reynolds, C. F., III (2016). Predictors and moderators of remission with aripiprazole augmentation in treatment-resistant late-life depression: An analysis of the IRL-GRey randomized clinical trial. *JAMA Psychiatry*, *73*(4), 329–336.

Karrer, T. M., McLaughlin, C. L., Guaglianone, C. P., & Samanez-Larkin, G. R. (2019). Reduced serotonin receptors and transporters in normal aging adults: A meta-analysis of PET and SPECT imaging studies. *Neurobiology of Aging*, *80*, 1–10.

Kavirajan, H., & Schneider, L. S. (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: A meta-analysis of randomised controlled trials. *The Lancet Neurology*, *6*(9), 782–792.

Keating, G. M. (2016). Tasimelteon: A review in non-24-hour sleep-wake disorder in totally blind individuals. *CNS Drugs*, *30*(5), 461–468.

Kellner, C. H., Husain, M. M., Knapp, R. G., McCall, W. V., Petrides, G., Rudorfer, M. V., … Lisanby, S. H. (2016a). A novel strategy for continuation ECT in geriatric depression: Phase 2 of the PRIDE study. *The American Journal of Psychiatry*, *173*(11), 1110–1118.

Kellner, C. H., Husain, M. M., Knapp, R. G., McCall, W. V., Petrides, G., Rudorfer, M. V., … Lisanby, S. H. (2016b). Right unilateral ultrabrief pulse ECT in geriatric depression: Phase 1 of the PRIDE study. *The American Journal of Psychiatry*, *173*(11), 1101–1109.

Kelly, D. L., Powell, M. M., Wehring, H. J., Sayer, M. A., Kearns, A. M., Hackman, A. L., … McEvoy, J. P. (2018). Adjunct aripiprazole reduces prolactin and prolactin-related adverse effects in premenopausal women with psychosis: Results from the DAAMSEL clinical trial. *Journal of Clinical Psychopharmacology*, *38*(4), 317–326.

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., … Uher, R. (2016). Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *The Canadian Journal of Psychiatry*, *61*(9), 540–560.

Kerrigan, D. D., Mangnall, Y. F., Read, N. W., & Johnson, A. G. (1991). Influence of acid-pepsin secretion on gastric emptying of solids in humans: Studies with cimetidine. *Gut*, *32*(11), 1295–1297.

Kim, R. B., Wandel, C., Leake, B., Cvetkovic, M., Fromm, M. F., Dempsey, P. J., … Wilkinson, G. R. (1999). Interrelationship between substrates and inhibitors of human CYP3A and P-glycoprotein. *Pharmaceutical Research*, *16*(3), 408–414.

Kirby, D., Harrigan, S., & Ames, D. (2002). Hyponatraemia in elderly psychiatric patients treated with selective serotonin reuptake inhibitors and venlafaxine: A retrospective controlled study in an inpatient unit. *International Journal of Geriatric Psychiatry*, *17*(3), 231–237.

Kishi, T., Matsunaga, S., & Iwata, N. (2017). A meta-analysis of memantine for depression. *Journal of Alzheimer's Disease*, *57*(1), 113–121.

Kishi, T., Matsunaga, S., Oya, K., Nomura, I., Ikuta, T., & Iwata, N. (2017). Memantine for Alzheimer's disease: An updated systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *60*(2), 401–425.

Kleijer, B. C., van Marum, R. J., Egberts, A. C., Jansen, P. A., Knol, W., & Heerdink, E. R. (2009). Risk of cerebrovascular events in elderly users of antipsychotics. *Journal of Psychopharmacology*, *23*(8), 909–914.

Klotz, U. (2009). Pharmacokinetics and drug metabolism in the elderly. *Drug Metabolism Reviews*, *41*(2), 67–76.

Knegtering, R., Baselmans, P., Castelein, S., Bosker, F., Bruggeman, R., & van den Bosch, R. J. (2005). Predominant role of the 9-hydroxy metabolite of risperidone in elevating blood prolactin levels. *The American Journal of Psychiatry*, *162*(5), 1010–1012.

Knights, K. M., Rowland, A., & Miners, J. O. (2013). Renal drug metabolism in humans: The potential for drug–endobiotic interactions involving cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT). *British Journal of Clinical Pharmacology*, *76*(4), 587–602.

Kok, R. M., Vink, D., Heeren, T. J., & Nolen, W. A. (2007). Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: An open, randomized, controlled trial. *The Journal of Clinical Psychiatry*, *68*(8), 1177–1185.

Konrat, C., Boutron, I., Trinquart, L., Auleley, G. R., Ricordeau, P., & Ravaud, P. (2012). Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. *PLoS One*, *7*(3), e33559.

Kranzler, H. R., Babor, T. F., & Lauerman, R. J. (1990). Problems associated with average alcohol consumption and frequency of intoxication in a medical population. *Alcoholism: Clinical and Experimental Research*, *14*(1), 119–126.

Krauthammer, C., & Klerman, G. L. (1978). Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. *Archives of General Psychiatry*, *35*(11), 1333–1339.

Kroon, L. A. (2007). Drug interactions with smoking. *American Journal of Health-System Pharmacy*, *64*(18), 1917–1921.

Kudo, S., & Ishizaki, T. (1999). Pharmacokinetics of haloperidol: An update. *Clinical Pharmacokinetics*, *37*(6), 435–456.

Kuehn, B. M. (2008). FDA: Antipsychotics risky for elderly. *Journal of the American Medical Association*, *300*(4), 379–380.

Labos, C., Dasgupta, K., Nedjar, H., Turecki, G., & Rahme, E. (2011). Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. *CMAJ: Canadian Medical Association Journal*, *183*(16), 1835–1843.

Lachs, M. S., & Pillemer, K. A. (2015). Elder abuse. *The New England Journal of Medicine*, *373*(20), 1947–1956.

Lacut, K., Le Gal, G., Couturaud, F., Cornily, G., Leroyer, C., Mottier, D., & Oger, E. (2007). Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism: Results from the EDITH case-control study. *Fundamental & Clinical Pharmacology*, *21*(6), 643–650.

Laitinen, M. L., Lonnroos, E., Bell, J. S., Lavikainen, P., Sulkava, R., & Hartikainen, S. (2015). Use of antidepressants among community-dwelling persons with Alzheimer's disease: A nationwide register-based study. *International Psychogeriatrics*, *27*(4), 669–672.

Lala, S. V., & Sajatovic, M. (2012). Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: A literature review. *Journal of Geriatric Psychiatry and Neurology*, *25*(1), 20–25.

Lam, S., Smith, C., & Gomolin, I. H. (2015). Memantine standard tablet and extended-release dosing considerations: A pharmacokinetic analysis. *Journal of the American Geriatrics Society*, *63*(2), 383–384.

Lampe, I. K., & Heeren, T. J. (2004). Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *International Psychogeriatrics*, *16*(4), 481–486.

Lampe, J. W., King, I. B., Li, S., Grate, M. T., Barale, K. V., Chen, C., … Potter, J. D. (2000). Brassica vegetables increase and apiaceous vegetables decrease cytochrome P450 1A2 activity in humans: Changes in caffeine metabolite ratios in response to controlled vegetable diets. *Carcinogenesis*, *21*(6), 1157–1162.

Laporte, S., Chapelle, C., Caillet, P., Beyens, M. N., Bellet, F., Delavenne, X., ... Bertoletti, L. (2017). Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: A meta-analysis of observational studies. *Pharmacological Research*, *118*, 19−32.

Laroche, M. L., Charmes, J. P., Nouaille, Y., Picard, N., & Merle, L. (2007). Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *British Journal of Clinical Pharmacology*, *63*(2), 177−186.

Lau, D. T. (2009). Standing on the shoulders of Mark H. Beers: More than a giant in geriatric medicine. *Clinical Therapeutics*, *31*(4), 822−824.

Lavan, A. H., Gallagher, P., Parsons, C., & O'Mahony, D. (2017). STOPPFrail (screening tool of older persons prescriptions in frail adults with limited life expectancy): Consensus validation. *Age Ageing*, *46*(4), 600−607.

Lavedan, C., Forsberg, M., & Gentile, A. J. (2015). Tasimelteon: A selective and unique receptor binding profile. *Neuropharmacology*, *91*, 142−147.

Lavretsky, H., Laird, K. T., Krause-Sorio, B., Heimberg, B. F., Yeargin, J., Grzenda, A., & Siddarth, P. (2020). A randomized double-blind placebo-controlled trial of combined escitalopram and memantine for older adults with major depression and subjective memory complaints. *The American Journal of Geriatric Psychiatry*, *28*(2), 178−190.

Lavretsky, H., Reinlieb, M., Cyr, N., St, Siddarth, P., Ercoli, L. M., & Senturk, D. (2015). Citalopram, methylphenidate, or their combination in geriatric depression: A randomized, double-blind, placebo-controlled trial. *The American Journal of Psychiatry*, *172*(6), 561−569.

Lawrence, D., Mitrou, F., & Zubrick, S. R. (2009). Smoking and mental illness: Results from population surveys in Australia and the United States. *BMC Public Health*, *9*, 285.

Lazarou, J., Pomeranz, B. H., & Corey, P. N. (1998). Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *Journal of the American Medical Association*, *279*(15), 1200−1205.

Le Couteur, D. G., & McLean, A. J. (1998). The aging liver. *Clinical Pharmacokinetics*, *34*(5), 359−373.

Le Roux, H., Gatz, M., & Wetherell, J. L. (2005). Age at onset of generalized anxiety disorder in older adults. *The American Journal of Geriatric Psychiatry*, *13*(1), 23−30.

Lebert, F., Stekke, W., Hasenbroekx, C., & Pasquier, F. (2004). Frontotemporal dementia: A randomised, controlled trial with trazodone. *Dementia and Geriatric Cognitive Disorders*, *17*(4), 355−359.

Lehmann, S. W., & Lee, J. (2013). Lithium-associated hypercalcemia and hyperparathyroidism in the elderly: What do we know? *Journal of Affective Disorders*, *146*(2), 151−157.

Lenze, E. J., Mulsant, B. H., Blumberger, D. M., Karp, J. F., Newcomer, J. W., Anderson, S. J., ... Reynolds, C. F., 3rd (2015). Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: A randomised, double-blind, placebo-controlled trial. *Lancet*, *386*(10011), 2404−2412.

Lesko, L. J., & Zineh, I. (2010). DNA, drugs and chariots: On a decade of pharmacogenomics at the US FDA. *Pharmacogenomics*, *11*(4), 507−512.

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine*, *130*(6), 461−470.

Levine, G. N., Bates, E. R., Bittl, J. A., Brindis, R. G., Fihn, S. D., Fleisher, L. A., ... Wijeysundera, D. N. (2016). 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *The Journal of Thoracic and Cardiovascular Surgery*, *152*(5), 1243−1275.

Levy, N. B. (1990). Psychopharmacology in patients with renal failure. *The International Journal of Psychiatry in Medicine*, *20*(4), 325−334.

Linde, K., Mulrow, C. D., Berner, M., & Egger, M. (2005). St John's wort for depression. *The Cochrane Database of Systematic Reviews* (2), Cd000448.

Lindeman, R. D., Tobin, J., & Shock, N. W. (1985). Longitudinal studies on the rate of decline in renal function with age. *Journal of the American Geriatrics Society*, *33*(4), 278−285.

Litvinenko, I. V., Odinak, M. M., Mogil'naya, V. I., & Emelin, A. Y. (2008). Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). *Neuroscience and Behavioral Physiology*, *38*(9), 937−945.

Liu, H., & Farley, J. M. (2005). Effects of first and second generation antihistamines on muscarinic induced mucus gland cell ion transport. *BMC Pharmacology*, *5*, 8.

Lloyd, S. L., & Striley, C. W. (2018). Marijuana use among adults 50 years or older in the 21st century. *Gerontology and Geriatric Medicine*, *4*, 2333721418781668.

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *The American Journal of Psychiatry*, *159*(7), 1119−1126.

Lund, M., Petersen, T. S., & Dalhoff, K. P. (2017). Clinical implications of P-glycoprotein modulation in drug-drug interactions. *Drugs*, *77*(8), 859−883.

Lundebjerg, N. E., Trucil, D. E., Hammond, E. C., & Applegate, W. B. (2017). When it comes to older adults, language matters: Journal of the American Geriatrics Society adopts modified American Medical Association style. *Journal of the American Geriatrics Society*, *65*(7), 1386−1388.

Maeda, K., Sugino, H., Akazawa, H., Amada, N., Shimada, J., Futamura, T., ... Kikuchi, T. (2014). Brexpiprazole I: In vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *Journal of Pharmacology and Experimental Therapeutics*, *350*(3), 589−604.

Mago, R., Tripathi, N., & Andrade, C. (2014). Cardiovascular adverse effects of newer antidepressants. *Expert Review of Neurotherapeutics*, *14*(5), 539−551.

Mahableshwarkar, A. R., Zajecka, J., Jacobson, W., Chen, Y., & Keefe, R. S. (2015). A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology*, *40*(8), 2025−2037.

Man, W. H., Wilting, I., Heerdink, E. R., Hugenholtz, G. W. K., Bognár, T., Ten Berg, M. J., ... van Maarseveen, E. M. (2019). Unbound fraction of clozapine significantly decreases with elevated plasma concentrations of the inflammatory acute-phase protein alpha-1-acid glycoprotein. *Clinical Pharmacokinetics*, *58*(8), 1069–1075.

Mannel, M. (2004). Drug interactions with St John's wort: Mechanisms and clinical implications. *Drug Safety*, *27*(11), 773–797.

Marcum, Z. A., Perera, S., Thorpe, J. M., Switzer, G. E., Castle, N. G., Strotmeyer, E. S., ... Hanlon, J. T. (2016). Antidepressant use and recurrent falls in community-dwelling older adults: Findings from the health ABC study. *Annals of Pharmacotherapy*, *50*(7), 525–533.

Martin, D. (2019). Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *The Lancet*, *393*(10168), 265–274.

Martinez, C., Jones, R. W., & Rietbrock, S. (2013). Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: A cohort study. *BMJ Open*, *3*(1), e002080.

Masnoon, N., Shakib, S., Kalisch-Ellett, L., & Caughey, G. E. (2017). What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*, *17*(1), 230.

Matsunaga, S., Kishi, T., & Iwata, N. (2014). Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: A systematic review and meta-analysis. *The International Journal of Neuropsychopharmacology*, *18*, 5.

Matthews, C. J., & Hall, T. L. (2014). A clozapine conundrum: Clozapine toxicity in an acute medical illness. *Australasian Psychiatry: Bulletin of Royal Australian and New Zealand College of Psychiatrists*, *22*(6), 543–545.

Mattson, M., Lipari, R. N., Hays, C., & Van Horn, S. L. (2013). A day in the *life of older adults: Substance use facts. The CBHSQ Report*. Rockville, MD: Substance Abuse and Mental Health Services Administration (US): 1–7.

Maust, D. T., Kales, H. C., McCammon, R. J., Blow, F. C., Leggett, A., & Langa, K. M. (2017). Distress associated with dementia-related psychosis and agitation in relation to healthcare utilization and costs. *The American Journal of Geriatric Psychiatry*, *25*(10), 1074–1082.

McCarthy, L. M., Visentin, J. D., & Rochon, P. A. (2019). Assessing the scope and appropriateness of prescribing cascades. *Journal of the American Geriatrics Society*, *67*(5), 1023–1026.

McClure, F. S., Gladsjo, J. A., & Jeste, D. V. (1999). Late-onset psychosis: Clinical, research, and ethical considerations. *American Journal of Psychiatry*, *156*(6), 935–940.

McCormack, P. L. (2015). Cariprazine: First global approval. *Drugs*, *75*(17), 2035–2043.

McGechan, A., & Wellington, K. (2005). Ramelteon. *CNS Drugs*, *19*(12), 1057–1065, discussion 1066-1057.

McKeith, I., Del Ser, T., Spano, P., Emre, M., Wesnes, K., Anand, R., ... Spiegel, R. (2000). Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. *Lancet*, *356*(9247), 2031–2036.

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D., ... Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88–100.

McLachlan, A. J., & Pont, L. G. (2011). Drug metabolism in older people—A key consideration in achieving optimal outcomes with medicines. *The Journals of Gerontology: Series A*, *67A*(2), 175–180.

McLean, A. J., & Le Couteur, D. G. (2004). Aging biology and geriatric clinical pharmacology. *Pharmacological Reviews*, *56*(2), 163–184.

Meeks, T. W., Vahia, I. V., Lavretsky, H., Kulkarni, G., & Jeste, D. V. (2011). A tune in "a minor" can "b major": A review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *Journal of Affective Disorders*, *129*(1–3), 126–142.

Mester, R., Toren, P., Mizrachi, I., Wolmer, L., Karni, N., & Weizman, A. (1995). Caffeine withdrawal increases lithium blood levels. *Biological Psychiatry*, *37*(5), 348–350.

Milosheska, D., Lorber, B., Vovk, T., Kastelic, M., Dolžan, V., & Grabnar, I. (2016). Pharmacokinetics of lamotrigine and its metabolite N-2-glucuronide: Influence of polymorphism of UDP-glucuronosyltransferases and drug transporters. *British Journal of Clinical Pharmacology*, *82*(2), 399–411.

Mobius, H. J., & Stoffler, A. (2003). Memantine in vascular dementia. *International Psychogeriatrics*, *15*(Suppl. 1), 207–213.

Mohamed, S., Johnson, G. R., Chen, P., Hicks, P. B., Davis, L. L., Yoon, J., ... Little, J. T. (2017). Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: The VAST-D randomized clinical trial. *Journal of the American Medical Association*, *318*(2), 132–145.

Mokhber, N., Azarpazhooh, M. R., Khajehdaluee, M., Velayati, A., & Hopwood, M. (2010). Randomized, single-blind, trial of sertraline and buspirone for treatment of elderly patients with generalized anxiety disorder. *Psychiatry and Clinical Neurosciences*, *64*(2), 128–133.

Monti, J. M., Spence, D. W., Buttoo, K., & Pandi-Perumal, S. R. (2017). Zolpidem's use for insomnia. *Asian Journal of Psychiatry*, *25*, 79–90.

Mori, E., Ikeda, M., Nagai, R., Matsuo, K., Nakagawa, M., & Kosaka, K. (2015). Long-term donepezil use for dementia with Lewy bodies: Results from an open-label extension of Phase III trial. *Alzheimer's Research & Therapy*, *7*(1), 5.

Mori, E., Ikeda, M., Nakagawa, M., Miyagishi, H., Yamaguchi, H., & Kosaka, K. (2015). Effects of donepezil on extrapyramidal symptoms in patients with dementia with Lewy bodies: A secondary pooled analysis of two randomized-controlled and two open-label long-term extension studies. *Dementia and Geriatric Cognitive Disorders*, *40*(3–4), 186–198.

Morley, J. E., & Adams, E. V. (2015). Rapid geriatric assessment. *Journal of the American Medical Directors Association*, *16*(10), 808–812.

Morris, M. C., Brockman, J., Schneider, J. A., Wang, Y., Bennett, D. A., Tangney, C. C., & van de Rest, O. (2016). Association of seafood consumption, brain mercury level, and APOE epsilon4 status with brain neuropathology in older adults. *Journal of the American Medical Association*, *315*(5), 489–497.

Murru, A., Popovic, D., Pacchiarotti, I., Hidalgo, D., Leon-Caballero, J., & Vieta, E. (2015). Management of adverse effects of mood stabilizers. *Current Psychiatry Reports*, *17*(8), 603.

Naegle, M. A. (2008). Screening for alcohol use and misuse in older adults: Using the Short Michigan Alcoholism Screening Test—Geriatric Version. *American Journal of Nursing*, *108*(11), 50−58, quiz 58-59.

Nagata, T., Nakajima, S., Shinagawa, S., Plitman, E., Nakayama, K., Graff-Guerrero, A., & Mimura, M. (2017). Baseline predictors of antipsychotic treatment continuation and response at week 8 in patients with Alzheimer's disease with psychosis or aggressive symptoms: An analysis of the CATIE-AD study. *Journal of Alzheimer's Disease*, *60*(1), 263−272.

Napoliello, M. J., & Domantay, A. G. (1991). Buspirone: A worldwide update. *British Journal of Psychiatry Supplement*, *12*, 40−44.

Nasreddine, W., & Beydoun, A. (2008). Valproate-induced thrombocytopenia: A prospective monotherapy study. *Epilepsia*, *49*(3), 438−445.

Nelson, J. C., & Devanand, D. P. (2011). A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *Journal of the American Geriatrics Society*, *59*(4), 577−585.

Nelson, J. C., & Papakostas, G. I. (2009). Atypical antipsychotic augmentation in major depressive disorder: A meta-analysis of placebo-controlled randomized trials. *The American Journal of Psychiatry*, *166*(9), 980−991.

Newell, J., Yesavage, J. A., Taylor, J. L., Kraemer, H. C., Munro, C. A., Friedman, L., … Noda, A. (2016). Sedation mediates part of Citalopram's effect on agitation in Alzheimer's disease. *Journal of Psychiatric Research*, *74*, 17−21.

Nichols, A. I., Abell, M., Chen, Y., Behrle, J. A., Frick, G., & Paul, J. (2013). Effects of desvenlafaxine on the pharmacokinetics of desipramine in healthy adults. *International Clinical Psychopharmacology*, *28*(2), 99−105.

Nicolussi, S., Drewe, J., Butterweck, V., & Meyer Zu Schwabedissen, H. E. (2019). Clinical relevance of St. John's wort drug interactions revisited. *British Journal of Pharmacology*.

Nolen, W. A., Licht, R. W., Young, A. H., Malhi, G. S., Tohen, M., Vieta, E., … Severus, E. (2019). What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. *Bipolar Disorder*, *21*(5), 394−409.

Noufi, P., Khoury, R., Jeyakumar, S., & Grossberg, G. T. (2019). Use of cholinesterase inhibitors in non-Alzheimer's dementias. *Drugs & Aging*, *36*(8), 719−731.

O'Brien, B., Green, C. E., Al-Jurdi, R., Chang, L., Lijffijt, M., Iqbal, S., … Mathew, S. J. (2019). Bayesian adaptive randomization trial of intravenous ketamine for veterans with late-life, treatment-resistant depression. *Contemporary Clinical Trials Communications*, *16*, 100432.

Ochs-Ross, R., Daly, E. J., Zhang, Y., Lane, R., Lim, P., Morrison, R. L., … Singh, J. B. (2019). Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression-TRANSFORM-3. *The American Journal of Geriatric Psychiatry*.

Olin, J. T., Schneider, L. S., Katz, I. R., Meyers, B. S., Alexopoulos, G. S., Breitner, J. C., … Lebowitz, B. D. (2002). Provisional diagnostic criteria for depression of Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *10*(2), 125−128.

O'Mahony, D., O'Sullivan, D., Byrne, S., O'Connor, M. N., Ryan, C., & Gallagher, P. (2015). STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing*, *44*(2), 213−218.

Omranifard, V., Shirzadi, E., Samandari, S., Afshar, H., & Maracy, M. R. (2014). Memantine add on to citalopram in elderly patients with depression: A double-blind placebo-controlled study. *Journal of Research in Medical Sciences*, *19*(6), 525−530.

Oo, K. Z., Aung, Y. K., Jenkins, M. A., & Win, A. K. (2016). Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: A systematic review and meta-analysis. *Australian and New Zealand Journal of Psychiatry*, *50*(9), 842−857.

Orgeta, V., Tabet, N., Nilforooshan, R., & Howard, R. (2017). Efficacy of antidepressants for depression in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *58*(3), 725−733.

Orzechowski, R. F., Currie, D. S., & Valancius, C. A. (2005). Comparative anticholinergic activities of 10 histamine H_1 receptor antagonists in two functional models. *European Journal of Pharmacology*, *506*(3), 257−264.

Ossenkoppele, R., Pijnenburg, Y. A., Perry, D. C., Cohn-Sheehy, B. I., Scheltens, N. M., Vogel, J. W., … Rabinovici, G. D. (2015). The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain*, *138*(Pt 9), 2732−2749.

Ostling, S., Palsson, S. P., & Skoog, I. (2007). The incidence of first-onset psychotic symptoms and paranoid ideation in a representative population sample followed from age 70-90 years. Relation to mortality and later development of dementia. *International Journal of Geriatric Psychiatry*, *22*(6), 520−528.

Ostling, S., Gustafson, D., Blennow, K., Borjesson-Hanson, A., & Waern, M. (2011). Psychotic symptoms in a population-based sample of 85-year-old individuals with dementia. *Journal of Geriatric Psychiatry and Neurology*, *24*(1), 3−8.

Ott, B. R., Blake, L. M., Kagan, E., & Resnick, M. (2007). Open label, multicenter, 28-week extension study of the safety and tolerability of memantine in patients with mild to moderate Alzheimer's disease. *Journal of Neurology*, *254*(3), 351−358.

Page, A. T., Clifford, R. M., Potter, K., Schwartz, D., & Etherton-Beer, C. D. (2016). The feasibility and effect of deprescribing in older adults on mortality and health: A systematic review and meta-analysis. *British Journal of Clinical Pharmacology*, *82*(3), 583−623.

Page, A. T., Potter, K., Clifford, R., McLachlan, A. J., & Etherton-Beer, C. (2016). Medication appropriateness tool for co-morbid health conditions in dementia: Consensus recommendations from a multidisciplinary expert panel. *Internal Medicine Journal*, *46*(10), 1189−1197.

Papakostas, G. I., Fava, M., & Thase, M. E. (2008). Treatment of SSRI-resistant depression: A meta-analysis comparing within- versus across-class switches. *Biological Psychiatry*, *63*(7), 699−704.

Papakostas, G. I., Fava, M., Baer, L., Swee, M. B., Jaeger, A., Bobo, W. V., & Shelton, R. C. (2015). Ziprasidone augmentation of escitalopram for major depressive disorder: Efficacy results from a randomized, double-blind, placebo-controlled study. *The American Journal of Psychiatry*, *172*(12), 1251−1258.

Pasina, L., Brucato, A. L., Falcone, C., Cucchi, E., Bresciani, A., Sottocorno, M., … Nobili, A. (2014). Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. *Drugs & Aging*, *31*(4), 283−289.

Passmore, M. J., Gardner, D. M., Polak, Y., & Rabheru, K. (2008). Alternatives to atypical antipsychotics for the management of dementia-related agitation. *Drugs & Aging*, *25*(5), 381–398.

Patteet, L., Morrens, M., Maudens, K. E., Niemegeers, P., Sabbe, B., & Neels, H. (2012). Therapeutic drug monitoring of common antipsychotics. *Therapeutic Drug Monitoring*, *34*(6), 629–651.

Pazan, F., Weiss, C., & Wehling, M. (2018). The EURO-FORTA (Fit fOR The Aged) list: International consensus validation of a clinical tool for improved drug treatment in older people. *Drugs & Aging*, *35*(1), 61–71.

Pazan, F., Weiss, C., & Wehling, M. (2019). The FORTA (Fit fOR The Aged) list 2018: Third version of a validated clinical tool for improved drug treatment in older people. *Drugs & Aging*, *36*(5), 481–484.

Pelton, G. H., Harper, O. L., Tabert, M. H., Sackeim, H. A., Scarmeas, N., Roose, S. P., & Devanand, D. P. (2008). Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study. *Int J Geriatr Psychiatry*, *23*(7), 670–676.

Pelton, G. H., Harper, O. L., Roose, S. P., Marder, K., D'Antonio, K., & Devanand, D. P. (2016). Combined treatment with memantine/es-citalopram for older depressed patients with cognitive impairment: A pilot study. *International Journal of Geriatric Psychiatry*, *31*(6), 648–655.

Perry, P. J., Zeilmann, C., & Arndt, S. (1994). Tricyclic antidepressant concentrations in plasma: An estimate of their sensitivity and specificity as a predictor of response. *Journal of Clinical Psychopharmacology*, *14*(4), 230–240.

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *British Journal of Pharmacology*, *153*(2), 199–215.

Perucca, E., Gatti, G., Cipolla, G., Spina, E., Barel, S., Soback, S., … Bialer, M. (1994). Inhibition of diazepam metabolism by fluvoxamine: A pharmacokinetic study in normal volunteers. *Clinical Pharmacology & Therapeutics*, *56*(5), 471–476.

Phelan, K. M., Mosholder, A. D., & Lu, S. (2003). Lithium interaction with the cyclooxygenase 2 inhibitors rofecoxib and celecoxib and other nonsteroidal anti-inflammatory drugs. *The Journal of Clinical Psychiatry*, *64*(11), 1328–1334.

Pierce, M., Linnebur, S. A., Pearson, S. M., & Fixen, D. R. (2019). Optimal melatonin dose in older adults: A clinical review of the literature. *Senior Care Pharmacy*, *34*(7), 419–431.

Ploeg, J., Matthew-Maich, N., Fraser, K., Dufour, S., McAiney, C., Kaasalainen, S., … Emili, A. (2017). Managing multiple chronic conditions in the community: A Canadian qualitative study of the experiences of older adults, family caregivers and healthcare providers. *BMC Geriatrics*, *17*(1), 40.

Poewe, W., Wolters, E., Emre, M., Onofrj, M., Hsu, C., Tekin, S., & Lane, R. (2006). Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: An active treatment extension study. *Movement Disorders*, *21*(4), 456–461.

Ponte, M. L., Wachs, L., Wachs, A., & Serra, H. A. (2017). Prescribing cascade. A proposed new way to evaluate it. *Medicina (B Aires)*, *77*(1), 13–16.

Porensky, E. K., Dew, M. A., Karp, J. F., Skidmore, E., Rollman, B. L., Shear, M. K., & Lenze, E. J. (2009). The burden of late-life generalized anxiety disorder: Effects on disability, health-related quality of life, and healthcare utilization. *The American Journal of Geriatric Psychiatry*, *17*(6), 473–482.

Porsteinsson, A. P., Drye, L. T., Pollock, B. G., Devanand, D. P., Frangakis, C., Ismail, Z., … Lyketsos, C. G. (2014). Effect of citalopram on agitation in Alzheimer disease: The CitAD randomized clinical trial. *Journal of the American Medical Association*, *311*(7), 682–691.

Poyurovsky, M., Bergman, J., Pashinian, A., & Weizman, A. (2014). Beneficial effect of low-dose mirtazapine in acute aripiprazole-induced akathisia. *International Clinical Psychopharmacology*, *29*(5), 296–298.

Pradhan, B. K., Chakrabarti, S., Irpati, A. S., & Bhardwaj, R. (2011). Distress due to lithium-induced polyuria: Exploratory study. *Psychiatry and Clinical Neurosciences*, *65*(4), 386–388.

Premoli, M., Aria, F., Bonini, S. A., Maccarinelli, G., Gianoncelli, A., Pina, S. D., … Mastinu, A. (2019). Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment. *Life Sciences*, *224*, 120–127.

Preskorn, S. H., Greenblatt, D. J., Flockhart, D., Luo, Y., Perloff, E. S., Harmatz, J. S., … Burt, T. (2007). Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. *Journal of Clinical Psychopharmacology*, *27*(1), 28–34.

Qaseem, A., Kansagara, D., Forciea, M. A., Cooke, M., & Denberg, T. D. (2016). Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 125–133.

Qato, D. M., Wilder, J., Schumm, L. P., Gillet, V., & Alexander, G. C. (2016). Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Internal Medicine*, *176*(4), 473–482.

Rahimi, J., & Kovacs, G. G. (2014). Prevalence of mixed pathologies in the aging brain. *Alzheimer's Research & Therapy*, *6*(9), 82.

Rahman, T., Clevenger, C. V., Kaklamani, V., Lauriello, J., Campbell, A., Malwitz, K., & Kirkland, R. S. (2014). Antipsychotic treatment in breast cancer patients. *The American Journal of Psychiatry*, *171*(6), 616–621.

Ralph, S. J., & Espinet, A. J. (2018). Increased all-cause mortality by antipsychotic drugs: Updated review and meta-analysis in dementia and general mental health care. *Journal of Alzheimer's Disease*, *2*(1), 1–26.

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(Pt 9), 2456–2477.

Raskind, M. A., Peskind, E. R., Veith, R. C., Beard, J. C., Gumbrecht, G., & Halter, J. B. (1988). Increased plasma and cerebrospinal fluid norepinephrine in older men: Differential suppression by clonidine. *Journal of Clinical Endocrinology and Metabolism*, *66*(2), 438–443.

Raskind, M. A., Peskind, E. R., Holmes, C., & Goldstein, D. S. (1999). Patterns of cerebrospinal fluid catechols support increased central noradrenergic responsiveness in aging and Alzheimer's disease. *Biological Psychiatry*, *46*(6), 756–765.

Reed, R. C., & Dutta, S. (2006). Does it really matter when a blood sample for valproic acid concentration is taken following once-daily administration of divalproex-ER? *Therapeutic Drug Monitoring*, *28*(3), 413−418.

Reeve, E., Gnjidic, D., Long, J., & Hilmer, S. (2015). A systematic review of the emerging definition of 'deprescribing' with network analysis: Implications for future research and clinical practice. *British Journal of Clinical Pharmacology*, *80*(6), 1254−1268.

Rej, S., Herrmann, N., & Shulman, K. (2012). The effects of lithium on renal function in older adults—A systematic review. *Journal of Geriatric Psychiatry and Neurology*, *25*(1), 51−61.

Rej, S., Herrmann, N., Shulman, K., Fischer, H. D., Fung, K., & Gruneir, A. (2017). Current psychotropic medication prescribing patterns in late-life bipolar disorder. *International Journal of Geriatric Psychiatry*, *32*(12), 1459−1465.

Renneboog, B., Musch, W., Vandemergel, X., Manto, M. U., & Decaux, G. (2006). Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *The American Journal of Medicine*, *119*(1), 71.e71-78.

Reus, V. I., Fochtmann, L. J., Eyler, A. E., Hilty, D. M., Horvitz-Lennon, M., Jibson, M. D., . . . Joel Yager, M. D. (2016). The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *American Journal of Psychiatry*, *173*(5), 543−546.

Reynolds, J. C. (1990). The clinical importance of drug interactions with antiulcer therapy. *Journal of Clinical Gastroenterology*, *12*(Suppl. 2), S54−S63.

Reynolds, C. F., III, Butters, M. A., Lopez, O., Pollock, B. G., Dew, M. A., Mulsant, B. H., . . . DeKosky, S. T. (2011). Maintenance treatment of depression in old age: A randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Archives of General Psychiatry*, *68*(1), 51−60.

Riker, R. R., Gagnon, D. J., Hatton, C., May, T., Seder, D. B., Stokem, K., & Fraser, G. L. (2017). Valproate protein binding is highly variable in ICU patients and not predicted by total serum concentrations: A case series and literature review. *Pharmacotherapy*, *37*(4), 500−508.

Robert, P., Lanctot, K. L., Aguera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., . . . Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, *54*, 71−76.

Rochon, P. A., & Gurwitz, J. H. (1995). Drug therapy. *Lancet*, *346*(8966), 32−36.

Roman, G. C., Salloway, S., Black, S. E., Royall, D. R., Decarli, C., Weiner, M. W., . . . Posner, H. (2010). Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: Differential effects by hippocampal size. *Stroke*, *41*(6), 1213−1221.

Romankiewicz, J. A. (1976). Effects of antacids on gastrointestinal absorption of drugs. *Primary Care*, *3*(3), 537−550.

Romijn, J. A. (2014). Hyperprolactinemia and prolactinoma. *Handbook of Clinical Neurology*, *124*, 185−195.

Rong, C., Carmona, N. E., Lee, Y. L., Ragguett, R. M., Pan, Z., Rosenblat, J. D., . . . McIntyre, R. S. (2018). Drug-drug interactions as a result of co-administering Delta(9)-THC and CBD with other psychotropic agents. *Expert Opinion on Drug Safety*, *17*(1), 51−54.

Ropacki, S. A., & Jeste, D. V. (2005). Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *The American Journal of Psychiatry*, *162*(11), 2022−2030.

Rossi, P., Serrao, M., & Pozzessere, G. (2002). Gabapentin-induced worsening of neuropsychiatric symptoms in dementia with Lewy bodies: Case reports. *European Neurology*, *47*(1), 56−57.

Roth, G. S., & Joseph, J. A. (1994). Cellular and molecular mechanisms of impaired dopaminergic function during aging. *Annals of the New York Academy of Sciences*, *719*, 129−135.

Roux, B., Sirois, C., Simard, M., Gagnon, M. E., & Laroche, M. L. (2019). Potentially inappropriate medications in older adults: A population-based cohort study. *Family Practice*.

Rowland, A., Miners, J. O., & Mackenzie, P. I. (2013). The UDP-glucuronosyltransferases: Their role in drug metabolism and detoxification. *The International Journal of Biochemistry & Cell Biology*, *45*(6), 1121−1132.

Sacchetti, E., Turrina, C., Cesana, B., & Mazzaglia, G. (2010). Timing of stroke in elderly people exposed to typical and atypical antipsychotics: A replication cohort study after the paper of Kleijer et al. *Journal of Psychopharmacology*, *24*(7), 1131−1132.

Sacchetti, E., Turrina, C., & Valsecchi, P. (2010). Cerebrovascular accidents in elderly people treated with antipsychotic drugs: A systematic review. *Drug Safety*, *33*(4), 273−288.

Sackeim, H. A., Prudic, J., Nobler, M. S., Fitzsimons, L., Lisanby, S. H., Payne, N., . . . Devanand, D. P. (2008). Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation*, *1*(2), 71−83.

Saidijam, M., Karimi Dermani, F., Sohrabi, S., & Patching, S. G. (2018). Efflux proteins at the blood-brain barrier: Review and bioinformatics analysis. *Xenobiotica*, *48*(5), 506−532.

Sajatovic, M., Blow, F. C., Ignacio, R. V., & Kales, H. C. (2005). New-onset bipolar disorder in later life. *The American Journal of Geriatric Psychiatry*, *13*(4), 282−289.

Sajatovic, M., Gyulai, L., Calabrese, J. R., Thompson, T. R., Wilson, B. G., White, R., & Evoniuk, G. (2005). Maintenance treatment outcomes in older patients with bipolar I disorder. *The American Journal of Geriatric Psychiatry*, *13*(4), 305−311.

Sajatovic, M., Ramsay, E., Nanry, K., & Thompson, T. (2007). Lamotrigine therapy in elderly patients with epilepsy, bipolar disorder or dementia. *International Journal of Geriatric Psychiatry*, *22*(10), 945−950.

Sajatovic, M., Dines, P., Fuentes-Casiano, E., Athey, M., Cassidy, K. A., Sams, J., . . . Tatsuoka, C. (2015). Asenapine in the treatment of older adults with bipolar disorder. *International Journal of Geriatric Psychiatry*, *30*(7), 710−719.

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., . . . Shulman, K. I. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disorder*, *17*(7), 689−704.

Sajatovic, M., Forester, B. P., Tsai, J., Kroger, H., Pikalov, A., Cucchiaro, J., & Loebel, A. (2016). Efficacy of lurasidone in adults aged 55 years and older with bipolar depression: Post hoc analysis of 2 double-blind, placebo-controlled studies. *The Journal of Clinical Psychiatry*, *77*(10), e1324–e1331.

Sakae, N., Josephs, K. A., Litvan, I., Murray, M. E., Duara, R., Uitti, R. J., & Dickson, D. W. (2019). Clinicopathologic subtype of Alzheimer's disease presenting as corticobasal syndrome. *Alzheimers Dement*, *15*(9), 1218–1228.

Salisbury, C., Johnson, L., Purdy, S., Valderas, J. M., & Montgomery, A. A. (2011). Epidemiology and impact of multimorbidity in primary care: A retrospective cohort study. *British Journal of General Practice*, *61*(582), e12–e21.

Salzman, C. (2005). *Clinical geriatric psychopharmacology*. Lippincott Williams & Wilkins.

Salzman, C., & Shader, R. I. (2015). Benzodiazepine use and risk for Alzheimer disease. *Journal of Clinical Psychopharmacology*, *35*(1), 1–3.

Sanagawa, A., Shiraishi, N., Sekiguchi, F., Akechi, T., & Kimura, K. (2019). Successful use of brexpiprazole for Parkinson's disease psychosis without adverse effects: A case report. *Journal of Clinical Psychopharmacology*, *39*(6), 685–687.

Sarris, J. (2013). St. John's wort for the treatment of psychiatric disorders. *Psychiatric Clinics of North America*, *36*(1), 65–72.

Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N., & Heald, J. L. (2017). Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*, *13*(2), 307–349.

Scarpace, P. J., Tumer, N., & Mader, S. L. (1991). Beta-adrenergic function in aging. Basic mechanisms and clinical implications. *Drugs & Aging*, *1*(2), 116–129.

Schmidt, R., Hofer, E., Bouwman, F. H., Buerger, K., Cordonnier, C., Fladby, T., … Sorbi, S. (2015). EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. *European Journal of Neurology*, *22*(6), 889–898.

Schneider, L. S., Dagerman, K., & Insel, P. S. (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. *The American Journal of Geriatric Psychiatry*, *14*(3), 191–210.

Schneider, L. S., Tariot, P. N., Dagerman, K. S., Davis, S. M., Hsiao, J. K., Ismail, M. S., … Lieberman, J. A. (2006). Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *The New England Journal of Medicine*, *355*(15), 1525–1538.

Schneider, L. S., Dagerman, K. S., Higgins, J. P., & McShane, R. (2011). Lack of evidence for the efficacy of memantine in mild Alzheimer disease. *Archives of Neurology*, *68*(8), 991–998.

Schneider, L. S., Frangakis, C., Drye, L. T., Devanand, D. P., Marano, C. M., Mintzer, J., … Lyketsos, C. G. (2016). Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: The CitAD randomized clinical trial. *The American Journal of Psychiatry*, *173*(5), 465–472.

Schulz, R., McGinnis, K. A., Zhang, S., Martire, L. M., Hebert, R. S., Beach, S. R., … Belle, S. H. (2008). Dementia patient suffering and caregiver depression. *Alzheimer Disease and Associated Disorders*, *22*(2), 170–176.

Segovia, G., Porras, A., Del Arco, A., & Mora, F. (2001). Glutamatergic neurotransmission in aging: A critical perspective. *Mechanisms of Ageing and Development*, *122*(1), 1–29.

Segura-Bruna, N., Rodriguez-Campello, A., Puente, V., & Roquer, J. (2006). Valproate-induced hyperammonemic encephalopathy. *Acta Neurologica Scandinavica*, *114*(1), 1–7.

Seligman, F., & Nemeroff, C. B. (2015). The interface of depression and cardiovascular disease: Therapeutic implications. *Annals of the New York Academy of Sciences*, *1345*, 25–35.

Sepehry, A. A., Lee, P. E., Hsiung, G. R., Beattie, B. L., Feldman, H. H., & Jacova, C. (2017). The 2002 NIMH provisional diagnostic criteria for depression of Alzheimer's disease (PDC-dAD): Gauging their validity over a decade later. *Journal of Alzheimer's Disease*, *58*(2), 449–462.

Seyffert, M., Lagisetty, P., Landgraf, J., Chopra, V., Pfeiffer, P. N., Conte, M. L., & Rogers, M. A. (2016). Internet-delivered cognitive behavioral therapy to treat insomnia: A systematic review and meta-analysis. *PLoS One*, *11*(2), e0149139.

Sharp, S. I., Francis, P. T., Elliott, M. S., Kalaria, R. N., Bajic, N., Hortobagyi, T., & Ballard, C. G. (2009). Choline acetyltransferase activity in vascular dementia and stroke. *Dementia and Geriatric Cognitive Disorders*, *28*(3), 233–238.

Sheffrin, M., Miao, Y., Boscardin, W. J., & Steinman, M. A. (2015). Weight loss associated with cholinesterase inhibitors in individuals with Dementia in a national healthcare system. *Journal of the American Geriatrics Society*, *63*(8), 1512–1518.

Sheikh Rezaei, S., Mittlbock, M., Reichardt, B., & Wolzt, M. (2019). SSRI co-medication with NOAC or VKA does not increase hospitalisation for bleeding: A retrospective nationwide cohort study in Austria 2010-2015. *International Journal of Geriatric Psychiatry*, *34*(8), 1194–1199.

Shine, B., McKnight, R. F., Leaver, L., & Geddes, J. R. (2015). Long-term effects of lithium on renal, thyroid, and parathyroid function: A retrospective analysis of laboratory data. *Lancet*, *386*(9992), 461–468.

Shiroma, P. R., Drews, M. S., Geske, J. R., & Mrazek, D. A. (2014). SLC6A4 polymorphisms and age of onset in late-life depression on treatment outcomes with citalopram: A Sequenced Treatment Alternatives to Relieve Depression (STAR*D) report. *The American Journal of Geriatric Psychiatry*, *22*(11), 1140–1148.

Shulman, K. I., Almeida, O. P., Herrmann, N., Schaffer, A., Strejilevich, S. A., Paternoster, C., … Sajatovic, M. (2019). Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: An ISBD task force report. *Bipolar Disorder*, *21*(2), 117–123.

Sin Fai Lam, C. C., Reeves, S. J., Stewart, R., & Howard, R. (2016). Service and treatment engagement of people with very late-onset schizophrenia-like psychosis. *BJPsych Bulletin*, *40*(4), 185–186.

Singh, R. R., & Nayak, R. (2016). Impact of FDA black box warning on psychotropic drug use in noninstitutionalized elderly patients diagnosed with dementia: A retrospective study. *Journal of Pharmacy Practice*, *29*(5), 495–502.

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimaki, M., & Sabia, S. (2017). Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry*, *74*(7), 712–718.

Skrobot, O. A., Black, S. E., Chen, C., DeCarli, C., Erkinjuntti, T., Ford, G. A., … Kehoe, P. G. (2018). Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimer's & Dementia*, *14*(3), 280–292.

Smith, S. M., Wallace, E., O'Dowd, T., & Fortin, M. (2016). Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *The Cochrane Database of Systematic Reviews*, *3*, Cd006560.

Sobieraj, D. M., Martinez, B. K., Hernandez, A. V., Coleman, C. I., Ross, J. S., Berg, K. M., … Baker, W. L. (2019). Adverse effects of pharmacologic treatments of major depression in older adults. *Journal of the American Geriatrics Society*, *67*(8), 1571–1581.

Soiza, R. L., Subbarayan, S., Antonio, C., Cruz-Jentoft, A. J., Petrovic, M., Gudmundsson, A., & O'Mahony, D. (2017). The SENATOR project: Developing and trialling a novel software engine to optimize medications and nonpharmacological therapy in older people with multimorbidity and polypharmacy. *Therapeutic Advances in Drug Safety*, *8*(3), 81–85.

Sonnerstam, E., Sjolander, M., Lovheim, H., & Gustafsson, M. (2018). Clinically relevant drug-drug interactions among elderly people with dementia. *European Journal of Clinical Pharmacology*, *74*(10), 1351–1360.

Spigset, O., Hagg, S., & Bate, A. (2003). Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: Data from the World Health Organization (WHO) database of adverse drug reactions. *International Clinical Psychopharmacology*, *18*(3), 157–161.

Spina, E., Pisani, F., & de Leon, J. (2016). Clinically significant pharmacokinetic drug interactions of antiepileptic drugs with new antidepressants and new antipsychotics. *Pharmacological Research*, *106*, 72–86.

Stahl, S. M. (2009). Mechanism of action of trazodone: A multifunctional drug. *CNS Spectrums*, *14*(10), 536–546.

Steinberg, M., Shao, H., Zandi, P., Lyketsos, C. G., Welsh-Bohmer, K. A., Norton, M. C., … Tschanz, J. T. (2008). Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County Study. *International Journal of Geriatric Psychiatry*, *23*(2), 170–177.

Steinman, M. A., & Hanlon, J. T. (2010). Managing medications in clinically complex elders: "There's got to be a happy medium. *Journal of the American Medical Association*, *304*(14), 1592–1601.

Stephen, L. J. (2003). Drug treatment of epilepsy in elderly people: Focus on valproic Acid. *Drugs & Aging*, *20*(2), 141–152.

Stewart, S. H., Koch, D. G., Burgess, D. M., Willner, I. R., & Reuben, A. (2013). Sensitivity and specificity of urinary ethyl glucuronide and ethyl sulfate in liver disease patients. *Alcoholism: Clinical and Experimental Research*, *37*(1), 150–155.

Stone, M., Laughren, T., Jones, M. L., Levenson, M., Holland, P. C., Hughes, A., … Rochester, G. (2009). Risk of suicidality in clinical trials of antidepressants in adults: Analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*, *339*, b2880.

Stone, J. A., Lester, C. A., Aboneh, E. A., Phelan, C. H., Welch, L. L., & Chui, M. A. (2017). A preliminary examination of over-the-counter medication misuse rates in older adults. *Research in Social and Administrative Pharmacy*, *13*(1), 187–192.

Suarez, J., Tartaglia, M. C., Vitali, P., Erbetta, A., Neuhaus, J., Laluz, V., & Miller, B. L. (2009). Characterizing radiology reports in patients with frontotemporal dementia. *Neurology*, *73*(13), 1073–1074.

Suh, D. C., Arcona, S., Thomas, S. K., Powers, C., Rabinowicz, A. L., Shin, H., & Mirski, D. (2004). Risk of antipsychotic drug use in patients with Alzheimer's disease treated with rivastigmine. *Drugs & Aging*, *21*(6), 395–403.

Sultan, R. S., Olfson, M., Correll, C. U., & Duncan, E. J. (2017). Evaluating the effect of the changes in FDA guidelines for clozapine monitoring. *The Journal of Clinical Psychiatry*, *78*(8), e933–e939.

Sultzer, D. L., Davis, S. M., Tariot, P. N., Dagerman, K. S., Lebowitz, B. D., Lyketsos, C. G., … Schneider, L. S. (2008). Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: Phase 1 outcomes from the CATIE-AD effectiveness trial. *The American Journal of Psychiatry*, *165*(7), 844–854.

Syed, H., Som, S., Khan, N., & Faltas, W. (2009). Doxylamine toxicity: Seizure, rhabdomyolysis and false positive urine drug screen for methadone. *BMJ Case Reports*, *2009*, bcr09.2008.0879.

Talaslahti, T., Alanen, H. M., Hakko, H., Isohanni, M., Hakkinen, U., & Leinonen, E. (2015). Patients with very-late-onset schizoprhenia-like psychosis have higher mortality rates than elderly patients with earlier onset schizophrenia. *International Journal of Geriatric Psychiatry*, *30*(5), 453–459.

Tampi, R. R., Tampi, D. J., Balachandran, S., & Srinivasan, S. (2016). Antipsychotic use in dementia: A systematic review of benefits and risks from meta-analyses. *Therapeutic Advances in Chronic Disease*, *7*(5), 229–245.

Tanaka, E. (2002). Toxicological interactions between alcohol and benzodiazepines. *Journal of Toxicology, Clinical Toxicology*, *40*(1), 69–75.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., … Carpenter, W. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research*, *150*(1), 3–10.

Tannenbaum, C., Farrell, B., Shaw, J., Morgan, S., Trimble, J., Currie, J., … Silvius, J. (2017). An ecological approach to reducing potentially inappropriate medication use: Canadian deprescribing network. *Canadian Journal on Aging*, *36*(1), 97–107.

Taragano, F. E., Allegri, R. F., & Lyketsos, C. (2008). Mild behavioral impairment: A prodromal stage of dementia. *Dementia & Neuropsychologia*, *2*(4), 256–260.

Tay, J., Tuladhar, A. M., Hollocks, M. J., Brookes, R. L., Tozer, D. J., Barrick, T. R., … Markus, H. S. (2019). Apathy is associated with large-scale white matter network disruption in small vessel disease. *Neurology*, *92*(11), e1157–e1167.

Taylor, C. P., Angelotti, T., & Fauman, E. (2007). Pharmacology and mechanism of action of pregabalin: The calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Research*, *73*(2), 137–150.

Telles-Correia, D., Barbosa, A., Cortez-Pinto, H., Campos, C., Rocha, N. B. F., & Machado, S. (2017). Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World Journal of Gastrointestinal Pharmacology and Therapeutics*, *8*(1), 26–38.

Terada, T., & Hira, D. (2015). Intestinal and hepatic drug transporters: Pharmacokinetic, pathophysiological, and pharmacogenetic roles. *Journal of Gastroenterology*, *50*(5), 508–519.

Terao, T., Ishida, A., Kimura, T., Yarita, M., & Hara, T. (2017). Preventive effects of lamotrigine in bipolar II versus bipolar I disorder. *The Journal of Clinical Psychiatry*, *78*(8), e1000–e1005.

Thase, M. E. (2007). STEP-BD and bipolar depression: What have we learned? *Current Psychiatry Reports*, *9*(6), 497–503.

Thase, M. E. (2016). Adverse effects of second-generation antipsychotics as adjuncts to antidepressants: Are the risks worth the benefits? *Psychiatric Clinics of North America*, *39*(3), 477–486.

Thomas, A. (2013). Is depression really different in older people? *International Psychogeriatrics*, *25*(11), 1739–1742.

Thomas, J. E., Caballero, J., & Harrington, C. A. (2015). The incidence of akathisia in the treatment of schizophrenia with aripiprazole, asenapine and lurasidone: A meta-analysis. *Current Neuropharmacology*, *13*(5), 681–691.

Tiihonen, J., Taipale, H., Mehtala, J., Vattulainen, P., Correll, C. U., & Tanskanen, A. (2019). Association of antipsychotic polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiatry*, *76*(5), 499–507.

Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., … Trojanowski, J. Q. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*, *136*(Pt 9), 2697–2706.

Tolou-Ghamari, Z., Zare, M., Habibabadi, J. M., & Najafi, M. R. (2013). A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*, *18*(Suppl. 1), S81–S85.

Toornvliet, R., van Berckel, B. N. M., Luurtsema, G., Lubberink, M., Geldof, A. A., Bosch, T. M., … Franssen, E. J. F. (2006). Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C]verapamil and positron emission tomography. *Clinical Pharmacology and Therapeutics*, *79*(6), 540–548.

Tornio, A., & Backman, J. T. (2018). Cytochrome P450 in pharmacogenetics: An update. *Advances in Pharmacology*, *83*, 3–32.

Tsuboi, T., Bies, R. R., Suzuki, T., Mamo, D. C., Pollock, B. G., Graff-Guerrero, A., … Uchida, H. (2013). Hyperprolactinemia and estimated dopamine D2 receptor occupancy in patients with schizophrenia: Analysis of the CATIE data. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *45*, 178–182.

Tunbridge, E. M., Attenburrow, M. J., Gardiner, A., Rendell, J. M., Hinds, C., Goodwin, G. M., … Geddes, J. R. (2017). Biochemical and genetic predictors and correlates of response to lamotrigine and folic acid in bipolar depression: Analysis of the CEQUEL clinical trial. *Bipolar Disorder*, *19*(6), 477–486.

Tunnicliff, G. (1991). Molecular basis of buspirone's anxiolytic action. *Pharmacology & Toxicology*, *69*(3), 149–156.

Tzimos, A., Samokhvalov, V., Kramer, M., Ford, L., Gassmann-Mayer, C., Lim, P., & Eerdekens, M. (2008). Safety and tolerability of oral paliperidone extended-release tablets in elderly patients with schizophrenia: A double-blind, placebo-controlled study with six-month open-label extension. *The American Journal of Geriatric Psychiatry*, *16*(1), 31–43.

Uchiyama, M., Nishio, Y., Yokoi, K., Hirayama, K., Imamura, T., Shimomura, T., & Mori, E. (2012). Pareidolias: Complex visual illusions in dementia with Lewy bodies. *Brain*, *135*(Pt 8), 2458–2469.

Ulrich, S., Neuhof, S., Braun, V., & Meyer, F. P. (1998). Therapeutic window of serum haloperidol concentration in acute schizophrenia and schizoaffective disorder. *Pharmacopsychiatry*, *31*(5), 163–169.

Unholzer, S., & Haen, E. (2015). Retrospective analysis of therapeutic drug monitoring data for treatment of bipolar disorder with lamotrigine. *Pharmacopsychiatry*, *48*(6), 211–214.

Van Gerpen, M. W., Johnson, J. E., & Winstead, D. K. (1999). Mania in the geriatric patient population: A review of the literature. *The American Journal of Geriatric Psychiatry*, *7*(3), 188–202.

van Melick, E. J., Wilting, I., Ziere, G., Kok, R. M., & Egberts, T. C. (2014). The influence of lithium on calcium homeostasis in older patients in daily clinical practice. *International Journal of Geriatric Psychiatry*, *29*(6), 594–601.

Vasudev, A., Chaudhari, S., Sethi, R., Fu, R., Sandieson, R. M., & Forester, B. P. (2018). A review of the pharmacological and clinical profile of newer atypical antipsychotics as treatments for bipolar disorder: Considerations for use in older patients. *Drugs & Aging*, *35*(10), 887–895.

Verbalis, J. G., Goldsmith, S. R., Greenberg, A., Korzelius, C., Schrier, R. W., Sterns, R. H., & Thompson, C. J. (2013). Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *The American Journal of Medicine*, *126*(10 Suppl. 1), S1–S42.

Vermeeren, A., Vets, E., Vuurman, E. F., Van Oers, A. C., Jongen, S., Laethem, T., … Sun, H. (2016). On-the-road driving performance the morning after bedtime use of suvorexant 15 and 30 mg in healthy elderly. *Psychopharmacology (Berl)*, *233*(18), 3341–3351.

Veronese, M. L., Gillen, L. P., Burke, J. P., Dorval, E. P., Hauck, W. W., Pequignot, E., … Greenberg, H. E. (2003). Exposure-dependent inhibition of intestinal and hepatic CYP3A4 in vivo by grapefruit juice. *The Journal of Clinical Pharmacology*, *43*(8), 831–839.

Verrotti, A., Scaparrotta, A., Grosso, S., Chiarelli, F., & Coppola, G. (2014). Anticonvulsant drugs and hematological disease. *Neurological Sciences*, *35*(7), 983–993.

Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., van Heuckelum, J. H., Veldhuijzen, D. S., … Patat, A. (2002). Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *Journal of Clinical Psychopharmacology*, *22*(6), 576–583.

Vik-Mo, A. O., Bencze, J., Ballard, C., Hortobagyi, T., & Aarsland, D. (2019). Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *90*(6), 728–730.

Villa, R. F., Ferrari, F., & Moretti, A. (2018). Post-stroke depression: Mechanisms and pharmacological treatment. *Pharmacology and Therapeutics*, *184*, 131–144.

Waade, R. B., Molden, E., Refsum, H., & Hermann, M. (2012). Serum concentrations of antidepressants in the elderly. *Therapeutic Drug Monitoring*, *34*(1), 25−30.

Wakefield, J. C., & First, M. B. (2012). Validity of the bereavement exclusion to major depression: Does the empirical evidence support the proposal to eliminate the exclusion in DSM-5? *World Psychiatry*, *11*(1), 3−10.

Wald, N. J., & Law, M. R. (2003). A strategy to reduce cardiovascular disease by more than 80%. *BMJ*, *326*(7404), 1419.

Wang, C. Y., Zhang, Z. J., Li, W. B., Zhai, Y. M., Cai, Z. J., Weng, Y. Z., … Zhou, H. H. (2004). The differential effects of steady-state fluvoxamine on the pharmacokinetics of olanzapine and clozapine in healthy volunteers. *The Journal of Clinical Pharmacology*, *44*(7), 785−792.

Wehling, M. (2008). [Drug therapy in the elderly: Too much or too little, what to do? A new assessment system: Fit for the aged (FORTA)]. *Deutsche Medizinische Wochenschrift*, *133*(44), 2289−2291.

Wehling, M. (2011). Guideline-driven polypharmacy in elderly, multimorbid patients is basically flawed: There are almost no guidelines for these patients. *Journal of the American Geriatrics Society*, *59*(2), 376−377.

Wehling, M. (2016). Older people, a plethora of drugs, and drug list approaches: Useful, efficacious, or a waste of time? *Journal of the American Medical Directors Association*, *17*(12), 1073−1075.

Weintraub, D., & Mamikonyan, E. (2019). The neuropsychiatry of Parkinson disease: A perfect storm. *The American Journal of Geriatric Psychiatry*, *27*(9), 998−1018.

Wijnen, P. A. H. M., Op Den Buijsch, R. A. M., Drent, M., Kuipers, P. M. J. C., Neef, C., Bast, A., … Koek, G. H. (2007). Review article: The prevalence and clinical relevance of cytochrome P450 polymorphisms. *Alimentary Pharmacology & Therapeutics*, *26*(s2), 211−219.

Wilkinson, G. R. (1997). The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans. *Advanced Drug Delivery Reviews*, *27*(2−3), 129−159.

Williams, J. A., Hyland, R., Jones, B. C., Smith, D. A., Hurst, S., Goosen, T. C., … Ball, S. E. (2004). Drug-drug interactions for UDP-glucuronosyltransferase substrates: A pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. *Drug Metabolism and Disposition: The Biological Fate of Chemicals*, *32*(11), 1201−1208.

Wilt, T. J., MacDonald, R., Brasure, M., Olson, C. M., Carlyle, M., Fuchs, E., … Kane, R. L. (2016). Pharmacologic treatment of insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians. *Annals of Internal Medicine*, *165*(2), 103−112.

Wise, E. A., Rosenberg, P. B., Lyketsos, C. G., & Leoutsakos, J.-M. (2019). Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *11*, 333−339.

Wisniowska, B., Tylutki, Z., Wyszogrodzka, G., & Polak, S. (2016). Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect—Comprehensive overview of clinical trials. *BMC Pharmacology and Toxicology*, *17*, 12.

Woods, S. P., Dawson, M. S., Weber, E., Gibson, S., Grant, I., & Atkinson, J. H. (2009). Timing is everything: Antiretroviral nonadherence is associated with impairment in time-based prospective memory. *Journal of the International Neuropsychological Society*, *15*(1), 42−52.

Woodward, M. C. (2003). Deprescribing: Achieving better health outcomes for older people through reducing medications. *Journal of Pharmacy Practice and Research*, *33*(4), 323−328.

Woolcott, J. C., Richardson, K. J., Wiens, M. O., Patel, B., Marin, J., Khan, K. M., & Marra, C. A. (2009). Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine*, *169*(21), 1952−1960.

Woolley, J. D., Khan, B. K., Murthy, N. K., Miller, B. L., & Rankin, K. P. (2011). The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *The Journal of Clinical Psychiatry*, *72*(2), 126−133.

Wragg, R. E., & Jeste, D. V. (1989). Overview of depression and psychosis in Alzheimer's disease. *The American Journal of Psychiatry*, *146*(5), 577−587.

Wylie, M. A., Shnall, A., Onyike, C. U., & Huey, E. D. (2013). Management of frontotemporal dementia in mental health and multidisciplinary settings. *International Review of Psychiatry*, *25*(2), 230−236.

Yamaori, S., Okamoto, Y., Yamamoto, I., & Watanabe, K. (2011). Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metabolism and Disposition*, *39*(11), 2049−2056.

Yamreudeewong, W., Wong, H. K., Brausch, L. M., & Pulley, K. R. (2009). Probable interaction between warfarin and marijuana smoking. *Annals of Pharmacotherapy*, *43*(7), 1347−1353.

Yang, L. P. (2014). Suvorexant: First global approval. *Drugs*, *74*(15), 1817−1822.

Yarnall, A. J., Sayer, A. A., Clegg, A., Rockwood, K., Parker, S., & Hindle, J. V. (2017). New horizons in multimorbidity in older adults. *Age and Ageing*, *46*(6), 882−888.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Beaulieu, S., Alda, M., … Berk, M. (2013). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2013. *Bipolar Disorder*, *15*(1), 1−44.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorder*, *20*(2), 97−170.

Yoshida, K., Roberts, R., Suzuki, T., Lebowitz, B., Reeves, S., Howard, R., … Uchida, H. (2017). Lack of early improvement with antipsychotics is a marker for subsequent nonresponse in behavioral and psychological symptoms of dementia: Analysis of CATIE-AD data. *The American Journal of Geriatric Psychiatry*, *25*(7), 708−716.

Yoshita, M., Taki, J., Yokoyama, K., Noguchi-Shinohara, M., Matsumoto, Y., Nakajima, K., & Yamada, M. (2006). Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. *Neurology*, *66*(12), 1850–1854.

Young, R. C., Mulsant, B. H., Sajatovic, M., Gildengers, A. G., Gyulai, L., Al Jurdi, R. K., ... Alexopoulos, G. S. (2017). GERI-BD: A randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. *The American Journal of Psychiatry*, *174*(11), 1086–1093.

Zídek, Z., Anzenbacher, P., & Kmoníčková, E. (2009). Current status and challenges of cytokine pharmacology. *British Journal of Pharmacology*, *157*(3), 342–361.

Zendulka, O., Dovrtelova, G., Noskova, K., Turjap, M., Sulcova, A., Hanus, L., & Jurica, J. (2016). Cannabinoids and cytochrome P450 interactions. *Current Drug Metabolism*, *17*(3), 206–226.

Zhang, Y., & Benet, L. Z. (2001). The gut as a barrier to drug absorption: Combined role of cytochrome P450 3A and P-glycoprotein. *Clinical Pharmacokinetics*, *40*(3), 159–168.

Zhang, H., Wang, L., Fan, Y., Yang, L., Wen, X., Liu, Y., & Liu, Z. (2019). Atypical antipsychotics for Parkinson's disease psychosis: A systematic review and meta-analysis. *Neuropsychiatric Disease and Treatment*, *15*, 2137–2149.

Zhao, Q. F., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., ... Yu, J. T. (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*, *190*, 264–271.

Zheng, L., Mack, W. J., Dagerman, K. S., Hsiao, J. K., Lebowitz, B. D., Lyketsos, C. G., ... Schneider, L. S. (2009). Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: The CATIE-AD study. *The American Journal of Psychiatry*, *166*(5), 583–590.

Zhou, S. F. (2008). Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Current Drug Metabolism*, *9*(4), 310–322.

Zhou, X., Keitner, G. I., Qin, B., Ravindran, A. V., Bauer, M., Del Giovane, C., ... Xie, P. (2015). Atypical antipsychotic augmentation for treatment-resistant depression: A systematic review and network meta-analysis. *The International Journal of Neuropsychopharmacology*, *18*(11), pyv060.

Zhou, Y., Ingelman-Sundberg, M., & Lauschke, V. M. (2017). Worldwide distribution of cytochrome P450 alleles: A meta-analysis of population-scale sequencing projects. *Clinical Pharmacology & Therapeutics*, *102*(4), 688–700.

This page intentionally left blank

Chapter 24

Technology-based mental health assessment and intervention

Christine E. Gould[1,2], Flora Ma[1,3], Julia R. Loup[4], Christine Juang[5], Erin Y. Sakai[5] and Renee Pepin[6]

[1]Geriatric Research Education and Clinical Center, VA Palo Alto Health Care System, Palo Alto, CA, United States, [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [3]Pacific Graduate School of Psychology, Palo Alto University, Palo Alto, CA, United States, [4]Department of Psychology, The University of Alabama, Tuscaloosa, AL, United States, [5]Psychology Service, VA Palo Alto Health Care System, Palo Alto, CA, United States, [6]Geisel School of Medicine at Dartmouth, Hanover, NH, United States

Introduction

The number of older Americans will double by 2060 (U.S. Census Bureau, 2017). This increase in the number of older Americans signifies growing mental health needs for which we are not prepared. Multiple factors will make it difficult to meet these needs without re-conceptualizing how we deliver care. First, the United States faces a severe geriatric mental health workforce shortage in that there are not enough trained providers or trainees in the pipeline to meet the future mental health needs (Institute of Medicine, 2012). Second, barriers, such as mobility and transportation difficulties, impede older adults' access to care (e.g., Pepin, Segal, & Coolidge, 2009). Third, the migration of older adults to rural areas (Walters, 2002) diminishes older adults' access to mental health services, as fewer providers are available in these locations (Wei, Sambamoorthi, Olfson, Walkup, & Crystal, 2005). Technologies, such as telephones, telehealth, computers, the Internet, and mobile devices, may provide solutions to the growing geriatric mental health needs. Technology has the potential to support older adults' needs ranging from increasing social connectedness to facilitating medication management and supporting independent living (Czaja, Boot, Charness, Rogers, & Sharit, 2017; Mynatt & Rogers, 2001; Rogers & Fisk, 2010). Moreover, technology-delivered assessment and interventions are scalable, can be delivered where older adults live, and can deliver evidence-based interventions with less provider time and contact compared with traditional face-to-face interventions.

Research on mental health technologies is rapidly advancing, but most studies omit older adults. Although older adults adopt technologies more slowly compared with younger adults, older adults' adoption of computers, home internet, and smartphones has been rapidly expanding in the United States (Lee et al., 2019; Pew Research Center, 2017). Similarly, in many countries, older adults increasingly use the internet for reasons related to their health (Crabb et al., 2012; Ewing, Thomas, & Schiessl, 2012). Despite this rapid increase in use, older adults encounter access-related barriers to technology use, specifically the lack of access to technological resources (e.g., personal computers, smartphones) or the high cost of internet and cell phone services (Pew Research Center, 2017). Older adults also benefit from training opportunities to learn and use technology (e.g., Czaja et al., 2017), but these opportunities are not always available. Finally, some technologies are either not suitable to be used with age-related disabilities (e.g., poor vision or arthritis) or may be harder to use by individuals with perceptual or mobility difficulties compared with the rest of the general population (Fisk, Rogers, Charness, Czaja, & Sharit, 2009).

Our chapter focuses on the use of technology to conduct mental health assessments and interventions with older adults. We review a broad range of technologies ranging from telephone-based interventions to virtual reality. When domains contain little research on mental health and aging, we incorporate related evidence from the literature.

Technology considerations for older users

When considering using technology-based assessments and interventions with older adults, one must first consider that older adult users face external factors, internal factors, and person-technology fit–related factors that may impact their

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00024-7

use of technology. The primary external factor that affects use of technology is access. With older adults, age-related income disparities are the primary factor limiting access to technology. Survey findings from the Pew Research Center (2017) document low adoption rates for various technologies among older adults compared with middle-aged and younger adults. However, among older adults, the largest digital divide exists for low-income older adults compared with their counterparts with higher incomes. Expensive data network or cellular service charges may preclude mobile device ownership among older individuals on fixed incomes (Trull & Ebner-Priemer, 2009).

A critical individual factor that influences technology use and adoption is the individual user's perceptions of technology and their experience with technology. One of the seminal models examining how perceptions are related to acceptance is the Technology Acceptance Model (TAM, Davis, 1985), a model initially developed to examine acceptance of computers. Davis posits that there are two sets of beliefs that influence the user's attitudes about using the technology: (1) the *perceived usefulness* and (2) the *perceived ease of use* of the technology. For example, Wild, Boise, Lundell, and Foucek (2008) demonstrated that older adults are willing to use technologies, such as sensor devices in smart homes, if the devices are perceived to be useful. Rogers and Fisk (2010) recommend that the benefit of using a particular technology should be emphasized for older users in accordance with this model. According to the model, even if a technology is perceived to be useful, it must also be perceived to be relatively easy to use. Thus, poor usability will limit technology adoption. Perceived loss of privacy may also turn older users away from adoption of technology (Charness & Boot, 2009).

With regard to usability, there are a number of individual factors unique to older adults that influence usability. Many older adults experience changes in hearing, vision, and tactile sensation that affect their perception of and interaction with devices such as touch screens, computer controls (i.e., touchpad, a mouse), and monitor displays. Normative and abnormal cognitive changes that occur as one age make it difficult to learn new technologies and perform complex tasks such as visual searches on complex displays or multitasking. The Center for Research and Education on Aging and Technology Enhancement (CREATE) developed a model of aging and technology that expands on the TAM. The CREATE model suggests that the success of technology design is based on the interaction of the technology characteristics (i.e., system demands and tasks demands) with the older user's needs and capabilities (Fisk et al., 2009). A full discussion of technology components that are important to include for older adults is beyond the scope of this chapter, but the interested reader is encouraged to review Fisk et al. (2009) and Pak and McLaughlin (2011).

Instructional training and education may help improve person-technology fit. A growing body of research has demonstrated that not only do older users benefit from instructional training on technology use, but also that older adults have experienced improved wellbeing with internet training (Shapira, Barak, & Gal, 2007) or cognitive benefits such as improved processing speed and episodic memory with iPad training (Chan, Haber, Drew, & Park, 2016). Furthermore, a randomized controlled trial (RCT) of an internet platform designed for older users [Personal Reminder Information and Social Management (PRISM) system] compared with a control condition (printed materials) demonstrated that the internet-based system improved participants' cognition, reduced loneliness, and increased perceived social support and wellbeing for up to six months (Czaja et al., 2017). The PRISM system provided internet access, email, games, daily photos and weather information, and vetted information and resources in an easy to navigate interface. Older adults who used the PRISM system also felt more comfortable and proficient and reported increased self-efficacy with computer usage relative to the control participants (Czaja et al., 2017). Thus, instructional support helps older adults use technology and some technologies even enhance older adults' lives through improvements in wellbeing and cognition. Herein, we focus on technology used to assess and intervene to improve older adults' mental health.

Assessment using technology

Technology-based assessments are gaining traction in mental health. However, special consideration is needed when applying these assessments to older adults. First, a provider should consider an individual's vision, hearing, and sense of touch (Fisk et al., 2009). Older adults may need to adjust the displays and interfaces (e.g., increasing font size) to complete assessments. Health conditions common in later life (e.g., arthritis) may also affect motor speed or ability when completing assessments, particularly on touch screen devices (Jenkins, Lindsay, Eslambolchilar, Thornton, & Talkes, 2016). Stylus pens may be used to improve a user's interaction with touch screens. Multiple aspects of cognitive processing are critical to technology-based assessments (Fisk et al., 2009). Working memory and procedural memory are needed to be able to perform activities, such as recalling which keys to use on a computer keyboard to respond to a stimulus in computerized assessments. Attention, particularly visual attention, is critical in detecting information on a display such as warning signs or buttons to click to proceed through the assessment. Experience and comfort with technology also play a significant role in technology-based assessments. Lack of experience with technology could lead to

unwillingness to try the assessments, lack of motivation, or anxiety about the technology-delivered assessments, which could in turn adversely affect the veracity of the findings. Finally, the technological device can affect performance on assessments (e.g., screen luminance levels; Seichepine et al., 2012). While these limitations must be considered, there is a growing body of evidence for the use of various technology-based assessments as described in the following sections.

Assessment via telehealth

Telehealth is a broad term that encompasses using technology to collect information, manage healthcare, and deliver interventions by a provider remotely. Herein, we focus on telehealth that utilizes online videoconferencing technology (i.e., computers, mobile phones, and the Internet) to concurrently share audio, video information, and data to communicate between a patient and a healthcare provider across two or more geographical health locations (Backhaus et al., 2012; Perle, Langsam, & Nierenberg, 2011). Videoconference-mediated assessments can benefit populations particularly those in remote areas. The advantages of telehealth assessments include improved access to care, patient satisfaction, convenience, and potential cost savings (Bashshur, Shannon, Bashshur, & Yellowlees, 2016; Czaja, 2016).

Teleneuropsychological assessments utilize videoconferencing technology and systems to administer neuropsychological measures (Cullum, Hynan, Grosch, Parikh, & Weiner, 2014). Methods vary, but generally patients view a remote examiner at a different geographical location on the screen (Wadsworth et al., 2018). The remote examiner may also have access to a mobile camera to view the participant and the test materials throughout test administration (Wadsworth et al., 2018). Often staff are available in-person to assist with the videoconferencing equipment. Some neuropsychological tests may require procedural modifications for teleneuropsychological assessments versus in-person test administration. For example, patients were asked to hold up their drawings from assessments such as the clock-drawing test to the camera for the examiners to score them and scores were subsequently double-checked when the remote examiner received the physical forms (Wadsworth et al., 2018). Valid and reliable test scores are important for clinical practice and for generalization of findings across studies; however, variability in teleneuropsychological administration and scoring techniques complicate the comparison of scores (Brearly et al., 2017). Future studies need to develop standardized methods for presenting detailed visual stimuli during assessments that require motor and visual abilities such as tests of processing speed and complex attention (Brearly et al., 2017).

Several studies examined feasibility and diagnostic reliability of cognitive assessment via telehealth. Of note are findings that reveal high sensitivity and specificity in diagnosing dementia (e.g., Alzheimer's disease) and in assessing cognitive functioning via telehealth (Cullum, Weiner, Gehrmann, & Hynan, 2006; Lee et al., 2000; Loh et al., 2005; Martin-Khan et al., 2012; Richardson, Frueh, Grubaugh, Egede, & Elhai, 2009). For example, Wadsworth and colleagues (2018) demonstrated the validity of teleneuropsychological assessments for discriminating cognitively impaired from nonimpaired older adults. Moreover, telemental health has shown to be effective in the assessment and diagnosis of a range of disorders compared to in-person interventions in older adults (Hilty et al., 2013). Comparable results were also found when telehealth neurocognitive assessments were administered in Spanish in-person versus telehealth with older rural Latino adults (Vahia et al., 2015). Furthermore, while in-person interviews were often preferred, most individuals accepted telehealth assessments rather than having to travel for face-to-face assessments (Menon et al., 2001). As such, research has shown that patients, including those with dementia, report reduced distraction as a result of less interpersonal anxiety or distracting external cues with teleneuropsychological assessments compared with in-person test administration (Jacobsen, Sprenger, Andersson, & Krogstad, 2003; Kirkwood, Peck, & Bennie, 2000; Sävenstedt, Zingmark, Hydén, & Brulin, 2005). Telehealth-based assessment is feasible, acceptable to older adults, and appears to yield comparable results to in-person assessments.

Computerized assessment

Computerized assessment is a broad term that includes measurement via computer or tablet. Much of the research conducted thus far has centered around cognitive testing. Computerized assessment can be particularly beneficial for cognitive testing due to potential for greater recording accuracy and precision of timed tasks, easy scoring, and standardized administration without biases. As such, researchers have both developed and translated a number of assessments for cognitive impairment via computer or tablet. While the literature on computerized assessment of psychiatric conditions is limited, some suggest that this mode of assessment could facilitate discussion of issues that are less frequently disclosed to providers (e.g., alcohol use; Nemes et al., 2004).

Users of computer-based assessments report that this format is feasible. Older adults and individuals with cognitive impairment have rated computer assessments easy to use and understand (e.g., Fillit, Simon, Doniger, & Cummings, 2008).

When asked about their computerized assessment experience, older adults generally report that they believe test results reflect their abilities, though many note the concern that factors such as health condition and motor control affected their performance (Robillard, Lai, Wu, Feng, & Hayden, 2018). Thus, it is important to broadly consider potential factors that may affect performance. While older adults see value in the computerized assessments, they may prefer that these assessments are used as an adjunct to, rather than a replacement for, care from clinicians (Robillard et al., 2018).

Assessment via tablet may present different functions than those offered on the computer. While tablets may be used for initial screening, their portability may facilitate monitoring progress over time. Older adults tend to respond positively to tablet-based assessments. In one survey, older adult participants (age range 65−88) were asked to imagine they were in a research study on antidepressants and subsequently introduced to iPad versions of the NIH Toolbox Psychological Wellbeing measure and the NIH Toolbox Cognition and Motor batteries (Lenze et al., 2016). Eighty-five percent believed that assessment before and after treatment was important and participants found tablet-based assessments generally acceptable.

When tablet- and computer-based assessments have been adapted from paper-and-pencil tests, equivalence across tests cannot be assumed and some suggest that it is particularly important that instructions are explicit (Jenkins et al., 2016). Considering technological familiarity and comfort are also crucial. Some suggest training for older adults to ensure sufficient understanding prior to the assessment (see Wild, et al., 2008) and ensuring that the user interface is clear. In addition, user attitudes toward the device may affect motivation and, subsequently, performance (Jenkins et al., 2016).

Experience sampling method

Experience sampling method (ESM) (Csikszentmihalyi & Larson, 1987) or ecological momentary assessment (EMA) (Stone & Shiffman, 1994) is a data collection methodology that provides clinicians and researchers a better understanding of individuals' daily affective experiences and activities. Historically, ESM/EMA mental health investigations included a variety of paper-and-pencil formats, occasionally coupled with electronic beepers or alarms (i.e., episodic) to signal a required entry (e.g., Moskowitz & Young, 2006; Ong, Bergeman, & Bisconti, 2004). More recently, research and clinical intervention work has progressed to incorporate mobile devices and wearables that enable data to be tracked through both episodic and continuous monitoring approaches. Tools include: (1) smartphone applications that prompt users to enter data or respond to questions throughout the day; (2) smartphones equipped with continuous health-tracking software; and (3) activity and location-tracking devices, including commercial wearables (e.g., FitBit and Apple smartwatches). Incorporation of these tools may allow for improved precision during personalized treatment planning. ESM/EMA tools also may help providers better understand a patient's particular expression of symptoms prior to initiating, during, or at the end of treatment.

The most common contemporary tool is ESM/EMA-enabled mobile applications (apps) that episodically prompt users to answer questions. Some apps survey individuals throughout the day about specific behaviors, medication adherence, or mood states. ESM/EMA apps include prompting for qualitative, open-ended responses about an individual's experience in the moment (see Fritz, Tarraf, Saleh, & Cutchin, 2017; King et al., 2016; Moore, Depp, Wetherell, & Lenze, 2016; Ramsey, Wetherell, Depp, Dixon, & Lenze, 2016). In a Mindfulness-Based Stress Reduction (MBSR) study, ESM/EMA methods were found to significantly increase sensitivity to symptom change across treatment groups for both depression and mindfulness measures by 25%−50% relative to traditional written measures, translating into a larger effect size for the MBSR intervention (Moore et al., 2016). Thus, using ESM/EMA with older adults may be a more sensitive measurement of symptoms when compared with traditional written measures.

ESM/EMA-enabled apps on smartphones also may collect continuous behavioral data or health-related data. Both episodic and continuous health tracking allows healthcare providers to monitor changes in health symptoms to determine the need for, or alteration of, interventions. For example, Boulos et al. (2011) described an ESM/EMA system built for older adults with multiple chronic illnesses. This system included an app that collected, organized, and relayed emergent health and GPS information from users' health trackers. These data were then transmitted to a secure online database accessible only to the healthcare provider. The users were able to view a summary of their health data on the app's interface. Such momentary data collection may capture more accurate, externally valid information from older adults. This information is likely to be more accurate compared with traditional self-report measures completed in office that rely on older adults' retrospective memory.

It also is common to use multiple tools or tools' capabilities, resulting in a more diverse data set. In one study, Fritz and colleagues (2017) employed smartphones' GPS location-tracking system (continuous data), camera, and built-in

ESM/EMA application tool to survey daily stress and activity patterns (episodic data) of older, community-dwelling African Americans in Detroit. Through GPS signal and daily photos of stress-inducing locations around their community (photography data not yet published), the older adults provided physical details of their neighborhood context. The use of photographs combined with ESM/EMA stress ratings may be a more ecologically valid way of measuring stress when compared with the collection of stress ratings without contextual information. As such, photographs allow clinicians to better understand the aspects of a patient's everyday environment that may be sustaining negative symptomology present during an intervention check in or clinic visit.

Commercial activity trackers and wearables collect continuous data on activity, movement, physiological measurements, or other continuous measures. These wearables are often used in conjunction with other ESM/EMA measures collected via mobile apps. Commercial wearables allow older users to interact frequently with their daily health and exercise records, thus facilitating self-monitoring of health and actions. In addition to monitoring physical health, activity tracking and monitoring features can also play a significant role in mental health treatment plans. For example, Chum and colleagues (2017) found that wearables can provide beneficial feedback in terms of patients' chosen actions, routines, and goals set in the wake of depressive symptomology. Narrowing their population focus, Preusse, Mitzner, Fausset, and Rogers (2017) investigated the usability and acceptance of the FitBit One wearable in conjunction with the MyFitnessPal app with older users. Once comfortable with the technology, older users expressed enthusiasm about collecting and visualizing the variation of their health data over time. These findings highlight the potential for wearables to positively influence older adults' desire and intention to engage in healthy behaviors.

Other assessment modalities

Smart-home technology

Smart-home technology involves the use of unobtrusive sensor systems, such as motion, contact, door, temperature sensors, or power meters, to provide data on changes or activities in the home environment (Dawadi, Cook, Schmitter-Edgecombe, & Parsey, 2013). While ESM/EMA activity sensors such as the FitBit similarly collect activity and health data directly from the individual, smart-home technologies sense where the individual is within their home in addition to sensing movement. For example, researchers are exploring the use of smart-home technology to detect possible cognitive decline or to monitor individuals with cognitive impairment (e.g., Gaugler et al., 2019). One study used unobtrusive in-home monitoring to identify motion and activity indices that differentiate older adults with mild cognitive impairment from those without (Hayes et al., 2008). Using smart-home technology and machine learning algorithms, another study quantified the quality of the performance of daily activities (e.g., sweeping, cooking, and dressing) and used those indices to predict older adults' cognitive status (Dawadi et al., 2013). Gaugler and colleagues (2019) examined a remote activity monitoring system as a way of assisting caregivers in monitoring their care recipients with dementia. The system sent alerts to family caregivers if behaviors were detected that represent a change from usual functioning. The researchers found that the remote activity monitoring was beneficial in specific situations such as monitoring of wandering, falls, and behavior changes, but did not improve caregiving outcomes. More research is underway to optimize data quality and their predictive power on cognitive functioning and detection of adverse events in individuals with cognitive impairment.

Virtual reality

Virtual reality (VR) is a technology that allows users to immerse themselves in computer-generated simulation that creates dynamic and three-dimensional (3D) images (Rizzo et al., 2000). Several assessment tools utilizing VR technology have been developed to measure different domains of cognitive functioning, including attention, memory, executive functioning, and visuospatial skills, as well as activities of daily living, such as driving or cooking (Schultheis, Himelstein, & Rizzo, 2002). VR-based assessments have the advantage of achieving higher ecological validity, compared to traditional neuropsychological assessments, due to higher resemblance to real-life tasks and real-world settings (Parsons, 2011; Schultheis et al., 2002). As completing a functional activity (e.g., navigating a new environment) often requires the coordination of multiple domains of cognitive functioning, VR-based assessments offer the opportunity to assess for a person's ability to carry out certain activities holistically and directly, as opposed to indirectly estimating the person's ability from tests of different cognitive domains. VR-based assessments allow for both ecological validity and a consistent testing environment. Examiners can maintain control over the environment and the objective measures of data collection in VR-based assessments, increasing reliability in stimulus presentation and more accurate scoring. VR-based driving evaluation is an example of a measure with higher ecological validity compared with cognitive

assessments. Researchers found that the VR-based driving evaluation discriminated between individuals with and without head injuries and identified age differences in participants' performance (Liu, Miyazaki, & Watson, 1999). Additional research has further highlighted the potential of VR-based assessments to detect cognitive impairment (e.g., Kang et al., 2008; Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012; Weniger, Ruhleder, Lange, Wolf, & Irle, 2011) and differentiate between types of dementia (e.g., Tu et al., 2015). More research is needed to further establish validity, reliability, and feasibility for the use of VR-based assessments with older adults.

Interventions

Technology-delivered interventions, also called technology-assisted interventions or behavioral intervention technologies (BITs), range in the delivery mode and in the extent to which a provider is involved. Telephone therapy and telehealth deliver services from a provider to a patient over a distance. These methods are consumable, which means a provider delivers the interventions and thus their time is a finite resource that is consumed with each patient visit (Muñoz, 2010). Automated or guided technology-delivered interventions that convey psychoeducation or therapeutic skills (e.g., audio-guided exercises) without a provider are deemed nonconsumable. Nonconsumable technology-delivered interventions have the potential to improve the reach of interventions and to address the geriatric mental health workforce shortage (Institute of Medicine, 2012; Lenze, 2015).

While automated interventions may use few provider resources, users desire assistance with the technical aspects of the interventions, questions about intervention content, and support/encouragement to follow-through with the intervention (Schueller, Tomasino, & Mohr, 2017). Models such as the Efficiency Model of Support (Schueller et al., 2017) suggest that support can be delivered via multiple communication modalities (i.e., text messages, emails, phone calls) and varied dosages (i.e., quantity, timing). The exact type and intensity of support that would benefit older users of BITs in the most efficient manner is unknown. However, we expect that because older adults are slower to adopt technologies compared with younger age groups (Pew Research Center, 2017), older users would have less experience with technology and would need more intensive and personalized support compared with the general adult population.

Telephone therapy

Telephone therapy involves delivering interventions by phone. Most studies examining telephone therapy for mental health utilize cognitive behavioral therapy (CBT) or other manualized treatments. Providers mail readings, worksheets, and handouts to supplement the telephone calls. Telephone therapy for older adults has been tested in investigations of anxiety (i.e., Brenes, Danhauer, Lyles, Hogan, & Miller, 2015) and depression (e.g., Barrera et al., 2017; Mohr et al., 2012). Brenes et al. (2015) compared telephone-delivered CBT (CBT-T) with supportive therapy for generalized anxiety disorder in adults aged 60 years and older in rural North Carolina. CBT-T was superior to supportive therapy in reducing worry severity and general anxiety symptoms. The CBT-T also was well liked by older adults. The advantage of CBT-T over supportive therapy persisted at the one-year follow-up (Brenes, Danhauer, Lyles, Anderson, & Miller, 2017). When compared with face-to-face CBT, CBT-T demonstrated equivalent efficacy (Mohr et al., 2012). A smaller study demonstrated the acceptability of telephone therapy [i.e., problem-solving therapy (PST)] for older, home-based veterans (Barrera et al., 2017). Finally, CBT-T attrition rates were found to be lower relative to face-to-face CBT in primary care patients (Mohr et al., 2012). An extension of telephone therapy is video-delivered therapy via a videophone, a telephone equipped with video display. In one study, the videophone was used in a caregiver intervention group for monthly education and skills training sessions for the caregivers, video lectures about Alzheimer's disease, support groups, and other resources (Czaja, Loewenstein, Schulz, Nair, & Perdomo, 2013). The majority of participants found the technology to be both valuable and easy to use. Videophones are not widely available, but the acceptability of this intervention suggests that telehealth in the home or internet-delivered interventions could help caregivers. In summary, findings suggest that telephone therapy using evidence-based treatments like CBT is efficacious and feasible. The implications are that telephone coaching or therapeutic contacts using evidence-based skills may be useful in complementing other technology-delivered interventions.

Telemental health interventions

In telemental health, mental health services are provided to a patient using videoconferencing. Telemental health is particularly beneficial for individuals who face access-to-care barriers such as being homebound or residing in rural areas with fewer mental health providers. Research has shown that telemental health is associated with high satisfaction and

acceptance across a variety of clinical populations for a broad range of services (Backhaus et al., 2012; Richardson et al., 2009). In general, older adults have comparable levels of satisfaction with telehealth modalities and face-to-face delivery of psychotherapy treatments (Egede et al., 2015; Jenkins-Guarnieri, Pruitt, Luxton, & Johnson, 2015).

Evidence-based interventions delivered via telehealth have comparable treatment outcomes to face-to-face interventions in older adults. For example, CBT for insomnia delivered via telehealth to older adults reduced insomnia and depressive symptoms in a nonrandomized prepost study (Lichstein et al., 2013). In a randomized trial comparing PST delivered in-person, PST delivered via telehealth (tele-PST) and telephone calls in homebound older adults, both in-person and tele-PST, resulted in significant reductions in depression and disability (Choi et al., 2014). Interestingly, the effects of the tele-PST intervention outlasted those of the in-person PST intervention when examined at 6-month follow-up assessments. Telemedicine-delivered evidenced-based psychotherapy for older veterans with major depression was equivalent to in-person treatment in reducing symptoms on both the Geriatric Depression Scale and the Beck Depression Inventory in a noninferiority trial (Egede et al., 2015). Telehealth interventions are a viable method of delivering evidence-based interventions to older adults.

Internet-based interventions

Internet-based interventions are generally well-established interventions (e.g., CBT) that are delivered via the Internet using modules to convey the intervention components rather than therapy delivered from a live therapist with two-way communication (e.g., telehealth). In internet-based interventions, users interact with, or respond to, preloaded content, which may include videos, readings, quizzes, assessments, and symptom tracking. Some interventions are entirely self-guided, while others include some level of person support, such as a therapist or provider.

Some advantages exist for internet interventions compared with interventions delivered by a provider, such as internet interventions requiring significantly less provider time (e.g., Zou et al., 2012). Internet-based interventions can increase access to mental health services and treatments (Dear et al., 2015) by addressing challenges related to individuals who tend to not seek healthcare services (Cockayne et al., 2011). Internet interventions may be preferred because of their anonymity and privacy, convenience, and lack of in-person contact (Ruggiero et al., 2006). Even older adults with cognitive impairment (i.e., mild to moderate dementia) were able to utilize simple digital devices to improve their mood and memory, as well as increase activities of daily living (van der Wardt, Bandelow, & Hogervorst, 2010).

Studies of internet interventions have shown sustainable and comparable benefits as traditional face-to-face treatments for reducing mental health symptoms including depression, anxiety, posttraumatic stress disorder (PTSD), and eating disorders in the general adult population (e.g., Andrews, Cuijpers, Craske, McEvoy, & Titov, 2010; Griffiths & Christensen, 2006). Specifically, online-guided life review interventions have shown sustainable benefits up to 12 months (Lamers, Bohlmeijer, Korte, & Westerhof, 2014).

Internet-based cognitive behavioral therapy

Internet-delivered CBT (iCBT) treatments (e.g., MoodGYM and BluePages) account for the majority of internet-based interventions. iCBT interventions range from being entirely self-administered to having limited therapist support provided via email and/or telephone. Self-guided iCBT interventions include automated components, such as emails, to increase treatment completion rate and encourage adherence to the self-guided interventions. Support provided in guided iCBT interventions includes email communication, text messaging, telephone calls, and videoconferencing with a therapist or peer support person.

Automated iCBT interventions have been tested in older adults and have been found to reduce symptoms of depression (e.g., Glozier et al., 2013; Spek et al., 2007). In one RCT, the iCBT condition yielded reductions in depressive symptoms in older adults when compared to a waitlist control group and in-person group-based CBT, but iCBT also had substantial attrition (Spek et al., 2007). Assessment conducted at a one-year follow-up demonstrated that the effects of iCBT were sustained and did not differ from the group-based CBT at one year. Another example of an automated intervention is e-couch, which provides psychoeducation about depression, risk factors, and effective treatments for individuals with depression and cardiovascular disease (Cockayne et al., 2011). E-couch uses CBT, interpersonal therapy, and relaxation techniques to address mental health difficulties including mild to moderate depression. In an RCT comparing e-couch with a health information condition, the e-couch intervention yielded larger declines in depressive symptoms, though the overall effect was small (Glozier et al., 2013). Automated iCBT shows some promise, but older adults may benefit from guidance in the context of iCBT interventions.

Guided iCBT interventions were also effective in reducing depression and anxiety symptoms in older adult samples. One study found that iCBT compared with a waitlist control reduced depression and anxiety at 3-month and 12-month follow-ups (Titov et al., 2015). Completion of the iCBT intervention was high with 85% of those randomized completing the intervention. Additionally, slight improvements in quality-adjusted life years (i.e., a standardized and commonly used measure of health-related quality of life) were observed following iCBT treatment. Titov et al. (2016) demonstrated that both guided and unguided iCBT reduced symptoms of anxiety and depression for older adults in an RCT comparing the two interventions. No differences in symptom reductions or participant satisfaction with the two interventions were observed. Another research group compared iCBT with coaching support, iCBT with online peer support, and a waitlist condition in a three-arm RCT with depressed older adults (Tomasino et al., 2017). Both iCBT with coaching and iCBT with peer support were superior to the waitlist condition in reducing depressive symptoms, which suggests that an online social network may be equivalent to coaching support (Tomasino et al., 2017). Older adults benefit from both automated and guided iCBT, but findings suggest that guided iCBT may have some advantages in terms of higher adherence rates compared with automated iCBT.

Other internet-based interventions

Life review therapy, an evidence-based treatment for depression (Butler, 1963; Westerhof & Bohlmeijer, 2014), has been adapted into an online-guided delivery format (Westerhof, Lamers, Postel, & Bohlmeijer, 2019). In life review therapy, older adults reflect on both negative and positive experiences to resolve past conflicts and gain acceptance of experiences. Westerhof and colleagues compared online life review therapy with counseling, online life review therapy with peer support, and a waitlist control in a pilot RCT. Findings demonstrated that the online versions were acceptable to middle-aged and older adults, but did not differ from the waitlist group in reducing depressive symptoms as reductions were noted in all groups. Another internet intervention, Integrative Testimonial Therapy (Integrative TT), targets PTSD symptoms in older adults with early life trauma (Knaevelsrud, Böttche, Pietrzak, Freyberger, & Kuwert, 2017). This intervention employs CBT and life review techniques alongside structured writing assignments and therapist facilitation to target PTSD symptoms. Integrative TT reduced PTSD symptoms in older adults relative to a waitlist control group. These additional studies suggest that older adults benefit from life review therapies adapted for internet-delivery in addition to iCBT. Further research is needed to examine the role of supportive training, experience of use, and computer skills as related to internet interventions in older adults (Czaja et al., 2012).

Interactive voice response and text message support

Interactive voice response (IVR) services allow users to call a phone number and interact with an automated system by entering numbers or using voice responses to the system's prompts regarding questions about self-management of mental health and health symptoms. Plain-text short message service (SMS) allows individuals to send and receive short messages on cellular devices (Sanner, Roland, & Braa, 2012). However, there is currently limited research on older adult use of IVR or SMS, particularly for mental health intervention. Aikens, Trivedi, Heapy, Pfeiffer, and Piette (2015) investigated the use of weekly IVR calls with depressed primary care patients (mean age = 50) at risk of nonadherence to antidepressant medications. Older adults who identified a support person at home to receive information about managing depression were more likely to improve their medication adherence and have reduced depressive symptoms. This finding highlights the potential cumulative effect of technology and social support in improving mental health outcomes. Another study demonstrated that the SMS function as part of a smartphone app effectively complements a peer support-delivered intervention (see mobile app interventions) to reinforce self-management training for older adults with serious mental illness (Fortuna et al., 2018). Overall, these findings suggest positive impact of using automated messaging such as IVR or SMS. Most uses of IVR and SMS focus on medication adherence or other concrete self-management behaviors, which in turn may contribute to older adults' mental health and wellbeing.

Mobile app interventions

Mental health mobile apps pervade mobile app marketplaces, yet the research lags behind the availability of apps (Bakker, Kazantzis, Rickwood, & Rickard, 2016). Moreover, of the extant research on mobile apps, older adults represent a minority of the participants included (if included at all). In a review focused on older users, Moussa and colleagues (2017) identified only seven articles that investigated mobile apps in older adults with mental health or cognitive problems. All seven articles focused on mobile app–based assessment and none examined mobile app–based interventions. The limited research on mobile app mental health interventions with older adults focuses on either theoretical

reviews (e.g., Kuerbis, Mulliken, Muench, Moore, & Gardner, 2017) or small-scale investigations of the acceptance, feasibility, and usability of mobile health (mHealth) interventions with older adults.

In a theoretical review, Kuerbis et al. (2017) described features that should be included in a mobile app intervention for older users based on a literature review. Some features encompass the intervention itself in terms of ease in design, purpose of the intervention. Other features include the need for training and support using manuals, providers, and technology assistance. Design-specific issues included the ability to recover from errors in an interface, use of universal design feature to account for physical and cognitive changes with aging, and inclusion of feedback notifications to users to let them know information has been submitted or tasks have been completed. The authors emphasized the importance of user-centered and universal design strategies to maximize usability of the interventions by all individuals. Their other recommendations include teaching older adults about the technology and the purpose of the intervention. Other issues such as access to the technology, ability to recover from errors within the interface, feedback provided within the intervention, and the presence of a clear purpose were recommended in the development and dissemination of mHealth interventions. Overall, these recommendations are consistent with general recommendations for using technology with older individuals or with novice users (e.g., Fisk et al., 2009).

Very few studies have described the development of mobile apps targeting mental health in older adults. In one such study, researchers developed and integrated a mobile app into an evidence-based psychosocial intervention (Integrated Illness Management and Recovery), traditionally delivered by peers, that helps middle-aged and older adults with serious mental illness and chronic health conditions (Fortuna, Lohman, Gill, Bruce, & Bartels, 2017). Fortuna and colleagues described a user-centered design approach to create their intervention (PeerTECH), including the development of 10 video modules to promote self-management of psychiatric conditions, medical problems as well as promoting empowerment and wellbeing. Other features within the app include HIPAA-compliant messaging to facilitate support with peer coaches. The authors employed user-centered design to create their intervention (PeerTECH) and then tested it with 10 users. Fortuna et al. (2018) investigated the feasibility and acceptability of the PeerTECH intervention in 10 older adults with serious mental illness and a chronic medical condition(s). Findings from the pilot study demonstrated that PeerTECH was successfully delivered using peers plus the technology support. A total of 8 of the 10 participants engaged in 10 or more sessions of the intervention. Additionally, the intervention resulted in improvements in self-management. Although these data are preliminary, they demonstrate the strength of user-centered design and the promise for using a mobile app–based intervention alongside peer support to improve self-management among individuals' serious mental illness.

Other studies of mobile app–based interventions have used existing apps and investigated the apps with older adult samples (Similä et al., 2018) or mixed-age samples (e.g., Areán et al., 2016). In one study that focused on older adults, Similä and colleagues examined Oiva, an app that teaches wellness using acceptance and commitment therapy techniques. The investigators studied this app in a small pilot study with older adults and caregivers in Finland. Findings included the identification of barriers to use related to the devices used in the study (i.e., small screen size) and the Oiva app itself (i.e., unable to increase font size). The older adults' experience and attitudes about technology were deemed to influence the acceptability of the app as well. Despite some positive feedback about the app, the substantial attrition makes it difficult to draw conclusions from this small study. Researchers examined the use of a mobile app (Win-Win aSleep) that supports individuals receiving CBT for insomnia (CBT-I) in a case study with an older adult (Chen, Hung, & Chen, 2016). Although the older adult experienced improvements in sleep including discontinuing of a hypnotic medication, the older adult encountered difficulties with the app interface (i.e., perceptual difficulties). Using a tablet helped the older adult overcome perceptual difficulties encountered when using a smaller device, but tablet use resulted in some technical difficulties with the intervention (i.e., one module did not function well on the tablet). With the growing adoption of smartphones by older adults, it follows that the research on mobile app–based interventions should encompass older users to encourage evaluation among users with varying levels of technology experience and perceptual/sensory abilities.

A review of clinicaltrials.gov reveals a number of ongoing trials of mobile health interventions with older adults with mental health conditions (e.g., depression). Future publication of findings from these ongoing studies will increase our understanding of the efficacy and effectiveness of mobile health interventions in older adults. Research on mobile app–based interventions for health behaviors in older adults is a rapidly growing field that can inform late-life mental health research as well. In one study, King and colleagues (2016) found that sedentary middle-age and older adults benefited from a mobile app–based intervention combined with EMA assessment of movement. The researchers designed the app to be simple and usable by older adults and mobile device novices. The research team compared three different types of motivational framing within the apps and found that the app that used virtual social support and social influences was the most efficacious of the apps tested in reducing sedentary behavior. The app used online message

boards, virtual teams, and competitions to foster social support related to reducing sedentary behavior. This finding mirrors similar findings in the internet interventions section, which demonstrated the benefit of guidance delivered by a provider/coach or by online social support (e.g., Tomasino et al., 2017).

Summary

Technology offers opportunities to improve scalability and expand access to psychological assessment and interventions to older adults. Technology-delivered assessment and interventions have been demonstrated to be feasible, acceptable, and effective, in some cases with greater accuracy and fidelity than those administered by a human. However, there are a number of considerations to keep in mind. First, access to computer and mobile technology and high-speed internet is limited by availability and cost. Older adults with low incomes and those living in rural areas experience significant barriers to connectivity and computer/mobile-based technology. Other approaches, such as using interventions delivered via DVD videos (Gould et al., 2019) or telephone therapy, may help these individuals access treatment. Second, age-related and individual factors that influence technology include perceptions of technology, abilities, experience with technology, and cognitive, perceptual, tactile, and mobility abilities. Third, many older adults benefit from instruction and coaching to help get the most out of computer/mobile-based technology. Fourth, many self-guided programs benefit from some type of augmentation or adjunct support to improve program retention and adherence. Finally, most computer/mobile technology design has not focused on older adults. As we know, older adults must find technology to be relevant and feasible to ensure uptake, therefore, to be most useful, older adults must be involved in user-centered design.

Acknowledgments

This work was supported by a Career Development Award (IK2 RX001478; PI: Gould) from the US Department of Veterans Affairs Rehabilitation Research and Development Service. Views expressed in this article are those of the authors and not necessarily those of the Department of Veterans Affairs or the Federal Government.

References

Aikens, J. E., Trivedi, R., Heapy, A., Pfeiffer, P. N., & Piette, J. D. (2015). Potential impact of incorporating a patient-selected support person into mHealth for depression. *Society of General Internal Medicine*, *30*, 797–803. Available from https://doi.org/10.1007/s11606-015-3208-7.

Andrews, G., Cuijpers, P., Craske, M. G., McEvoy, P., & Titov, N. (2010). Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: A meta-analysis. *PLoS One*, *5*, e13196.

Areán, P. A., Hallgren, K. A., Jordan, J. T., Gazzaley, A., Atkins, D. C., Heagerty, P. J., & Anguera, J. A. (2016). The use and effectiveness of mobile apps for depression: Results from a fully remote clinical trial. *Journal of Medical Internet Research*, *18*(12), e330. Available from https://doi.org/10.2196/jmir.6482.

Backhaus, A., Agha, Z., Maglione, M. L., Repp, A., Ross, B., Zuest, D., … Thorp, S. R. (2012). Videoconferencing psychotherapy: A systematic review. *Psychological Services*, *9*(2), 111–131.

Bakker, D., Kazantzis, N., Rickwood, D., & Rickard, N. (2016). Mental health smartphone apps: Review and evidence-based recommendations for future developments. *JMIR Mental Health*, *3*, e7. Available from https://doi.org/10.2196/mental.4984.

Barrera, T. L., Cummings, J. P., Armento, M., Cully, J. A., Bush Amspoker, A., Wilson, N. L., … Stanley, M. A. (2017). Telephone-delivered cognitive-behavioral therapy for older, rural veterans with depression and anxiety in home-based primary care. *Clinical Gerontologist*, *40*(2), 114–123.

Bashshur, R. L., Shannon, G. W., Bashshur, N., & Yellowlees, P. M. (2016). The empirical evidence for telemedicine interventions in mental disorders. *Telemedicine and e-Health*, *22*(2), 87–113. Available from https://doi.org/10.1089/tmj.2015.0206.

Boulos, M. N. K., Wheeler, S., Tavares, C., & Jones, R. (2011). How smartphones are changing the face of mobile and participatory healthcare: an overview, with example from eCAALYX. *BioMed Eng OnLine*, *10*(24). Available from https://doi.org/10.1186/1475-925X-10-24.

Brearly, T. W., Shura, R. D., Martindale, S. L., Lazowski, R. A., Luxton, D. D., Shenal, B. V., & Rowland, J. A. (2017). Neuropsychological test administration by videoconference: A systematic review and meta-analysis. *Neuropsychology Review*, *27*(2), 174–186. Available from https://doi.org/10.1007/s11065-017-9349-1.

Brenes, G. A., Danhauer, S. C., Lyles, M. F., Anderson, A., & Miller, M. E. (2017). Long-term effects of telephone-delivered psychotherapy for late-life GAD. *American Journal of Geriatric Psychiatry*, *25*, 1249–1257. Available from https://doi.org/10.1016/j.jagp.2017.05.013.

Brenes, G. A., Danhauer, S. C., Lyles, M. F., Hogan, P. E., & Miller, M. (2015). Telephone-delivered cognitive behavioral therapy and telephone-delivered nondirective supportive therapy for rural older adults with generalized anxiety disorder: A randomized clinical trial. *JAMA Psychiatry*, *72*, 1012–1020.

Butler, R. N. (1963). The life-review: An interpretation of reminiscence in the aged. *Psychiatry*, *26*(1), 65–76.

Chan, M. Y., Haber, S., Drew, L. M., & Park, D. C. (2016). Training older adults to use tablet computers: Does it enhance cognitive function? *The Gerontologist*, *56*, 475–484. Available from https://doi.org/10.1093/geront/gnu057.

Charness, N., & Boot, W. R. (2009). Aging and information technology use: Potential and barriers. *Current Directions in Psychological Science*, *18*(5), 253–258.

Chen, Y., Hung, Y., & Chen, H. (2016). Mobile application-assisted cognitive behavioral therapy for insomnia in an older adult. *Telemedicine and e-Health*, *22*(4), 332–334.

Choi, N. G., Marti, C. N., Bruce, M. L., Hegel, M. T., Wilson, N. L., & Kunik, M. E. (2014). Six-month postintervention depression and disability outcomes of in-home telehealth problem-solving therapy for depressed, low-income homebound older adults. *Depression and Anxiety*, *31*(8), 653–661.

Chum, J., Kim, M. S., Zielinski, L., Bhatt, M., Chung, D., Yeung, S., … O'neill, L. (2017). Acceptability of the Fitbit in behavioural activation therapy for depression: A qualitative study. *Evidence-based Mental Health*, *20*(4), 128–133.

Cockayne, N. L., Glozier, N., Naismith, S. L., Christensen, H., Neal, B., & Hickie, I. B. (2011). Internet-based treatment for older adults with depression and co-morbid cardiovascular disease: Protocol for a randomised, double-blind, placebo controlled trial. *BMC Psychiatry*, *11*(1), 10.

Crabb, R. M., Cavanagh, K., Proudfoot, J., Learmonth, D., Rafie, S., & Weingardt, K. R. (2012). Is computerized cognitive-behavioural therapy a treatment option for depression in late-life? A systematic review. *British Journal of Clinical Psychology*, *51*(4), 459–464.

Csikszentmihalyi, M., & Larson, R. (1987). Validity and reliability of the experience-sampling method. *Journal of Nervous & Mental Disease*, *175*, 526–537.

Cullum, C. M., Hynan, L. S., Grosch, M., Parikh, M., & Weiner, M. F. (2014). Teleneuropsychology: Evidence for video teleconference-based neuropsychological assessment. *Journal of the International Neuropsychological Society*, *20*(10), 1–6. Available from https://doi.org/10.1017/S1355617714000872.

Cullum, C. M., Weiner, M. F., Gehrmann, H. R., & Hynan, L. S. (2006). Feasibility of telecognitive assessment in dementia. *Assessment*, *13*(4), 385–390.

Czaja, S. J. (2016). Long-term care services and support systems for older adults: The role of technology. *American Psychologist*, *71*(4), 294–301. Available from https://doi.org/10.1047/a0040258.

Czaja, S. J., Boot, W. R., Charness, N., Rogers, W. A., & Sharit, J. (2017). Improving social support for older adults through technology: Findings from the PRISM randomized controlled trial. *The Gerontologist*, *58*(3), 467–477.

Czaja, S. J., Loewenstein, D., Schulz, R., Nair, S. N., & Perdomo, D. (2013). A videophone psychosocial intervention for dementia caregivers. *American Journal of Geriatric Psychiatry*, *21*, 1071–1081.

Czaja, S. J., Sharit, J., Lee, C. C., Nair, S. N., Hernández, M. A., Arana, N., & Fu, S. H. (2012). Factors influencing use of an e-health website in a community sample of older adults. *Journal of the American Medical Informatics Association*, *20*(2), 277–284. Available from https://doi.org/10.1136/amiajnl-2012-000876.

Davis, F.D. (1985). *A technology acceptance model for empirically testing new end-user information systems: Theory and results* (Doctoral dissertation, Massachusetts Institute of Technology).

Dawadi, P. N., Cook, D. J., Schmitter-Edgecombe, M., & Parsey, C. (2013). Automated assessment of cognitive health using smart home technologies. *Technology and Health Care*, *21*(4), 323–343.

Dear, B. F., Zou, J. B., Ali, S., Lorian, C. N., Johnston, L., Sheehan, J., … Titov, N. (2015). Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety: A randomized controlled trial. *Behavior Therapy*, *46*(2), 206–217.

Egede, L. E., Acierno, R., Knapp, R. G., Lejuez, C., Hernandez-Tejada, M., Payne, E. H., & Frueh, B. C. (2015). Psychotherapy for depression in older veterans via telemedicine: A randomised, open-label, non-inferiority trial. *The Lancet Psychiatry*, *2*(8), 693–701. Available from https://doi.org/10.1016/S2215-0366(15)00122-4.

Ewing, S., Thomas, J., & Schiessl, J. (2012). *CCi Digital Futures 2012: The internet in Australia*. Melbourne: ARC Centre of Excellence for Creative Industries and Innovation, Swinburne University of Technology.

Fillit, H., Simon, E. S., Doniger, G. M., & Cummings, J. L. (2008). Practicality of a computerized system for cognitive assessment in the elderly. *Alzheimer's and Dementia*, *4*(1), 14–21.

Fisk, A. D., Rogers, W. A., Charness, N., Czaja, S. J., & Sharit, J. (2009). *Designing for older adults: Principles and creative human factors approaches*. Boca Raton, FL: CRC Press.

Fortuna, K. L., DiMilia, P. R., Lohman, M. C., Bruce, M. L., Zubritsky, C. D., Halaby, M. R., … Bartels, S. J. (2018). Feasibility, acceptability, and preliminary effectiveness of a peer-delivered and technology supported self-management intervention for older adults with serious mental illness. *Psychiatric Quarterly*, *89*(2), 293–305.

Fortuna,, K. L., Lohman, M. C., Gill, L. E., Bruce, M. L., & Bartels, S. J. (2017). Adapting a psychosocial intervention for smartphone delivery to middle-aged and older adults with serious mental illness. *American Journal of Geriatric Psychiatry*, *25*(8), 819–828. Available from https://doi.org/10.1016/j.jagp.2016.12.007.

Fritz, H., Tarraf, W., Saleh, D. J., & Cutchin, M. P. (2017). Using a smartphone-based ecological momentary assessment protocol with community dwelling older African Americans. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *72*(5), 876–887.

Gaugler, J. E., Zmora, R., Mitchell, L. L., Finlay, J. M., Peterson, C. M., McCarron, H., & Jutkowitz, E. (2019). Six-month effectiveness of remote activity monitoring for persons living with dementia and their family caregivers: An experimental mixed methods study. *The Gerontologist*, *59*(1), 78–89.

Glozier, N., Christensen, H., Naismith, S., Cockayne, N., Donkin, L., Neal, B., … Hickie, I. (2013). Internet-delivered cognitive behavioural therapy for adults with mild to moderate depression and high cardiovascular disease risks: A randomized attention-controlled trial. *PLoS One*, *8*(3), e59139.

Gould, C. E., Kok, B. C., Ma, V. K., Wetherell, J. L., Sudheimer, K., & Beaudreau, S. A. (2019). Video-delivered relaxation intervention reduces late-life anxiety: A pilot randomized controlled trial. *The American Journal of Geriatric Psychiatry*, *27*, 514−525. Available from https://doi.org/10.1016/j.jagp.2018.

Griffiths, K. M., & Christensen, H. (2006). Review of randomised controlled trials of internet interventions for mental disorders and related conditions. *Clinical Psychologist*, *10*(1), 16−29.

Hayes, T. L., Abendroth, F., Adami, A., Pavel, M., Zitzelberger, T. A., & Kaye, J. A. (2008). Unobtrusive assessment of activity patterns associated with mild cognitive impairment. *Alzheimer's & Dementia*, *4*(6), 395−405.

Hilty, D. M., Ferrer, D. C., Parish, M. B., Johnston, B., Callahan, E. J., & Yellowlees, P. M. (2013). The effectiveness of telemental health: A 2013 review. *Telemedicine and e-Health*, *19*(6), 444−454.

Institute of Medicine (IOM). (2012). The mental health and substance use workforce for older adults: In whose hands*?* Washington, DC: National Academies Press.

Jacobsen, S. E., Sprenger, T., Andersson, S., & Krogstad, J. M. (2003). Neuropsychological assessment and telemedicine: A preliminary study examining the reliability of neuropsychology services performed via telecommunication. *Journal of the International Neuropsychological Society*, *9*(3), 472−478. Available from https://doi.org/10.1017/S1355617703930128.

Jenkins, A., Lindsay, S., Eslambolchilar, P., Thornton, I. M., & Talkes, A. (2016). Administering cognitive tests through tech screen tablet devices: Potential issues. *Journal of Alzheimer's Disease*, *54*(3), 1169−1182.

Jenkins-Guarnieri, M. A., Pruitt, L. D., Luxton, D. D., & Johnson, K. (2015). Patient perceptions of telemental health: Systematic review of direct comparisons to in-person psychotherapeutic treatments. *Telemedicine and e-Health*, *21*(8), 652−660.

Kang, Y. J., Ku, J., Han, K., Kim, S. I., Yu, T. W., Lee, J. H., & Park, C. I. (2008). Development and clinical trial of virtual reality-based cognitive assessment in people with stroke: Preliminary study. *CyberPsychology & Behavior*, *11*(3), 329−339.

King, A. C., Hekler, E. B., Grieco, L. A., Winter, S. J., Sheats, J. L., Buman, M. P., … Cirimele, J. (2016). Effects of three motivationally targeted mobile device applications on initial physical activity and sedentary behavior change in midlife and older adults: A randomized trial. *PLoS One*, *11*(6), e0156370.

King, D. B., Sixsmith, A., Yaghoubi-Shahir, H., Sadeghi, M., Razmara, M., & O'Rourke, N. (2016). An ecological momentary sampling tool for movement patterns and psychiatric symptom variability: A pilot study. *Gerontechnology*, *14*(2), 105−109.

Kirkwood, K. T., Peck, D. F., & Bennie, L. (2000). The consistency of neuropsychological assessments performed via telecommunication and face to face. *Journal of Telemedicine and Telecare*, *6*(3), 147−151.

Knaevelsrud, C., Böttche, M., Pietrzak, R. H., Freyberger, H. J., & Kuwert, P. (2017). Efficacy and feasibility of a therapist-guided internet-based intervention for older persons with childhood traumatization: A randomized controlled trial. *American Journal of Geriatric Psychiatry*, *25*(8), 878−888.

Kuerbis, A., Mulliken, A., Muench, F., Moore, A., & Gardner, D. (2017). Older adults and mobile technology: Factors that enhance and inhibit utilization in the context of behavioral health. *Mental Health and Addiction Research*, *2*, 1−11. Available from https://doi.org/10.15761/MHAR.1000136.

Lamers, S. M., Bohlmeijer, E. T., Korte, J., & Westerhof, G. J. (2014). The efficacy of life-review as online-guided self-help for adults: A randomized trial. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *70*(1), 24−34.

Lee, C. C., Czaja, S. J., Moxley, J. H., Sharit, J., Boot, W. R., Charness, N., & Rogers, W. A. (2019). Attitudes toward computers across adulthood from 1994 to 2013. *The Gerontologist*, *59*(1), 22−33.

Lee, J. H., Kim, J. H., Jhoo, J. H., Lee, K. U., Kim, K. W., Lee, D. Y., & Woo, J. I. (2000). A telemedicine system as a care modality for dementia patients in Korea. *Alzheimer Disease & Associated Disorders*, *14*(2), 94−101.

Lenze, E. J. (2015). Solving the geriatric mental health crisis in the 21st century. *JAMA Psychiatry*, *72*(10), 967−968.

Lenze, E. J., Ramsey, A., Brown, P. J., Reynolds, C. F., Mulsant, B. H., Lavretsky, H., & Roose, S. P. (2016). Older adults' perspectives on clinical research: A focus group and survey study. *American Journal of Geriatric Psychiatry*, *24*(10), 893−902.

Lichstein, K. L., Scogin, F., Thomas, S. J., DiNapoli, E. A., Dillon, H. R., & McFadden, A. (2013). Telehealth cognitive behavior therapy for co-occurring insomnia and depression symptoms in older adults. *Journal of Clinical Psychology*, *69*(10), 1056−1065.

Liu, L., Miyazaki, M., & Watson, B. (1999). Norms and validity of the DriVR: A virtual reality driving assessment for persons with head injuries. *Cyberpsychology & Behavior*, *2*(1), 53−67.

Loh, P. K., Maher, S., Goldswain, P., Flicker, L., Ramesh, P., & Saligari, J. (2005). Diagnostic accuracy of telehealth community dementia assessments. *Journal of the American Geriatrics Society*, *53*(11), 2043−2044.

Martin-Khan, M., Flicker, L., Wootton, R., Loh, P. K., Edwards, H., Varghese, P., … Gray, L. C. (2012). The diagnostic accuracy of telegeriatrics for the diagnosis of dementia via video conferencing. *Journal of the American Medical Directors Association*, *13*(5), 487−e19.

Menon, A. S., Kondapavalru, P., Krishna, P., Chrismer, J. B., Raskin, A., Hebel, J. R., & Ruskin, P. E. (2001). Evaluation of a portable low cost videophone system in the assessment of depressive symptoms and cognitive function in elderly medically ill veterans. *The Journal of Nervous and Mental Disease*, *189*(6), 399−401.

Mohr, D. C., Ho, J., Duffecy, J., Reifler, D., Sokol, L., Burns, M. N., … Siddique, J. (2012). Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: A randomized trial. *Journal of the American Medical Association*, *307*(21), 2278−2285.

Moore, R. C., Depp, C. A., Wetherell, J. L., & Lenze, E. J. (2016). Ecological momentary assessment versus standard assessment instruments for measuring mindfulness, depressed mood, and anxiety among older adults. *Journal of Psychiatric Research*, *75*, 116–123.

Moskowitz, D. S., & Young, S. N. (2006). Ecological momentary assessment: What it is and why it is a method of the future in clinical psychopharmacology. *Journal of Psychiatry and Neuroscience*, *31*(1), 13.

Moussa, Y., Mahdanian, A. A., Yu, C., Segal, M., Looper, K. J., Vahia, I. V., & Rej, S. (2017). Mobile health technology in late-life mental illness: A focused literature review. *The American Journal of Geriatric Psychiatry*, *25*(8), 865–872.

Muñoz, R. F. (2010). Using evidence-based internet interventions to reduce health disparities worldwide. *Journal of Medical Internet Research*, *12*(5), e60.

Mynatt, E. D., & Rogers, W. A. (2001). Developing technology to support the functional independence of older adults. *Ageing International*, *27*(1), 24–41.

Nemes, S., Rao, P. A., Zeiler, C., Munly, K., Holtz, K. D., & Hoffman, J. (2004). Computerized screening of substance abuse problems in a primary care setting: Older vs younger adults. *The American Journal of Drug and Alcohol Abuse*, *30*(3), 627–642.

Ong, A. D., Bergeman, C. S., & Bisconti, T. L. (2004). The role of daily positive emotions during bereavement. *Journal of Gerontology: Psychological Sciences.*, *59B*, 168–176.

Pak, R., & McLaughlin, A. (2011). *Designing displays for older adults*. Boca Raton, FL: CRC Press.

Parsons, T. D. (2011). *Neuropsychological assessment using virtual environments: Enhanced assessment technology for improved ecological validity*. *Advanced computational intelligence paradigms in healthcare 6. Virtual reality in psychotherapy, rehabilitation, and assessment* (pp. 271–289). Berlin, Heidelberg: Springer.

Pepin, R., Segal, D. L., & Coolidge, F. L. (2009). Intrinsic and extrinsic barriers to mental health care among community-dwelling younger and older adults. *Aging & Mental Health*, *13*(5), 769–777.

Perle, J. G., Langsam, L. C., & Nierenberg, B. (2011). Controversy clarified: An updated review of clinical psychology and tele-health. *Clinical Psychology Review*, *31*(8), 1247–1258.

Pew Research Center (2017). *Tech adoption climbs among older adults*. <http://www.pewinternet.org/wp-content/uploads/sites/9/2017/05/PI_2017.05.17_Older-Americans-Tech_FINAL.pdf> (Accessed 5.10.18)

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., & Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: Influence of active and passive encoding. *Neuropsychologia*, *50*(5), 592–602.

Preusse, K. C., Mitzner, T. L., Fausset, C. B., & Rogers, W. A. (2017). Older adults' acceptance of activity trackers. *Journal of Applied Gerontology*, *36*(2), 127–155.

Ramsey, A. T., Wetherell, J. L., Depp, C., Dixon, D., & Lenze, E. (2016). Feasibility and acceptability of smartphone assessment in older adults with cognitive and emotional difficulties. *Journal of Technology in Human Services*, *34*(2), 209–223.

Richardson, L. K., Frueh, C. B., Grubaugh, A. L., Egede, L., & Elhai, J. D. (2009). Current directions in videoconferencing tele-mental health research. *Clinical Psychology: Science and Practice*, *16*(3), 323–338.

Rizzo, A., Buckwalter, J.G., van der Zaag, C., Neumann, U., Thiébaux, M., Chua, C., ... Larson, P. (2000). Virtual environment applications in clinical neuropsychology. In *Proceedings IEEE Virtual Reality 2000* (pp. 63–70). IEEE.

Robillard, J. M., Lai, J. A., Wu, J. M., Feng, T. L., & Hayden, S. (2018). Patient perspectives of the experience of a computerized cognitive assessment in a clinical setting. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*, 297–303.

Rogers, W. A., & Fisk, A. D. (2010). Toward a psychological science of advanced technology design for older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *65*(6), 645–653.

Ruggiero, K. J., Resnick, H. S., Acierno, R., Coffey, S. F., Carpenter, M. J., Ruscio, A. M., ... Bucuvalas, M. (2006). Internet-based intervention for mental health and substance use problems in disaster-affected populations: A pilot feasibility study. *Behavior Therapy*, *37*(2), 190–205.

Sanner, T. A., Roland, L. K., & Braa, K. (2012). From pilot to scale: Towards an mHealth typology for low-resource contexts. *Health Policy and Technology*, *1*(3), 155–164.

Sävenstedt, S., Zingmark, K., Hydén, L. C., & Brulin, C. (2005). Establishing joint attention in remote talks with the elderly about health: A study of nurses' conversation with elderly persons in teleconsultations. *Scandinavian Journal of Caring Sciences*, *19*(4), 317–324.

Schueller, S. M., Tomasino, K. N., & Mohr, D. C. (2017). Integrating human support into behavioral intervention technologies: The efficiency model of support. *Clinical Psychology: Science and Practice*, *24*(1), 27–45.

Schultheis, M. T., Himelstein, J., & Rizzo, A. A. (2002). Virtual reality and neuropsychology: Upgrading the current tools. *The Journal of Head Trauma Rehabilitation*, *17*(5), 378–394.

Seichepine, D. R., Neargarder, S., McCallum, M. E., Tabor, K., Riedel, T. M., Gilmore, G. C., & Cronin-Golomb, A. (2012). Luminance affects age-related deficits in object detection: Implications for computerized psychological assessments. *Psychology and Aging*, *27*(2), 522–528.

Shapira, N., Barak, A., & Gal, I. (2007). Promoting older adults' well-being through Internet training and use. *Aging & Mental Health*, *11*(5), 477–484.

Similä, H., Immonen, M., Toska-Tervola, J., Enwald, H., Keränen, N., Kangas, M., ... Korpelainen, R. (2018). Feasibility of mobile mental wellness training for older adults. *Geriatric Nursing*, *39*, 499–505. Available from https://doi.org/10.1016/j.gerinurse.2018.02.001.

Spek, V., Nyklíček, I., Smits, N., Cuijpers, P., Riper, H., Keyzer, J., & Pop, V. (2007). Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: A randomized controlled trial. *Psychological Medicine*, *37*(12), 1787–1806.

Stone, A. A., & Shiffman, S. (1994). Ecological momentary assessment (EMA) in behavioral medicine. *Annals of Behavioral Medicine*, *16*(3), 199–202.

Titov, N., Dear, B. F., Ali, S., Zou, J. B., Lorian, C. N., Johnston, L., … Fogliati, V. J. (2015). Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: A randomized controlled trial. *Behavior Therapy*, *46* (2), 193–205.

Titov, N., Fogliati, V. J., Staples, L. G., Gandy, M., Johnston, L., Wootton, B., … Dear, B. F. (2016). Treating anxiety and depression in older adults: Randomised controlled trial comparing guided v. self-guided internet-delivered cognitive-behavioural therapy. *British Journal of Psychology Open*, *2*(1), 50–58.

Tomasino, K. N., Lattie, E. G., Ho, J., Palac, H. L., Kaiser, S. M., & Mohr, D. C. (2017). Harnessing peer support in an online intervention for older adults with depression. *The American Journal of Geriatric Psychiatry*, *25*(10), 1109–1119.

Trull, T. J., & Ebner-Priemer, U. W. (2009). Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment and clinical research: Introduction to the special section. *Psychological Assessment*, *21*(2), 457–462.

Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial translation—A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex*, *67*, 83–94.

U.S. Census Bureau (2017). *National population projections*. <http://www.census.gov/programs-surveys/popproj.html> (Accessed 13.09.18).

Vahia, I. V., Ng, B., Camacho, A., Cardenas, V., Cherner, M., Depp, C. A., … Agha, Z. (2015). Telepsychiatry for neurocognitive testing in older rural Latino adults. *The American Journal of Geriatric Psychiatry*, *23*(7), 666–670.

van der Wardt, V., Bandelow, S., & Hogervorst, E. (2010). *The relationship between cognitive abilities, well-being and use of new technologies in older people*. *Proceedings of the 28th Annual European Conference on Cognitive Ergonomics* (pp. 333–334). ACM.

Wadsworth, H. E., Dhima, K., Womack, K. B., Hart, J., Weiner, M. F., Hynan, L. S., & Cullum, C. M. (2018). Validity of teleneuropsychological assessment in older patients with cognitive disorders. *Archives of Clinical Neuropsychology*, *33*, 1040–1045. Available from https://doi.org/10.1093/arclin/acx140.

Walters, W. H. (2002). Later-life migration in the United States: A review of recent research. *Journal of Planning Literature*, *17*(1), 37–66.

Wei, W., Sambamoorthi, U., Olfson, M., Walkup, J. T., & Crystal, S. (2005). Use of psychotherapy for depression in older adults. *American Journal of Psychiatry*, *162*(4), 711–717.

Weniger, G., Ruhleder, M., Lange, C., Wolf, S., & Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia*, *49*(3), 518–527.

Westerhof, G. J., & Bohlmeijer, E. T. (2014). Celebrating fifty years of research and applications in reminiscence and life review: State of the art and new directions. *Journal of Aging Studies*, *29*, 107–114. Available from https://doi.org/10.1016.j.jaging.2014.02.003.

Westerhof, G. J., Lamers, S. M. A., Postel, M. G., & Bohlmeijer, E. T. (2019). Online therapy for depressive symptoms: An evaluation of counselor-led and peer-supported life review therapy. *The Gerontologist*, *59*(1), 135–146.

Wild, K., Boise, L., Lundell, J., & Foucek, A. (2008). Unobtrusive in-home monitoring of cognitive and physical health: Reactions and perceptions of older adults. *Journal of Applied Gerontology*, *27*(2), 181–200.

Zou, J. B., Dear, B. F., Titov, N., Lorian, C. N., Johnston, L., Spence, J., … Sachdev, P. (2012). Brief internet-delivered cognitive behavioral therapy for anxiety in older adults: A feasibility trial. *Journal of Anxiety Disorders*, *26*(6), 650–655.

Further reading

Cuijpers, P., Donker, T., van Straten, A., Li, J., & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A systematic review and meta-analysis of comparative outcome studies. *Psychological Medicine*, *40*, 1943–1957.

Czaja, S. J., Charness, N., Fisk, A. D., Hertzog, C., Nair, S. N., Rogers, W. A., & Sharit, J. (2006). Factors predicting the use of technology: Findings from the Center for Research and Education on Aging and Technology Enhancement (CREATE). *Psychology and Aging*, *21*(2), 333.

Czaja, S. J., Sharit, J., & Nair, S. N. (2008). Usability of the Medicare health web site. *Journal of the American Medical Association*, *300*(7), 790–792.

Davis, F. D., Bagozzi, R. P., & Warshaw, P. R. (1989). User acceptance of computer technology: A comparison of two theoretical models. *Management Science*, *35*(8), 982–1003.

Dear, B. F., Zou, J., Titov, N., Lorian, C., Johnston, L., Spence, J., … Knight, R. G. (2013). Internet-delivered cognitive behavioural therapy for depression: A feasibility open trial for older adults. *Australian & New Zealand Journal of Psychiatry*, *47*(2), 169–176.

Dear, B. F., Zou, J. B., Ali, S., Lorian, C. N., Johnston, L., Terides, M. D., … Titov, N. (2015). Examining self-guided internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety and depression: Two feasibility open trials. *Internet Interventions*, *2*(1), 17–23.

Egede, L. E., Acierno, R., Knapp, R. G., Walker, R. J., Payne, E. H., & Frueh, B. C. (2016). Psychotherapy for depression in older veterans via telemedicine: Effect on quality of life, satisfaction, treatment credibility, and service delivery perception. *The Journal of Clinical Psychiatry*, *77*(12), 1704–1711.

Elsegood, K., & Powell, D. (2008). Computerised cognitive-behaviour therapy (cCBT) and older people: A pilot study to determine factors that influence willingness to engage with cCBT. *Counselling & Psychotherapy Research*, *8*, 189–192. Available from https://doi.org/10.1080/14733140802163914.

Emmelkamp, P. M. G. (2005). Technological innovations in clinical assessment and psychotherapy. *Psychotherapy and Psychosomatics*, *74*, 336–343. Available from https://doi.org/10.1159/000087780.

Heron, K. E., & Smyth, J. M. (2010). Ecological momentary interventions: Incorporating mobile technology into psychosocial and health behaviour treatments. *British Journal of Health Psychology*, *15*(1), 1–39.

Rogers, W. A., Meyer, B., Walker, N., & Fisk, A. D. (1998). Functional limitations to daily living tasks in the aged: A focus group analysis. *Human Factors*, *40*(1), 111–125.

Spek, V., Cuijpers, P., Nyklíček, I., Smits, N., Riper, H., Keyzer, J., & Pop, V. (2008). One-year follow-up results of a randomized controlled clinical trial on internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years. *Psychological Medicine*, *38*(5), 635–639.

Titov, N., Dear, B. F., Johnston, L., Lorian, C., Zou, J., Wootton, B., ... Rapee, R. M. (2013). Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: Randomised controlled trial. *PLoS One*, *8*(7), e62873.

Titov, N., Dear, B. F., Johnston, L., McEvoy, P. M., Wootton, B., Terides, M. D., ... Rapee, R. M. (2014). Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: A 12-month follow-up of a randomised controlled trial. *PLoS One*, *9*(2), e89591.

This page intentionally left blank

Chapter 25

Community and home care for mentally ill older adults

Erin Cassidy-Eagle

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States

Introduction

America's population of adults age 65 and older is projected to increase from 40.3 million to 72.1 million between the years 2010 and 2030 (Institute of Medicine, 2012). This increase has ignited the ongoing discussion around creating effective mechanisms and sufficient resources for older adults suffering from a range of mental health needs, both in community and residential care settings. Older adults' rates of care-seeking and attitudes toward mental health treatments have experienced a positive change. Although previous studies have reported that only half of older adults with symptoms sought treatment for their mental health conditions, through either primary or specialty care (Klap, Unroe, & Unutzer, 2003), this appears to be shifting with the current baby boom generation, who report being even more positive about help-seeking than their younger counterparts (Mackenzie, Scott, Mather, & Sareen, 2008). As such, barriers to getting appropriate support for mental health are more likely due to lack of resources combined with increasing need.

About 8% of those 65 and older meet criteria for a mental health disorder (Klap et al., 2003), not including those with subsyndromal symptoms. Although the percentage of older adults with a diagnosable mental disorder is lower than those in younger age groups, they often present with comorbid physical and cognitive challenges that make treatment more complicated. For example, a homebound patient suffering from depression, decreased mobility, and limited financial resources may have more trouble accessing treatment and following through with care recommendations due to issues such as transportation and cost. In addition to the recognized clinical complexity, our current network of psychiatric care providers is struggling to adequately serve the mental health need of older adults (Blair & Espinoza, 2015; Institute of Medicine, 2012) and this problem is primed to get worse. Older adults with mental health conditions contribute disproportionately to rising health care costs, yet the number of geriatric mental health specialists is inadequate (Institute of Medicine, 2012). Increased efforts to disseminate treatments with established effectiveness to these vulnerable and at-risk groups are essential to staving off a public health crisis. As stated by the Institute of Medicine in its 2012 report on the geriatric mental health workforce: *The burden of mental illness and substance use disorders in older adults in the United States borders on a crisis. Yet, this crisis is largely hidden from the public and many of those who develop policy and programs to care for older people* (Institute of Medicine, 2012). This statement is further substantiated by the finding that more than two-thirds of those over 65 will need assistance from others due to decreases in functioning (Kemper, Komisar, & Alecxih, 2005). Addressing this crisis depends upon improving access to care. Effective strategies to support the mental health of older adults in both home and residential community settings will go far in helping older adults age successfully and access needed mental health support at the lowest cost.

Who is seeking mental health care?

Older patients have numerous comorbid medical and neurological conditions that complicate both evaluation and treatment. While most psychiatric prescribing for older adults is currently done by primary care providers, few adults receive adequate trials of medications or see a mental health specialist and effective collaborative care models (e.g., the IMPACT and PROSPECT studies of treatment for depression) (Unutzer et al., 2002) have not been widely implemented. Older minority patients experience even greater disparities in mental health care. There are different subpopulations

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00025-9

of older adults suffering from mental illness, including those that have severe, long-term psychiatric disabilities, those with new-onset conditions, or premorbid conditions that have been exacerbated to the point of disability, with increasing age.

Where do older adults with mental illness reside?

The vast majority of older adults reside in their homes in the community, including those suffering from a range of types and severities of mental illnesses. This trend continues into the eighth decade, where more than three-quarters of older adults live in their own homes, the majority of which are occupied by a single household member who is more likely to be female (Fernald, 2014). In a report by the Joint Center for Housing Studies of Harvard University (Fernald, 2014), it was reported that only 2% of older adults reside in residential care, including assisted living, skilled nursing facilities, or inpatient hospice care. The sheer numbers paint a different picture, indicating that approximately 37% of older adults age 65 + will reside in one or more long-term care facilities during the course of their life, with an average length of stay being 1 year. Along with this increase in utilization, a range of long-term care options have become increasingly popular, an example of which is the homelike attraction marketed by assisted living facilities.

Residential care options

Individuals seek out long-term care options for several reasons, usually including a need for support around emotional, physical, and/or cognitive limitations. The goal of long-term, residential care is not focused on curing various medical conditions, but instead is focused on either short-term rehabilitation, as well as supporting long-term residents in maximizing their functioning and quality of life in the context of a chronic illness or increased disability. There are different categories of residential care facilities for the elderly (RCFEs), including independent living facilities, assisted living facilities, skilled nursing homes, and continuing care retirement communities, which typically have units spanning the continuum of care levels to enable older adults to "age in place." The vast majority of older adults move into one of the levels of residential care as a result of physical and/or cognitive decline that is difficult to manage at home due to a lack of social and financial resources or need for a higher level of care for safety and quality of life concerns or as a result of proactive planning for future perceived needs.

RCFEs (e.g., independent/assisted living facilities) are designed to provide a supportive care setting that allows and cultivates independence, while simultaneously providing assistance for those residents with functional and cognitive limitations. RCFEs, and assisted living facilities specifically, serve the needs of patients unable to remain at home but still more functioning than those requiring round the clock care. Their popularity with residents and families stems from their lower-cost, more homelike environment, and emphasis on quality of life (Mitchell & Kemp, 2000). Although the structure of assisted living facilities, also known as residential care, has been in flux over the past decade, their philosophy has remained constant, which is to provide an environment that allows and cultivates independence, while simultaneously providing assistance for those residents with functional and cognitive limitations, thereby supporting the goal of "aging in place." They provide daily meals, assistance with activities of daily living, 24-hour oversight, activities, transportation, and a range of specialty units and room types, including memory units for those with dementia. Nursing homes are state-licensed facilities that provide 24-hour room and board, supervision, and skilled nursing care. Assisted living facilities in particular differ significantly in terms of their resources, pay structure, number of staff and residents both within and across states. Although once solely private pay, these facilities now serve an ever-increasingly diverse population, more similar to the population historically seen in skilled nursing settings. Several state and governmental programs fund assisted living facilities care, including supplemental security income (SSI), long-term care insurance, and Medicaid, with one or more being accepted in assisted living facilities in most states (Mollica, 2009). This trend will continue as payers search for attractive, lower-cost alternatives to meet the demands of the "baby boomers" entering the system.

Assisted living facilities went through a period of significant growth in the past two decades, attracting patients with lower care needs away from skilled nursing, with now the range of RCFEs stabilizing in size (Clement & Khushalani, 2015). Assisted living facilities serve between 835,000 and 1 million residents nationally (Caffrey, Harris-Kojetin, & Sengupta, 2015), but due to high costs, concerns about care quality, and the need for older adults to move out of their neighborhood networks, the popularity has waned somewhat. The 1.4 million residents served by the more costly and structured skilled nursing facilities, approximately 3 million residents annually, has also been simultaneously declining over the last decade (Caffrey et al., 2015; Fernald, 2014). The centers for disease control and prevention (CDC) estimates that the number of older adults receiving care will increase from 15 million in 2000 to an astounding

27 million in 2050 (Harris-Kojetin et al., 2016). This massive shift has prompted the growth of naturally forming independent retirement communities began to rise (Pfeifer, 2016), where groups of older adults organize to contract with needed services that enable them to stay in their homes. Older adults continue to find residential options costly, isolating and sometimes deficient in providing consistent care (Pfeifer, 2016), calling for more efforts to create options that maximize autonomy, access to appropriate care, and affordability.

Conditions most frequently seen/treated in facilities

The most common mental illnesses treated through successful residential and home-based programs for older adults are depression, anxiety, and cognitive decline. Programs studied that have met with success provide treatment ranging from medication management to group and individual therapy (Reifler & Bruce, 2014). One example of a successful outreach effort includes training residents of a community to identify and refer older adults who would likely benefit from treatment who are also homebound. A summary of 10 successful programs by Reifler and Bruce (2014), highlighted the great unmet need for mental health services for older adults who are unable to travel to an office-based setting and the need for research across settings to better establish best practices.

In conventional housing, older adults with a range of mild-to-moderate psychiatric and cognitive symptoms can access care support through home health aides and homemaker services. When support resources, either financial or social, are depleted, or the preferences for more care present themselves, residential care can be explored. Despite requiring less care than nursing home patients, independent and assisted living facility residents present significant care challenges for limited staff due to impairments in sleep, cognition, and a range of other psychological, functional, and medical challenges. A study of assisted living facilities in Maryland by Samus et al. (2013) found that across a 12-month period, three-quarters of the residents suffered from a cognitive disorder, with primary symptoms of agitation, irritability, and "night time behaviors," and 15% were diagnosed with a noncognitive mental disorder, the most prevalent of which was depression. Such growth in numbers has not been met with similar levels of scientific study or policy and programmatic changes, resulting in the continued challenge to create appropriate support resources adapted for setting specific needs. Assisted living facilities are required to only admit residents with mental health issues that can be appropriately managed in the long-term setting. All but 10 states assist residents in accessing mental health care (Mollica, 2009). A literature review of relevant studies also found similar rates of depression and overall psychological well-being between assisted living versus nursing home care settings (Wysocki et al., 2015), suggesting that interventions may translate across care settings. Similarly, demographics of residents admitted to assisted living versus skilled nursing facilities have also found considerable overlap in staffing, medical care needs, and levels of disability (Han, Trinkoff, Storr, Lerner, & Yang, 2017). Newly admitted residents are commonly in earlier stages of a range of conditions, making them an ideal target for early intervention programs that could stave off more rapid cognitive decline and increased physical disability, but care could be continued into the later stages of disability if needed.

Opportunities and needs for mental health research—sleep as an example

Increasingly, there are examples of successful interventions being implemented in residential settings, but more research is needed. There are several advantages to conducting a range of psychiatric and rehabilitative care interventions in institutional settings, including addressing symptoms of a range of disorders prior to their becoming entrenched and the fact that residents are more efficiently reached due to the lack of need for transportation.

One example of a successful research endeavor is that of a program to address the sleep disturbances commonly seen in those also suffering from mild cognitive impairment (MCI) in an independent and assisted living setting. Compared to older adults in the community, independent and assisted living facilities are likely to have a high concentration of residents with MCI (Elliott, Horgas, & Marsiske, 2008) and residents suffering from disturbed sleep (Martin, Alam, Harker, Josephson, & Alessi, 2008; Samus et al., 2013). A recent study found that older adults with sleep-related problems, who were otherwise healthy, were more likely to be diagnosed with MCI or dementia 2 years later than those with no sleep problems (Lobo et al., 2008). In addition, sleep disruption, among other neuropsychiatric symptoms, appears to greatly impact clinical outcomes of residents, including the presence/progression of dementia (Geda et al., 2008), increased transfer from residential to nursing home settings (Aud, 2004), and increased all-cause mortality (Parthasarathy et al., 2015). It is likely that improving sleep disturbances may have the additive effect of improving a broad range of other psychiatric and physical aspects of functioning, to which sleep is somehow connected. Cognitive behavioral treatments have been shown to significantly improve a range of sleep, functional, health, and psychiatric outcomes in older adults in both home and residential settings. With targeted training, such interventions have been

successfully administered by senior volunteers, sleep coaches, and frontline residential staff such as advanced practice nurses (Alessi et al., 2016; Cassidy-Eagle, Siebern, Unti, & Glassman, 2016; Espie, Inglis, & Harvey, 2001).

Cassidy-Eagle and colleagues implemented a six-session, adapted version of a cognitive behavioral intervention for insomnia to older adults ($N = 28$) across two residential facilities (Cassidy-Eagle, Siebern, Unti, Glassman, & O'Hara, 2018a). Results were promising, indicating that the intervention was successful in improving both objective and subjective ratings of sleep quality. In addition, there were some improvements noted in a measure of executive functioning (Cassidy-Eagle, Siebern, Unti, Glassman, & O'Hara, 2018b), leading to the hope that future interventions for sleep or other psychiatric disorders might also positively impact the cognitive functioning of older adults.

Conclusion

Although there are currently a range of long-term care options for older adults and those suffering from a range of mental illnesses, there are several areas that could be targeted for change. First, simple logistics, including increased transportation to outside social engagements or off-site appointments with care providers, will enable residents to maintain consistency and increase access to treatment, particularly as few facilities offer on-site treatment options and few providers are able to do home visits. Second, the creation of affordable housing options, combined with in-home care, for those older adults wishing to remain in their current neighborhoods would allow for the maintenance of social networks. Third, finding ways to engage able, older adults in community activities that would benefit from the time and energy of volunteers would simultaneously provide the older person with a continued sense of purpose and motivation to stay physically and cognitively active. Increasing the range of social activities hosted within facilities, particularly for those who have difficulties traveling due to functional limitations, is a fourth idea to support the mental well-being of residents. Finally, more research needs to be conducted that specifies the type, size, etc. studied due to incredible diversity in facility characteristics. Characteristics of the facilities studied (e.g., size, services, demographics of those served, etc.), similar outcomes (e.g., medical and psychiatric trajectories), and comparable measurement tools will help to synthesize outcome data in a more meaningful way (Wysocki et al., 2015). With such information, future care and support of older adults with mental illnesses residing both in community and home settings can be optimized to the full extent possible.

References

Alessi, C., Martin, J. L., Fiorentino, L., Fung, C. H., Dzierzewski, J. M., Rodriguez Tapia, J. C., … Mitchell, M. N. (2016). Cognitive behavioral therapy for insomnia in older veterans using nonclinician sleep coaches: Randomized controlled trial. *Journal of the American Geriatrics Society*, *64*(9), 1830–1838. Available from https://doi.org/10.1111/jgs.14304.

Aud, M. A. (2004). Residents with dementia in assisted living facilities. The role of behavior in discharge decisions. *Journal of Gerontological Nursing*, *30*(6), 16–26.

Blair, T. R., & Espinoza, R. T. (2015). Medicare, medicaid, and mental health care: Historical perspectives on reforms before the US Congress. *The Journal of the American Medical Association*, *314*(21), 2231–2232. Available from https://doi.org/10.1001/jama.2015.13328.

Caffrey, C., Harris-Kojetin, L., & Sengupta, M. (2015). Variation in residential care community resident characteristics, by size of community: United States, 2014. *NCHS Data Brief*, *223*, 1–8.

Cassidy-Eagle, E., Siebern, A., Unti, L., & Glassman, J. (2016). *Using senior volunteers to facilitate sleep intervention groups for older adults in residential care.* Paper presented at the Association for Behavioral and Cognitive Therapies, New York, NY.

Cassidy-Eagle, E., Siebern, A., Unti, L., Glassman, J., & O'Hara, R. (2018a). Cognitive behavioral treatment for insomnia in older adults with mild cognitive impairment in independent living facilities: A pilot study. *Journal of Sleep Disorders and Medical Care*, *1*(1), 1–6. Available from https://doi.org/10.16966/2577-882X.105.

Cassidy-Eagle, E., Siebern, A., Unti, L., Glassman, J., & O'Hara, R. (2018b). Neuropsychological functioning in older adults with mild cognitive impairment and insomnia randomized to CBT-I or control group. *Clinical Gerontologist*, *41*(2), 136–144. Available from https://doi.org/10.1080/07317115.2017.1384777.

Clement, J. P., & Khushalani, J. (2015). Does assisted living capacity influence case mix at nursing homes? *Gerontology and Geriatric Medicine*, *1*. Available from https://doi.org/10.1177/2333721415587449, 2333721415587449.

Elliott, A. F., Horgas, A. L., & Marsiske, M. (2008). Nurses' role in identifying mild cognitive impairment in older adults. *Geriatric Nursing (New York, N.Y.)*, *29*(1), 38–47. Available from https://doi.org/10.1016/j.gerinurse.2007.04.015.

Espie, C. A., Inglis, S. J., & Harvey, L. (2001). Predicting clinically significant response to cognitive behavior therapy for chronic insomnia in general medical practice: Analysis of outcome data at 12 months posttreatment. *Journal of Consulting and Clinical Psychology*, *69*(1), 58–66.

Fernald, M. (2014). *Housing America's older adults: Meeting the needs of an aging population*. Cambridge, MA: Joint Center for Housing Studies of Harvard University.

Geda, Y. E., Roberts, R. O., Knopman, D. S., Petersen, R. C., Christianson, T. J., Pankratz, V. S., ... Rocca, W. A. (2008). Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. *Archives of General Psychiatry*, *65*(10), 1193−1198. Available from https://doi.org/10.1001/archpsyc.65.10.1193.

Han, K., Trinkoff, A. M., Storr, C. L., Lerner, N., & Yang, B. K. (2017). Variation across U.S. assisted living facilities: Admissions, resident care needs, and staffing. *Journal of Nursing Scholarship*, *49*(1), 24−32. Available from https://doi.org/10.1111/jnu.12262.

Harris-Kojetin, L., Sengupta, M., Park-Lee, E., Valverde, R., Caffrey, C., Rome, V., & Lendon, J. (2016). Long-term care providers and services users in the United States: Data from the national study of long-term care providers, 2013-2014. *Vital and Health Statistics*, *3*(38), 1−105, x−xii.

Institute of Medicine. (2012). In J. Eden, K. Maslow, M. Le, & D. Blazer (Eds.), *The mental health and substance use workforce for older adults: In whose hands?* Washington, DC: National Academies Press (US).

Kemper, P., Komisar, H. L., & Alecxih, L. (2005). Long-term care over an uncertain future: What can current retirees expect? *Inquiry*, *42*(4), 335−350. Available from https://doi.org/10.5034/inquiryjrnl_42.4.335.

Klap, R., Unroe, K. T., & Unutzer, J. (2003). Caring for mental illness in the United States: A focus on older adults. *The American Journal of Geriatric Psychiatry*, *11*(5), 517−524.

Lobo, A., Lopez-Anton, R., de-la-Camara, C., Quintanilla, M. A., Campayo, A., & Saz, P. (2008). Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. *Neurotoxicity Research*, *14*(2-3), 263−272. Available from https://doi.org/10.1007/bf03033815.

Mackenzie, C. S., Scott, T., Mather, A., & Sareen, J. (2008). Older adults' help-seeking attitudes and treatment beliefs concerning mental health problems. *The American Journal of Geriatric Psychiatry*, *16*(12), 1010−1019. Available from https://doi.org/10.1097/JGP.0b013e31818cd3be.

Martin, J. L., Alam, T., Harker, J. O., Josephson, K. R., & Alessi, C. A. (2008). Sleep in assisted living facility residents versus home-dwelling older adults. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*(12), 1407−1409.

Mitchell, J. M., & Kemp, B. J. (2000). Quality of life in assisted living homes: A multidimensional analysis. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *55*(2), P117−127.

Mollica, R. L. (2009). *State medicaid reimbursement policies and practices in assisted living*. Washington, D.C.: National Center for Assisted Living/American Health Care Association.

Parthasarathy, S., Vasquez, M. M., Halonen, M., Bootzin, R., Quan, S. F., Martinez, F. D., & Guerra, S. (2015). Persistent insomnia is associated with mortality risk. *The American Journal of Medicine*, *128*(3), 268−275 e262. Available from https://doi.org/10.1016/j.amjmed.2014.10.015.

Pfeifer, G. M. (2016). Helping elders 'Age in Place'. *The American Journal of Nursing*, *116*(10), 20−21. Available from https://doi.org/10.1097/01.NAJ.0000503290.97605.8f.

Reifler, B. V., & Bruce, M. L. (2014). Home-based mental health services for older adults: A review of ten model programs. *The American Journal of Geriatric Psychiatry*, *22*(3), 241−247. Available from https://doi.org/10.1016/j.jagp.2012.12.002.

Samus, Q. M., Onyike, C. U., Johnston, D., Mayer, L., McNabney, M., Baker, A. S., ... Rosenblatt, A. (2013). 12-month incidence, prevalence, persistence, and treatment of mental disorders among individuals recently admitted to assisted living facilities in Maryland. *International Psychogeriatrics*, *25*(5), 721−731. Available from https://doi.org/10.1017/S1041610212002244.

Unutzer, J., Katon, W., Callahan, C. M., Williams, J. W., Jr., Hunkeler, E., Harpole, L., ... IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. (2002). Collaborative care management of late-life depression in the primary care setting: A randomized controlled trial. *The Journal of the American Medical Association*, *288*(22), 2836−2845.

Wysocki, A., Butler, M., Kane, R. L., Kane, R. A., Shippee, T., & Sainfort, F. (2015). Long-term services and supports for older adults: A review of home and community-based services versus institutional care. *Journal of Aging & Social Policy*, *27*(3), 255−279. Available from https://doi.org/10.1080/08959420.2015.1024545.

This page intentionally left blank

Chapter 26

Forensic and ethical issues

Mousa S. Botros[1,2,3], Julie E. Guzzardi[1,2,3], Regina M. Carney[3], Spencer Eth[1,3] and Gregory B. Leong[4]

[1]Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, United States, [2]Mental Health and Behavioral Sciences Service, Miami VA Healthcare System, Miami, FL, United States, [3]Mental and Behavioral Health Service, Jackson Health System, Miami, FL, United States, [4]Department of Psychiatry and Behavioral Sciences, Keck School of Medicine of the University of Southern California, Los Angeles, CA, United States

Forensic and ethical issues involving the aged encompass all of the ones that can be faced by any other adult; however, their frequency and complexity may be greater, reflecting age-dependent differences in the prevalence of important psychiatric and medical conditions that are the substrate for these legal and ethical concerns. Advancing age invariably results in a progressive loss of functional capacity of all biological systems. Further, old age is associated with an increasing likelihood of the specific degenerative changes within the central nervous system characteristic of dementia. Other body systems are also exposed to an accelerating risk of malfunction and disease, which can then directly, or indirectly as a side effect of the therapeutic intervention, give rise to organic mental syndromes. Finally, functional psychiatric disorders can also develop anew in later life (Gallo & Lebowitz, 1999; Trollor, Anderson, Sachdev, Brodaty, & Andrews, 2007). The growth in number and proportion of the aged is unprecedented in the US history, potentially doubling in the next 25 years to about 72 million. By 2030, it is expected that the aged will account for 20% of the US population (CDC, 2013). Over 20% of adults aged 60 and over suffer from a mental or neurological disorder (excluding headache disorders) and 6.6% of all disability (disability-adjusted life years, DALYs) among them is attributed to mental and neurological disorders (WHO, 2017). The appearance of mental and neuropsychiatric disturbances in the geriatric population plays a significant role in generating forensic and ethical concerns.

This chapter will identify three critical themes that can clarify the legal and ethical analysis of the myriad problems found in a geriatric population at risk of mental, physical, and neuropsychiatric illnesses. There are other specific capacities, such as sexual consent capacity and driving capacity that are not the main foci of this chapter. The following clinical vignette serves to illustrate the themes of competency, consent, and confidentiality that will be explored in depth in the sections that follow (Veatch, 1976).

> *Mr. B is a 70-year-old Alzheimer's disease patient who has a history of cardiac arrhythmia. Mr. B has been confined to an intermediate-care facility because of his tendency to wander away from home and become lost. Mr. B's devoted wife of 50 years, who herself has grown quite frail, constantly laments her husband's deterioration, especially since he no longer consistently recognizes her during her daily visits with him. Although technically Mr. B is a voluntary patient in the facility, Mrs. B's routines provide consent for all medical procedures and treatments. One day, without her knowledge, Mr. B is transferred to a local hospital in order to replace the failing battery in his cardiac pacemaker. When notified of this action, Mrs. B expresses outrage and insists that nothing further be done to her husband. Mrs. B adamantly refuses permission for the minor surgery required to replace the pacemaker. As she explains: "What does he have to live for? Nothing! He has no memory, and he is slowly turning into a vegetable. I know he prefers death to that kind of miserable existence."*

Competency

As suggested by the case of Mr. and Mrs. B, the concept of competency is central to any discussion of legal and ethical issues in the aged. Competency, or the lack of competency, plays an important role in determining whether older individuals, such as Mr. B, will be free to act in all of the ways that they have throughout their lives. For instance, deciding where to live, consenting to medical care, buying or selling assets, and writing a will all presuppose a person's

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00026-0

competence. The loss of these capabilities, in a sense, results in a process of diminished autonomy in which the senior citizen comes to rely increasingly on caretakers for life direction.

Beginning at birth, American law grants a succession of rights and privileges to individuals as their chronological age advances. Federal and state regulations govern the precise age one may first vote, operate a motor vehicle, purchase alcohol, enter the armed forces, and practice medicine. In another context, the law determines a threshold age for exercising the right to a jury trial, for being found guilty of a crime and for being subject to capital punishment. These age-dependent legal functions presume that a certain degree of cognitive maturation has accompanied chronological age. This generally occurs with the growth of a child according to accepted models of cognitive development (Piaget & Inhelder, 1969). Although the acquisition of relevant cognitive skills parallels to some extent the legal expectations of a juvenile (Billick, 1986), the age criterion for some older-adult activities appears driven by political processes rather than developmental capabilities. It is difficult to imagine the particular neuropsychological ability that first matures at 35 years of age and only then qualifies a citizen to serve as the president of the United States. Similarly, there does not appear to be a cognitive or functional marker of infirmity that defines 62 or 65 years as the appropriate age for entitlement to social security and medicare benefits.

The principal legal concept that underlies the practice of forensic geropsychiatry in both the civil and criminal arenas is competency. In common parlance, competency refers to the capacity to understand the nature and consequences of an intended act. However, the actual legal usage of competency seems to defy a precise definition, as it varies with the specific act that is being assessed, with the local statutes that set the criteria for that particular competency, and with the individual's functional ability and the context in which the act is to be carried out (Grisso, 1987). For legal purposes, adulthood routinely confers the status of competency for the full range of civil and criminal acts, unless there has been a formal adjudication of incompetency by the court. Capacity, when used in the medical context, is evaluated by a physician and refers to the patient's mental ability to understand, appreciate, manipulate, and utilize information about an illness and proposed treatment options to conclude a rational decision that represents preferences and values. Traditionally, the term capacity was used to describe a clinical finding while competency was used in reference to a legal determination. However, in clinical practice settings, capacity and competency have often been used interchangeably leading to confusion. Moreover, the distinction between the two terms has become less useful as the term capacity is increasingly employed in the law, especially in matters of civil law (Moye, Marson, & Edelstein, 2013).

The notion of developmental competency, or competency achieved through the acquisition of relevant cognitive skills (Billick, 1986), may serve as an analogy for the concept of developmental incompetency, which can arise when those cognitive skills are lost in the process of aging. While developmental competency carries the assurance of legal competency with the entrance into adulthood, developmental incompetency does not automatically render an individual incompetent at any age without a causative clinical condition through a formal judicial hearing. Moreover, even if an individual is found incompetent to perform a certain act, that person is not necessarily incompetent for another. While a clinical condition is required as a causative reason, a finding that such condition causes an inability to adequately manage one's personal or financial affairs is necessary (Sabatino & Basinger, 2000). The standard of proof necessary for judicial finding of incompetency is that of "clear and convincing" evidence (Grannum v Berard, 1967). Based on evidence presented by licensed health care practitioners and others, it is set at a standard between the high level of proof required for criminal convictions, that is, "beyond a reasonable doubt" and the lowest level of "preponderance of the evidence" (Leo, 1999).

Competency in civil law

Matters of civil law of interest to mental health practitioners may be divided into those actions that concern property and those that involve health care. In the property category, will-making, entering into a contract, and ability to manage finances cover the gamut of situations requiring an adult to be competent to participate in such acts. In the health care category, consent to medical treatment is the principal issue that involves both the competent and incompetent adult.

Financial capacity

Financial capacity is a medico-legal construct representing the person's ability to independently manage financial affairs in a manner consistent with personal self-interest and values (Marson & Hebert, 2008a). It generally encompasses specific capacities as testamentary capacity, contractual capacity, and donative capacity. Financial capacity in the elderly is a fundamental issue given older adults are vulnerable to losing both financial skills and judgment as well as the ability to detect and consequently prevent financial exploitation (Stiegel, 2012). In a recent longitudinal study,

financial capacity was noted to be substantially impaired in patients with mild Alzheimer's disease at baseline and showed rapid decline over a period of year relative to the comparison group (Martin et al., 2008).

Testamentary capacity

Testamentary capacity or the capacity to execute a will falls within the broader concept of financial capacity and is a cardinal forensic issue encountered in the geropsychiatric population. In order to establish testamentary capacity, the following capabilities are typically required from the author of the will, the testator, in all US jurisdictions:

1. the testator knows the nature of the act; what a will is, understands he or she is making a will;
2. the testator knows the nature and extent of his or her property;
3. the testator knows who are his or her natural heirs; and
4. the testator has a plan or manner in which his or her property will be disposed and appreciates the effects of his act (Melton, Petrila, Poythress, & Slobogin, 1987).

Depending on the state-relevant law on testamentary capacity, the absence of one or more of these elements can serve as grounds for a court to invalidate a will. Due to public policy supporting the orderly probating of wills and distribution of assets to heirs, courts have traditionally applied a low legal threshold for finding testamentary capacity (Marson & Hebert, 2008b).

In assessing the contribution of mental disorder on testamentary capacity, aspects that directly affect the four criteria listed above are relevant for legal purposes. Mental disorder *per se* does not negate testamentary capacity. However, the judicial presumption of capacity may be rebutted in court, especially in the presence of the disorientation of a delirium, the intellectual deterioration of a dementia or the paranoid delusions of an organic or functional psychosis. In addition, undue influence can also be used as a basis to nullify a will. Undue influence must have been exerted with sufficient force to overcome the free will of the testator and substitute the wishes of another person (Perr, 1981). Delusional thinking, which does not substitute the wishes of another person but replaces the will-maker's free choice with the product of psychosis, may also qualify as undue influence. In a recent study, testamentary capacity was noted to be often challenged due to radical change from a previous will (72% of cases) or alleged undue influence (56% of cases) (e.g. coercion, compulsion, deception) and the most common psychiatric condition noted in the challenged cases was dementia (40% of cases) (Shulman, Cohen, & Hull, 2005).

Testamentary capacity can also become an issue after the testator dies, and the validity of the will is challenged in probate court, often by a disinherited relative. Nonetheless, because many people are living longer with significant impairment in their cognitive functioning, wills could become increasingly susceptible to legal challenge (Redmond, 1987). The postmortem psychiatric evaluation of the testamentary capacity could then be based only on a retrospective analysis of the mental state reconstructed from available historical data.

Contractual capacity

Closely related to testamentary capacity is the contractual capacity of an elderly person to enter into a legally binding contract, such as a business agreement or marriage (Glezer & Devido, 2017). A late-life wedding, especially when the elderly spouse has a considerable estate, can precipitate a dispute between the adult children and the new bride or groom. Likewise, when an elderly person purchases, or more likely sells an interest in a business or similar financial entity, his or her capacity to enter into that contract can be contested by a concerned family member. The legal standard for capacity to enter into a contract is similar to the standards for other legal competencies and generally requires that the person knows the nature and purpose of the contract, the probable consequences of the acts specified by the contract, and that the decision to enter into the contract is not the result of undue influence.

As in the case of testamentary capacity, the question of one's competency to contract turns on precisely how the mental disorder interferes with the proposed action. For example, a severely cognitively impaired individual will be unable to understand the many ramifications of a financial business transaction. Enforcement of that contract would thus demand a more stringent legal standard for competency than would hold for that same individual composing a will. Similarly, orientation in all spheres would seem to be necessary in order to wed. Challenges to marriages or business contracts can occur before the elderly person's death. Further, such challenges can be raised before the actual marriage or formal signing of a contract, and under these circumstances, an evaluation of mental status can be conducted while the individual in question is alive, rather than posthumously, as is the case in a disputed will after the testator's death.

What may arise more commonly than testamentary incapacity in persons suffering from declining mental health is a functional inability to manage appropriately the person's own finances. Such a person can have a proxy designated by the court to oversee the incompetent person's estate. Depending upon the particular state, the person so appointed is known as a conservator, probate guardian, or committee of the person. Procedures and legal standards for appointment of a substitute decision-maker vary by jurisdiction. From a clinical standpoint, competency in this area involves a cognitive as well as a functional ability to handle one's own finances. The mental functions that are often evaluated by the court include those basic to money matters, such as acquisition and conservation of resources, and those functions that organize the proper use of money to assure that basic independent life tasks are performed.

Surrogate decision-makers

For states that have adopted the Uniform Probate Code, guardianship grants to a proxy decision-maker control over a person, while conservatorship grants a substitute decision-maker control over a person's property (Baker, 1986). Thus, guardians are empowered to offer medical consent and to select a suitable residence, including a nursing care facility, for their wards. In other states, the roles of the guardian and conservator may be reversed, but the essential functions of managing person and property are similar across jurisdictions. The courts generally look to family members or close friends as first choices to be appointed as surrogate decision-makers.

Cognitive impairment can progress beyond disabling a person from handling financial affairs to crippling one's ability to provide for the basic necessities of life. In many states, there are mental health statutes governing situations in which an individual, as a result of mental disorders such as dementia or psychosis, cannot provide for or accept the offer of the basic necessities of life, such as food, clothing, and shelter. That individual can then be found *gravely disabled*, allowing for the court to appoint a guardian or conservator with specific delegated powers to remedy the individual's incapacities. Gravely disabled persons may be incapable of living by themselves or in the family home, dictating their admission to a locked facility. Mr. B, who was presented earlier in this chapter, could be deemed gravely disabled. Despite having a wife to care for him, Mr. B's penchant for wandering away from home, coupled with his lack of memory for the route back, placed him in continued peril.

In the context of a surrogate decision-maker's efforts to provide for the person's basic survival needs, there may arise a conflict between notions of individual autonomy and social paternalism. Though some elderly suffer from such severe cognitive impairment that the loss of independence and autonomy is inconsequential, most remain keenly aware of their dependent status. Unlike child development, in which increasing independence from parental control is achieved, the geriatric phase of the life cycle often heralds an unremitting reversal of autonomy. This issue is implicated in the demoralization experienced by the dependent elderly when first admitted to chronic care facilities and may be an etiological factor explaining the staggering morbidity and mortality suffered by this group.

A point of caution is indicated in discussing the problem of self-abuse or self-neglect in the aged. While cognitively impaired individuals do not uncommonly perform these behaviors, such actions may also represent a method of suicide that is uniquely available to depressed, bedridden elderly. Health care providers should be alert to this form of silent suicide, which may be expressed through such acts as self-starvation or noncompliance with essential medical treatment (Simon, 1989). Psychiatrist Robert Simon (1989) surmises that the success rate of this method may approach 100%. Simon further argues that while some of these patients have nearly intact cognition, they are *affectively* incompetent to make health care decisions by virtue of their severe depression. By extension, professionals should be sensitive to the possibility that incompetence driven by affective disorders or pseudodementia (Wells, 1979) may be eroding the judgment and ability of many of the infirm elderly. If this is suspected, a formal psychiatric consultation may be helpful in resolving this question.

Voluntary informed consent

The issue of competency to consent to or refuse medical care is of utmost importance to patients, family members, and health care providers. Historically, physicians were afforded considerable latitude in discharging their duty to care for the sick (Jonsen, Siegler, & Winslade, 1986). Since physicians were asked to use their expertise to treat patients, any infringement of their ability to act freely could negate their effectiveness and might result in harm. The desire, ability, and a request to help provide a powerful justification for the unlimited freedom to deliver medical care governed solely by the patient's condition. This model of beneficent medical paternalism flourished for millennia, only to be supplanted this century by case law that has irrevocably shattered the presumption that the physician is the final decision-maker.

The glorious or perhaps inglorious tradition of medical paternalism, depending on one's views, has given way to a newer era of patients' rights (Katz, 1984).

In the landmark case of *Schloendorff v. Society of New York Hospital* (1914) (p. 126), New York state Justice Benjamin Cardozo opined:

> *"Every human being of adult years of sound mind has a right to determine what shall be done with his own body, and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages . . . this is true except in a case of an emergency where the patient is unconscious, and where it is necessary to operate before consent can be obtained."*

More recently, a federal appellate court, in the case of *Canterbury v. Spence* (1972), mandated that the attending physician must disclose all information a reasonable patient would need to know in order to make an informed judgment about treatment. These decisions are but two of many court rulings that underscore the right of competent adult patients to all relevant information upon which to base a voluntary and informed choice whether to accept or refuse the recommended medical care in non-emergency situations. These then compose the three elements of a valid informed consent: information disclosure, competency, and voluntariness. Commentators have offered alternative conceptualizations of informed consent according to other organizing factors. An applied clinical model was set forth comprising four core decisional abilities: voicing a choice regarding a decision, understanding the decision and choices, appreciation of consequences, and reasoning about the choices (Grisso & Appelbaum 1998). While such schema may be more clinically useful, they can be readily subsumed by the case law−derived components of informed consent suggested above.

In a valid informed consent, disclosure involves a process of explaining to the patient in the language of a layperson the following relevant elements: the nature and purpose of the proposed treatment, alternatives to that treatment, and the hoped-for benefits and possible risks of the proposed treatment and its alternatives, including the option of refusing treatment and allowing the disease process to progress naturally. Capacity, in reference to a valid informed consent in medical situations, would depend on whether the patient retains the ability to make a reasoned choice, even if the physician does not recommend the particular alternative selected by the patient. Voluntariness refers to a consent given without undue influence, such as that imposed by an implied threat of abandonment by the health care team or by a paranoid delusion involving the proposed treatment. Though the three elements of informed consent for medical treatment are listed separately, they are not necessarily mutually exclusive. In order to make a truly valid decision, the patient must have access to sufficient information (disclosure) and operate in an environment free of undue influence (voluntariness).

Closely following the emerging legal emphasis on information disclosure has been an evolution in the ethical standard of honesty in the doctor−patient relationship. As recently as a generation ago, the policy of deception concerning catastrophic diagnoses was widely practiced. Compassionate physicians sincerely believed that it would be harmful to their patients to reveal the presence of a fatal illness. It is now generally accepted that lying is morally wrong and that physicians, regardless of motive, are not exempt from the duty to tell the truth (Bok, 1978). This view emphasizes the importance of the patient's standing as an autonomous moral agent. Further, there is empirical evidence confirming the supposition that patients wish to learn the truth no matter how painful it may be. A recent systematic review of 23 studies (9065 respondents) showed the vast majority of individuals with and without cognitive impairment prefers to be informed about a diagnosis of dementia (Dungen et al., 2014).

The process of information sharing should respect individual patient needs. A delirious patient is rarely in a position to be confronted with complex cognitive material. Similarly, patients with dementia are commonly present with characteristic fragility of their ego defenses. If suddenly challenged with an overwhelming cognitive task, a patient may respond with a catastrophic reaction of agitation and panic. Consequently, the discretionary withholding of information that would be immediately disturbing to an impaired patient is legally and ethically permissible under the rubric of therapeutic privilege as noted in clinical practice (Low, McGrath, Swaffer, & Brodaty, 2018). However, the physician retains an obligation to confide the necessary information as soon as possible within the limitations imposed by the patient's deficits (Overman & Stoudermire, 1988).

Every adult is presumed by law to be competent to offer voluntary informed consent. Not infrequently a patient will be referred for psychiatric consultation because of noncompliant or uncooperative behavior (Perl & Shelp, 1982). The idiosyncratic exercise of one's self-determination may or may not signify an underlying mental illness. If that patient is competent to consent, the choice of medical treatment is the exclusive right of the patient alone (Eth & Robb, 1986). However, many illnesses afflicting the elderly affect mentation and can render the patient less able to perform cognitive tasks. If an aged patient experiences difficulty comprehending the risks and benefits associated with treatment, the

possibility of incapacity should be investigated. The physician is responsible for the rigorous, detailed assessment of the patient's mental status. In such circumstances, clinicians commonly engage patients' families and others involved in their lives as health care proxies when exploring medical decisions (Dunn et al., 2013; Overton et al., 2013). In a recent study, preferred alternative decision-makers were notably aligned with their mentally ill family members concerning treatment-related medical decisions and underlying life values (Roberts & Kim, 2016). The court is uniquely empowered to rule on whether that patient's cognitive and functional deficits necessitate the appointment of a substitute decision-maker. In most instances, patients are deemed to have capacity if they are capable of appreciating the elements of the consent process. Hence, they should be able to demonstrate an understanding of relevant information, a consideration of alternatives, and an ability to express their preference for or against treatment. Under this minimal standard some demented, psychotic, or severely depressed patients will be found to have the capacity to consent. From an ethical perspective, it is clear that our society values individual liberty, allowing capacitated patients with significant mental illness to equally choose the treatment option of their choice.

There are situations, especially in cases of permanent and severe cognitive dysfunction, in which geriatric patients lack the capacity to give informed consent. In *Superintendent of Belchertown State School v. Saikewicz* (1977), the Massachusetts Supreme Court ruled that the right to accept or reject medical treatment of a terminally ill, profoundly intellectually disabled and incompetent 67-year-old patient residing in a state institution would be based on the substituted-judgment doctrine. However, since in fact Saikewicz's intellectual disability had resulted in lifelong incompetence, so that he had never previously expressed a preference on how to proceed if stricken with a terminal illness, his proxy consenter was forced to rely on an estimation of what would be in Saikewicz's best interests, rather than what he had indicated would be his preference in a comparable situation. The substituted judgment would attempt to formulate the exact decision that the incompetent person would have made if he or she were competent, by considering all of the positive and negative factors surrounding the alternative treatments according to the patient's own value system.

However, in these cases, the court is the ultimate authority in rendering a substituted decision. The seminal precedent for this doctrine is the Karen Ann Quinlan case (*In re Quinlan*, 1976), in which the New Jersey Supreme Court granted this patient's father the authority to substitute his judgment, based on his unique relationship and insight, as to what his daughter would have wanted if she were competent under the actual circumstances.

Not all states consistently follow the doctrine of substituted judgment. For example, consider the celebrated New York case of *In re Eichner* (1981). Brother Fox was an 83-year-old Roman Catholic friar who had spoken of his desire never to be maintained by extraordinary means if stricken with a terminal illness. Unfortunately, he subsequently suffered a cardiac arrest during hernia surgery and lapsed into a persistent vegetative state requiring respiratory life support. The director of his religious order, Father Eichner, with the approval of Brother Fox's surviving relatives, asked to be appointed Brother Fox's guardian, in order to sanction the discontinuation of ventilatory assistance. The local district attorney opposed this request. Despite Brother Fox's death while on the respirator, the case worked its way through the New York court system, arriving at its highest court, the New York State Court of Appeals. The Court of Appeals held that the lower court had ruled properly in respecting Father Eicher's decision to terminate ventilatory assistance. But the court chose not to rely on the substituted-judgment doctrine, since there was clear and convincing evidence that Brother Fox had explicitly articulated his particular wish before becoming incompetent. Brother Fox's case illustrates the issue of an adult who, while competent, expressed his choice, and who later became incompetent as a result of illness. While precedents vary by state, the *Saikewicz* and *Eichner* cases demonstrate the dilemmas and complexities of law that can be encountered with geriatric persons who are incompetent to consent to their medical care.

Competent adults have the right not only to accept a proposed medical treatment but also to decline permission, even if that decision ultimately leads to their death. Under these circumstances, treatment refusal confers a *de facto* right to die. However, the vicissitudes of medical illness are not such that a person will necessarily be competent at the time a decision to consent to medical treatment must be made. Thus, there needs to be a mechanism to ensure that competent patients who have preferences about their medical care will be permitted to control their destiny, even in the event of a terminal illness causing severe mental impairments. Since California's Natural Death Act of 1976, a total of 40 states have allowed the use of living wills (Baker, 1986). A living will is a written document prepared by a person while competent, which specifies the circumstances under which the declarant will permit the cessation of extraordinary treatment designed to prolong life, and thereby allow death in accordance with the natural progression of illness. The will must contain two signatures and can be revoked at any time (Baker, Parr, & Yesavage, 1986).

Durable power of attorney laws regulates how an incapacitated individual can control certain decisions by giving another individual the legal authority to decide on their behalf. Although the option of designating an individual (attorney-in-fact) to assume responsibility for managing financial affairs is commonplace, the extension of this mechanism to medical decision-making is by no means universal.

A durable power of attorney for health care, like a living will, concerns the possibility of future incompetency, but in addition, permits flexibility for situations that arise that are not specifically enumerated in the living will. This latitude maximizes the likelihood that the person's general wishes expressed while competent will be followed in case of future incapacity (Steinbrook & Lo, 1984). For example, the proxy nominated in the durable power of attorney document may refuse to permit the use of penicillin in the treatment of pneumonia for a comatose patient, if it does not disagree with the patient's living will.

With increasing numbers of geriatric patients entering psychiatric treatment, issues pertaining to terminal care have become inescapable and intensely controversial (Eth, 1990). Depending on a combination of medical factors, patients with advanced degenerative dementia and other catastrophic conditions may enter a terminal phase of their illness, during which time their level of function will have markedly deteriorated. Like Saikewicz and Brother Fox, many of these patients will have had guardians or other surrogate decision-makers appointed. However, the question of exactly what type of care is appropriate under these dire circumstances is being asked with great urgency (Bellacosa, 1990). Eventually, the painful decision must be faced about whether to initiate, continue, or withdraw the variety of life-support measures sustaining the patient (Wanzer et al., 1989). Hospital staffs quickly realize that their actions in initiating or withdrawing a life-sustaining treatment, such as mechanical ventilation, may become the proximate cause of death (Miles, Singer, & Siegler, 1989). The issue is especially difficult when the targeted treatment is the continued administration of fluid and nutritional support.

Until recently, a critical moral distinction was drawn between ordinary and extraordinary care (as illustrated by Father Eicher's opinion of artificial ventilation). Physicians and other health professionals were felt to be ethically obligated to deliver all ordinary forms of care to all patients. Extraordinary care, however, ought to be ordered only if there were a compelling reason to employ extreme measures. Over the last several years, our escalating technical sophistication has blurred the boundary between ordinary and extraordinary. For example, is hemodialysis, a procedure routinely performed at home, now to be considered ordinary and therefore mandatory care for all terminally ill patients? The novel concept of proportionality, popularized by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983), has replaced the largely arbitrary and nonindividualized categories of ordinary and extraordinary care. Proportionate care can be defined as a treatment that has at least a reasonable likelihood of providing benefits that outweigh the burdens for that particular patient. In disproportionate care, the ratio of benefits to burdens is reversed. Thus, an ordinary-appearing treatment that briefly prolongs the life of a patient in agony is disproportionate care and ought to be avoided, while an extremely painful and intrusive procedure that is curative may be proportionate and highly desirable. Although introduced primarily by medical ethicists, this method of analysis has been embraced in several court decisions (e.g., *Barber v. Superior Court*, 1983).

The US Supreme Court confronted the *right to die* issue for the first time in its 1989–1990 term (*Cruzan v. Director, Missouri Department of Health*, 1990). The case involved a request to discontinue gastrostomy feedings by the parents of a 32-year-old woman who had been in a persistent vegetative state for over 7 years as a result of a motor vehicle accident. The Missouri high court held that there was insufficient evidence of the patient's own wishes about whether she would want the artificial feedings stopped, despite testimony by her family of her statements that she would never want to live as a "vegetable." The Supreme Court, in a five-to-four decision, ruled that nutrition and hydration are forms of medical treatment that can be refused by a competent patient in the same way as can any other care. However, a state may choose to require clear and convincing evidence of an incompetent patient's wishes about foregoing medical treatment before allowing a surrogate to terminate care. Therefore, in the absence of compelling evidence, the Court refused to grant Ms Cruzan's parents' request to discontinue feedings, although if such prior evidence was available for another comatose patient, artificial nutrition could be suspended.

An ethical consensus is forming around several policy positions in the care of elderly patients. Authority for all medical decisions rest exclusively with competent patients. For those patients who have been adjudicated incompetent to consent, their legal surrogate is entrusted with the right to make the relevant medical decisions for them. Consistent with local law, the surrogate should follow the patient's previously communicated instructions with regard to desirable forms of care (Lo, Rouse, & Dornbrand, 1990). Only in the absence of clear and convincing directives concerning the patient's preferences, the surrogate should choose a course consistent with the generally accepted interest in preserving life. In cases where further medical care imposes unacceptable burdens, as would be true for irreversibly comatose, terminally ill patients, then all such efforts may ethically cease. Disproportionate treatment of any type that confers no benefit, including fluid and nutritional support, would not be given. Hospital staff who hold dissenting religious or moral views may be replaced by other staff members comfortable with the agreed-upon-care plan.

A number of other issues remain outside the scope of moral consensus. Murphy (1988) has suggested that cardiopulmonary resuscitation (CPR) for severely demented patients in long-term care settings is never indicated. He contends

that a substitute decision-maker's refusal to endorse a do-not-resuscitate order in such cases may be motivated by guilt or misinformation. Accordingly, a physician ought to unilaterally withhold CPR since it is usually futile and always cruel to a patient who cannot comprehend its therapeutic intent. This argument is admittedly paternalistic and intensely controversial, as it explicitly conflicts with the rights of patients or their surrogates to expect and insist upon customary treatment efforts.

The practice of euthanasia, which has been exhorted as humane, remains both illegal and unethical in the United States. Active, voluntary euthanasia is the deliberate termination of a terminally ill patient's life at his or her own request. A number of medical institutions in Holland have developed procedures to enable physicians to participate in mercy killings in an acceptable and controllable manner (deWachter, 1989). The identical action openly perpetrated in an American hospital would surely result in prompt legal and professional sanctions (American College of Physicians, 1989). Nevertheless, patients' rights advocates, the Hemlock Society, and others continue to assert the desirability of permitting physicians to relieve a patient's suffering by granting an immediate, painless death. One medical commentator has woefully predicted that euthanasia programs in the United States are likely to appear in the near future (Sprung, 1990). However, the moral and legal objections to physician-assisted death seem to be well articulated and strongly held by most of the professions (Singer & Siegler, 1990).

Competency in criminal law

While the population of elderly adult criminals is certainly smaller than that of younger age groups, it is not altogether insignificant (Goldstein, 1987). A high number of arrests in the geriatric population are due to "driving under the influence." The geriatric population commits violent crimes similar to young people but in much smaller numbers (Palmiotto, Kingshott, & Hegstrom, 2013). If a geriatric criminal commits a crime while significantly mentally impaired, or later develops such an impairment, then the issue of mental competency in the criminal justice system could become a significant factor in the outcome of the legal proceedings.

The first occasion at which legal competency can arise in the criminal justice system involves the mental capacity to waive *Miranda* rights. These rights derive from the landmark US Supreme Court decision, *Miranda v. Arizona* (1966), which required police officers to warn potential criminal defendants of their constitutional right against self-incrimination and their right to counsel before police interrogation. Miranda warnings also contain the caveat that should a defendant choose to speak to the police, those statements can be used as evidence in future legal proceedings. The waiver of these rights presumes that the act was voluntary, knowing, and intelligent. In essence, the forfeiture of Miranda rights parallels the informed-consent process permitting medical treatment. Thus, a certain minimal level of cognitive functioning is required in order for individuals competently to waive their rights.

Research has shown that minors have varying degrees of comprehension in executing a *Miranda* waiver (Ferguson & Douglas, 1970; Grisso, 1981). Moreover, case law has invalidated confessions obtained from minors whose competency to waive *Miranda* rights was considered faulty because of age (e.g., *In re Patrick W*, 1972) or intellectual disability (e.g., *In re Roderick P*, 1979, 1980). A similar paradigm can be conceptualized for older adults. Those with impairment in cognitive function owing to dementia or other organic mental disorders could, in theory, be found incompetent to waive *Miranda* rights. This forensic issue would most likely be raised after the defendant had made legally damaging statements, if the question of competence had not been considered by the police at the time of the *Miranda* warning. In the absence of significant cognitive dysfunction, a *Miranda* waiver could permit the admission into evidence of an elderly suspect's confession, even if that confession was influenced by delusional beliefs or auditory hallucinations (*Colorado v. Connelly*, 1986).

The trial process for those accused of crimes begins with the first meeting with an attorney and does not conclude until the pronouncement of a sentence by the judge. The Anglo-American legal tradition has shaped our belief that a defendant must be competent to stand trial throughout this period. Our present legal standard derives from the landmark US Supreme Court case, *Dusky v. United States* (1960), which defines the criteria for competency to stand trial. In order to be found competent to stand trial, the defendant must demonstrate: (1) "sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding"; and (2) "a rational as well as factual understanding of the proceedings taken against him" (p. 402).

Clinical evaluation of competency to stand trial has been well studied, with various investigators proposing the use of specific instruments to assess this competency (Grisso, 1987; McGarry, Lipsett, & Lelos, 1973). While the most frequent conditions associated with a legal finding of incompetency to stand trial are psychotic disorders, a severely cognitively impaired person could also meet at least one of the criteria necessary to qualify for incompetency to stand trial.

A finding of incompetency to stand trial does not dismiss the legal action against the defendant, but merely delays the courtroom proceedings until such time that the defendant's mental condition has improved and competency is restored. While most defendants with psychotic disorders can be effectively treated such that they regain competence, defendants suffering from mental conditions associated with permanent cognitive dysfunction are unlikely to improve to the extent that they can become competent to stand trial. Depending on the particular jurisdiction and the nature of the criminal charges, a defendant who will not be able to meet the standard in the foreseeable future may find the charges dismissed with or without accompanying civil commitment. In cases of minor crimes perpetrated by individuals who are unlikely to regain their competency in the foreseeable future, the US Supreme Court (*Jackson v. Indiana*, 1972) has limited the incarceration of those defendants found incompetent to stand trial. In addition, several states have statutes setting specific time limits during which a defendant can be held as incompetent to stand trial.

Our legal definitions of who is capable of committing a crime derive from English common law (Platt & Diamond, 1966). With regard to age, all juveniles under 7 years old were historically considered to lack the capacity to commit a crime, while criminal intent was possible under certain circumstances for minors between the ages of 7 and 14. Most states continue to follow English common law by providing young children an *infancy defense* of incompetency. For example, in California, minors under the age of 14 are by law not capable of committing a crime, unless there is *clear proof* that they knew the wrongfulness of their behavior (*People v. Olsen*, 1984).

Another class of persons who are incapable of committing a crime are the legally insane. The District of Columbia and 47 states have established an insanity defense, based either on a variation of the *M'Naghten* rules (*Regina v. M'Naghten*, 1843) or on the American Law Institute (ALI) Model Penal Code rule (Callahan, Mayer, & Steadman, 1987). The *M'Naghten* prototype states that a defendant would have been legally insane if, at the time of the crime, he or she was incapable of knowing (understanding or appreciating) the nature and quality of the act or was incapable of distinguishing right from wrong. The ALI rule states that the defendant would have been legally insane if, at the time of the crime, he or she lacked substantial capacity to appreciate the criminality of the act or to conform his or her behavior to the requirements of law. Putting aside a complex analysis of these insanity standards, both contain a wrongfulness clause by which a defendant can be found insane. Platt and Diamond (1966) have pointed out the similarity between the infancy defense for young children and the insanity defense used to negate criminal responsibility for older adolescents and adults. A critical component of the insanity defense involves the competency to commit a crime or the capacity to comprehend that the act was wrong or illegal. Like young children, older adults who suffer from impairment in cognitive functioning may not have the requisite mental capacity to commit crimes, though they can have the physical ability to do so.

In many jurisdictions, laws providing for diminished capacity, diminished responsibility, or partial insanity can reduce the severity of the criminal charge if the defendant is convicted. For example, without proof that a person had the requisite mental state, a defendant who stood accused of homicide would be convicted of manslaughter instead of murder. Severely cognitively impaired individuals may qualify under these provisions. In addition, if a crime is committed while under the influence of medication-induced organicity, the perpetrator could be considered involuntarily intoxicated and thereby relieved of criminal responsibility on the basis of the insanity or unconsciousness defense. On the other hand, these defenses would be invalidated if the crime followed the knowing ingestion of alcohol or drugs, including prescription drugs, when the deleterious side-effects are understood. The increased vulnerability to the untoward effects of ingested substances, especially alcohol, with advancing age potentially raises the legal issue of voluntary intoxication in a variety of criminal cases.

The Supreme Court ruled in *Ford v. Wainwright* (1986) that convicts sentenced to capital punishment cannot be executed if they are mentally incompetent. Competency to be executed, though determined by state law, generally requires that an individual knows the nature and consequences of the impending punishment, that is, the reason for the execution and its finality. In the *Ford* case, the prisoner first became incompetent when he developed a psychosis while incarcerated on death row. In contrast, the Supreme Court ruled that intellectual disability *per se* was the insufficient cause to commute a death sentence (Penry v. Lynaugh, 1989).

While execution is rare in adult prisoners, it is even less likely to occur in the geriatric population. In the penalty-phase hearing of a capital trial, the jurors are instructed to consider all mitigating as well as aggravating factors before imposing the death sentence (*Lockett v. Ohio*, 1978). In the case of an elderly defendant, advanced age itself could be construed as a mitigating factor, as well as the knowledge that the imposition of a long prison sentence accomplishes the same fatal outcome. According to the article 4 (5) of American Convention on Human Rights, capital punishment shall not be imposed on persons who, at the time of the crime committed, were over the age of 70. By 2011, of the 93 countries in the world that retained the death penalty, 10 explicitly prohibited the execution of an individual that has reached a specific age limit, ranging from 60 in Guatemala to 80 in Taiwan.

Competency to be a witness, or testimonial capacity, could arise in either the civil or criminal setting. The evaluation of this competency involves assessing the witness's reliability of memory, ability to perceive reality accurately, vulnerability to suggestion, and understanding of the obligation to testify truthfully (Melton et al., 1987). Of particular relevance to the elderly witness is an evaluation of the reliability of memory, since disorders associated with aging are more likely to affect memory than the other three capacities. If a witness' fitness is challenged in court, the trial judge can conduct a qualification examination (voir dire) before that witness is permitted to testify.

Confidentiality

Confidentiality has stood the test of time as a fundamental covenant of medical practice; both the Hippocratic Oath and the current Principles of Medical Ethics (American Psychiatric Association, 2013) contain a pledge of silence regarding professional secrets. However, strict confidentiality is not an absolute value. Relevant patient information may be legally and ethically released without the patient's consent, as necessary to protect life, or under proper legal compulsion. Sharing information authorized by the patient presents no difficulties. Psychiatrists may also need to document certain confidential clinical data in order to institute civil commitment or conservatorship proceedings. In these instances, the decision to overrule a patient's insistence on secrecy is consistent with legal regulations and the desire to preserve life. In addition, all jurisdictions have enacted mandatory reporting laws to alert the authorities of potentially harmful conditions. For example, statutes commonly require health care providers to report patients suffering from any one of several communicable diseases to the local public health department. In the case of the elderly persons, there are two principal reportable conditions: elder abuse and the elderly person as a danger to self or other.

Akin to child abuse−reporting laws, many states have enacted statutes to protect the aged from abuse, which can assume many forms: passive or active neglect; verbal, emotional, or psychological abuse; physical abuse; material or financial misappropriation; and violation of rights (Kosberg, 1987). However, the problem is oftentimes invisible, as it occurs within the home and out of public view. Unlike child-abuse regulations, elder-abuse laws have been criticized as being imprecise, variable across jurisdictions, ineffective, and an infringement on personal liberty (Faulkner, 1982; Salend, Kane, Satz, & Pynoos, 1984).

Since the California Supreme Court decision of *Tarasoff v. Regents of the University of California* (1976), federal and state courts (Mills, Sullivan, & Eth, 1987) have adjudicated similar rules propounding the psychotherapist's legal duty to protect others when and if a patient has made a serious threat of physical harm toward an identifiable victim. In a situation of threatened violence toward others, the geriatric patient would be treated in an identical fashion as other adult patients. Moreover, serving and protecting the public interest, California has specifically mandated the reporting by physicians of diseases associated with dementia, including Alzheimer's disease and related disorders (California Health and Safety Code Section 103900). The purpose of this statute is the protection of motorists and pedestrians from a vehicle operator who may be impaired. In fact, several duty-to-protect cases involving psychiatric patients have arisen when third parties suffered injuries in automobile accidents (Felthous, 1990).

Perhaps the most common, though far less dramatic, are the conflicts over confidentiality arising in the context of involvement with the elderly patient's family. The wish to share clinical impressions with concerned relatives in order to facilitate treatment planning may clash with the patient's insistence that all clinical material remain private. Even in the first visit, the health care professional may wish to question family members in order to augment an incomplete or confusing history obtained from a cognitively impaired patient. In the case of a progressive dementia, the role of family support broadens as the patient becomes increasingly disabled. It is therefore advisable early in the treatment to obtain, while the patient is competent, written consent for release of information. Occasionally that permission is refused, as the incapacitated patients may insist on strict confidentiality as a way of gaining some control over their lives. This problem may be more likely in a situation in which adult children have assumed caretaking roles for their own parents. Interpretation of this dynamic may promote resolution of the conflict. If, however, the patient adamantly refuses to permit disclosure, the physician is effectively prevented from violating confidentiality until such time as the patient relents or a conservator is appointed by the court. Ultimately, appropriate medical information, such as the diagnosis of a hereditary disease, may be divulged to family members after the patient's death (American Psychiatric Association, 1987).

Boundary issues

Despite numerous attempts at cost control, the total personal health care expenditures in the United States have continued to accelerate. The health care share of GDP is expected to rise from 17.9% in 2016 to 19.7% by 2026 (CMS, 2017).

Economic reality dictates that some form of rationing may be inevitable. Callahan (1990) in particular has criticized the explosion of expensive new medical technology and our expectation of unlimited scientific progress. In an era of budgetary controls, the use of new technology must be contained, even at the expense of potential life-extending benefits. Economists and ethicists have also decried the provision of excessive care to the dying, care that wastes finite resources and may actually harm rather than help fatally ill patients (Scitovsky & Capron, 1986).

Articles have appeared in the literature suggesting that physicians are already allocating scarce critical care resources according to such factors as bed availability and prognosis (Luce, 1990). What remains unresolved is the significance of age in determining the priority for scarce medical-care resources. Does the foreshortened life expectancy and diminished vigor of old age justify placing the elderly at the end of the waiting line for transplants, intensive care beds, and magnetic resonance imaging scans? At least one commentator (Kilner, 1989) has argued that age *per se* is not an appropriate criterion; rather, medical factors independent of age should alone determine the patient's eligibility and priority for expensive and scarce specialized care. However, it has been abundantly clear that the elderly receive a disproportionately small share of the available mental health care services. While the average medical patient with a psychiatric diagnosis has a 40% chance of consulting a psychiatrist, the probability for an otherwise comparable elderly patient is only 3% (Schurman, Kramer, & Mitchell, 1985). In a recent palliative care program directors survey, only 10% identified a psychiatrist as a member of the treatment team (Patterson, Croom, Teverovsky, & Arnold, 2014).

Research consent in the elderly

The importance of research in geriatric mental health cannot be overvalued. Without clinical investigation, progress in the understanding and treatment of psychiatric disorders will be stifled. Although there is no dispute over the need for research, there are many obstacles to its conduct in this patient population. For instance, as a function of cognitive deficits and old age, Alzheimer's disease victims, especially if they reside in long-term care facilities, are particularly vulnerable to exploitation by overzealous researchers. The best means of safeguarding the process of patient participation is through careful attention to the requirement of voluntary informed consent, which is generally recognized as a prerequisite for the inclusion of human subjects in biomedical research (Thorogood et al., 2018).

In 2003, a task force on decisional capacity examined and proposed the process of determination of decisional capacity in subjects participating in research protocols (Jeste et al., 2003). The assessment of decision-making capacity procedure included using a standardized and validated instrument that can be tailored to the intended study as the MacArthur Competence Assessment Tool (Appelbaum & Grisso, 1995, 2001), followed by a post consent quiz to explore and document the subject's knowledge of the critical and essential elements in the informed consent form. Study investigators may suggest alternative procedures for assessing decision-making capacity though these must be reviewed by the Institutional Review Board prior to subject enrollment. The assessment is followed by documentation of the process, the decision-making capacity determination and the instrument and post-test used for this matter.

Consent functions both to protect the unsuspecting patient from deceptive recruitment and to permit the willing patient to enter a study that promises little benefit and potential risk. Consequently, the consent process well serves the investigator and subject alike.

Informed consent for research, as for medical care, presupposes that the patient has the mental ability to comprehend the study procedures with their attendant risks and benefits. Incompetent patients lack the mental capacity to offer meaningful consent to treatment or research. However, it is these very patients, for example, those with pronounced Alzheimer's disease, who may be the most desirable subjects. Although the patient's surrogate can offer substitute consent for treatment, some constraints are placed on a surrogate's ability to expose another person to the research situation. The altruistic decision to sacrifice bodily integrity for the sake of others ought to be reserved for the individual in jeopardy (Eth & Mills, 1989). One approach to mitigating this limitation is to distinguish therapeutic from nontherapeutic research. According to this dichotomy, proxy decision-makers may freely approve those research projects in which there is the intent and reasonable probability of improving the health or well-being of the subject, such as an experimental drug protocol. Patients' representatives would be limited in their ability to consent to those nontherapeutic studies that carry only minimal risk. Consent for future studies could be solicited from patients in early stages of illnesses while they had the level of decision-making capacity necessary to conclude a meaningful choice and express their preferences about future participation in research and data sharing. An argument could be made that the previously obtained consent would be binding later when the patient was no longer competent (Thorogood, Deschênes St-Pierre, & Knoppers, 2017).

Conclusion

This chapter's review of forensic and ethical issues may appear daunting at first glance. Many clinicians find these sorts of problems especially vexing, because they involve areas in the law and moral philosophy seemingly far removed from their usual medical and psychiatric concerns. However, taken together, these legal and ethical difficulties are seen to arise from a small number of manageable principles accessible to the professional reader. By identifying underlying themes of competency, consent, or confidentiality, a variety of common dilemmas can be framed and analyzed to suggest a reasonable resolution. In that vein, serious attention to the forensic and ethical domains will enhance clinical efficacy and personal satisfaction in working with this age group.

References

American College of Physicians. (1989). Ethics manual. *Annals of Internal Medicine*, *111*, 245–252, 327–335.

American Psychiatric Association. (1987). Guidelines on confidentiality. *American Journal of Psychiatry*, *144*, 1522–1526.

American Psychiatric Association. (2013). *Principles of medical ethics*. Arlington, VA: American Psychiatric Association.

Appelbaum, P. S., & Grisso, T. (1995). The MacArthur Treatment Competence Study. I: Mental illness and competence to consent to treatment. *Law and Human Behavior*, *19*(2), 105–126.

Appelbaum, P. S., Grisso, T. (2001). The macarthur competence assessment tool for clinical research. doi:10.1037/t11946-000.

Baker, F. M. (1986). Legal issues affecting the older patient. *Hospital and Community Psychiatry*, *37*, 1091–1093.

Baker, F. M., Parr, I. N., & Yesavage, J. A. (1986). *An overview of legal issues in geriatric psychiatry*. Washington, DC: American Psychiatric Association.

Barber v. Superior Court, 147 Cal. App. 3d 1006, 195 Cal, Rptr. 484 (1983).

Bellacosa, J. W. (1990). The fusion of medicine and law for in extremis: Health and medical decisions. *Bulletin of the American Academy of Psychiatry and the Law*, *18*, 5–21.

Billick, S. B. (1986). Developmental competency. *Bulletin of the American Academy of Psychiatry and the Law*, *14*, 301–309.

Bok, S. (1978). *Lying: Moral choice in public and private life*. New York: Pantheon.

Callahan, D. (1990). Rationing medical progress: The way to affordable health care. *New England Journal of Medicine*, *322*, 1810–1813.

Callahan, L., Mayer, C., & Steadman, H. J. (1987). Insanity defense reforms in the United States—Post-Hinckley. *Mental and Physical Disability Law Reporter*, *11*, 54–59.

Canterbury v. Spence, 464 F.2d 772 (D.C. Circuit 1972).

Centers for Disease Control and Prevention. The state of aging and health in America 2013. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.

CMS office of the actuary releases 2017-2026 projections of national health expenditures. (2018, February 14). Retrieved from https://www.cms.gov/newsroom/press-releases/cms-office-actuary-releases-2017-2026-projections-national-health-expenditures

Colorado v. Connelly, 107 S.Ct. 515 (1986).

Cruzan v. Director, Missouri Department of Health, US. Supreme Court, No. 88–1503, (Decided June 25. 1990).

deWachter, M. A. M. (1989). Active euthanasia in the Netherlands. *Journal of the American Medical Association*, *262*, 3316–3319.

Dungen, P. V., Kuijk, L. V., Marwijk, H. V., Wouden, J. V., Charante, E. M., Horst, H. V., & Hout, H. V. (2014). Preferences regarding disclosure of a diagnosis of dementia: A systematic review. *International Psychogeriatrics*, *26*(10), 1603–1618. Available from https://doi.org/10.1017/s1041610214000969.

Dunn, L. B., Fisher, S. R., Hantke, M., Appelbaum, P. S., Dohan, D., Young, J. P., & Roberts, L. W. (2013). "Thinking about it for somebody else": Alzheimers disease research and proxy decision makers translation of ethical principles into practice. *The American Journal of Geriatric Psychiatry*, *21*(4), 337–345. Available from https://doi.org/10.1016/j.jagp.2012.11.014.

Dusky v. United States, 362 U.S. 402 (1960).

Eth, S. (1990). Psychiatric ethics: Entering the 1990s. *Hospital and Community Psychiatry*, *41*, 384–386.

Eth, S., & Mills, M. J. (1989). Ethical issue (in organic mental syndromes). In T. B. Karasu (Ed.), *Treatments of psychiatric disorders* (pp. 994–1008). Washington, DC: American Psychiatric Association.

Eth, S., & Robb, J. W. (1986). Informed consent. In D. K. Kentsmith, S. A. Salladay, & P. A. Miya (Eds.), *Ethics in mental health practice* (pp. 83–110). Orlando, FL: Grune & Stratton.

Faulkner, L. R. (1982). Mandating the reporting of suspected cases of elder abuse: An inappropriate, ineffective and ageist response to the abuse of older adults. *Family Law Quarterly*, *16*, 69–91.

Felthous, A. R. (1990). The duty to warn or protect to prevent automobile accidents. In R. I. Simon (Ed.), *American psychiatric press review of clinical psychiatry and the law* (Volume 1, pp. 221–238). Washington, DC: American Psychiatric Press.

Ferguson, B., & Douglas, A. C. (1970). A study of juvenile waiver. *San Diego Law Review*, *7*, 39–54.

Ford v. Wainwright, 106 S.Ct. 2595 (1986).

Gallo, J. J., & Lebowitz, B. D. (1999). The epidemiology of common late-life mental disorders in the community: Themes for the new century. *Psychiatric Services*, *50*(9), 1158–1166. Available from https://doi.org/10.1176/ps.50.9.1158.

Glezer, A., & Devido, J. J. (2017). Evaluation of the capacity to marry. *Journal of the American Academy of Psychiatry and the Law*, *45*(3), 292–297.

Goldstein, R. L. (1987). Non compos mentis: The psychiatrist's role in guardianship and conservatorship proceedings involving the elderly. In R. Rosner, & H. I. Schwartz (Eds.), *Geriatric psychiatry and the law* (pp. 269–278). New York: Plenum.

Grisso, T. (1981). *Juveniles' waiver of rights: Legal and psychological competency*. New York: Plenum.

Grisso, T. (1987). *Evaluating competencies*. New York: Plenum.

Grisso, T., & Appelbaum, P. (1998). *Assessing competence to consent to treatment: A guide for physicians and other health professionals*. New York: Oxford University.

Grannum v Berard, 422 P 2d 812, 814 (Wash 1967).

In re Eichner, 438 N.Y.S. 266 (1981).

In re Quinlan, 70 NJ. 355 A.2d, cert. denied 429 US. 992, (1976).

Jackson v. Indiana, 925 S.CL 1845, 32 L.Ed.2d 694 (1972).

Jeste, D., Braff, D., Dunn, L., Johnson, S., Masys, D., Palmer, B., ... Scheiderman, L. (2003, January). *Procedures for determination of decisional capacity in persons participating in research protocols by The UCSD Task Force on Decisional Capacity*. <https://irb.ucsd.edu/DecisionalCapacityAssessment.pdf>.

Jonsen, A. R., Siegler, M., & Winslade, W. J. (1986). *Clinical ethics* (2nd Ed). New York: Macmillan.

Katz, J. (1984). *The silent world of doctor and patient*. New York: Free Press.

Kilner, J. F. (1989). Age criteria in medicine: Are the medical justifications ethical? *Archives of Internal Medicine*, *149*, 2343–2346.

Kosberg, J. I. (1987). Abuse of the elderly: An overview of the problem and solutions. In R. Rosner, & H. I. Schwartz (Eds.), *Geriatric psychiatry and the law*. New York: Plenum.

Leo, R. J. (1999). Competency and the capacity to make treatment decisions: A primer for primary care physicians. *Primary Care Companion to the Journal of Clinical Psychiatry*, *1*(5), 131–141.

Lo, B., Rouse, F., & Dornbrand, L. (1990). Family decision-making on trial: Who decides for incompetent patients? *New England Journal of Medicine*, *322*, 1228–1232.

Lockett v. Ohio, 57 L.Ed.2d 870 (1978).

Low, L., McGrath, M., Swaffer, K., & Brodaty, H. (2018). Communicating a diagnosis of dementia: A systematic mixed studies review of attitudes and practices of health practitioners. *Dementia*, *18*, 2856–2905.

Luce, J. M. (1990). Ethical principles in critical care. *Journal of the American Medical Association.*, *263*, 696–700.

Marson, D. C., & Hebert, T. (2008a). Financial capacity. In B. L. Cutler (Ed.), *Encyclopedia of psychology and the law* (Vol. 1, pp. 313–316). Sage Publications.

Marson, D. C., & Hebert, T. (2008b). Testamentary capacity. In B. L. Cutler (Ed.), *Encyclopedia of Psychology and the Law* (Vol. 2, pp. 798–801). Sage Publications.

Martin, R., Griffith, H. R., Belue, K., Harrell, L., Zamrini, E., Anderson, B., ... Marson, D. (2008). Declining financial capacity in patients with mild Alzheimer disease: A one-year longitudinal study. *The American Journal of Geriatric Psychiatry*, *16*(3), 209–219. Available from https://doi.org/10.1097/jgp.0b013e318157cb00.

McGarry, A.L., Lipsett, P.D., & Lelos, D. (1973). *Competency to stand trial and mental illness: Final report. (DHEW Publ. No. (HSM) 73-9105)*. Rockville, MD: National Institute of Mental Health.

Melton, G. B., Petrila, J., Poythress, N. G., & Slobogin, C. (1987). *Psychological evaluations for the courts*. New York: Guilford.

Miles, S. H., Singer, P. A., & Siegler, H. (1989). Conflicts between patients' wishes to forego treatment and the policies of health care facilities. *New England Journal of Medicine*, *321*, 48–50.

Mills, M. J., Sullivan, G., & Eth, S. (1987). Protecting third parties: A decade after Tarasoff. *American Journal of Psychiatry*, *144*, 68–74.

Miranda v. Arizona, 384 US. 436, 1966.

Moye, J., Marson, D. C., & Edelstein, B. (2013). Assessment of capacity in an aging society. *The American Psychologist*, *68*(3), 158–171.

Murphy, D. J. (1988). Do-not-resuscitate orders: Time for reappraisal in long-term-care institutions. *Journal of the American Medical Association*, *260*, 2098–2101.

Overman, W., & Stoudermire, A. (1988). Guidelines for legal and financial counseling of Alzheimer's disease patients and their families. *American Journal of Psychiatry*, *145*, 1495–1500.

Overton, E., Appelbaum, P. S., Fisher, S. R., Dohan, D., Roberts, L. W., & Dunn, L. B. (2013). Alternative decision-makers perspectives on assent and dissent for dementia research. *The American Journal of Geriatric Psychiatry*, *21*(4), 346–354. Available from https://doi.org/10.1016/j.jagp.2013.01.027.

Palmiotto, M., Kingshott, B., & Hegstrom, C. (2013). Older criminals and the crimes they commit.

Patterson, K. R., Croom, A. R., Teverovsky, E. G., & Arnold, R. (2014). Current state of psychiatric involvement on palliative care consult services: Results of a national survey. *Journal of Pain and Symptom Management*, *47*(6), 1019–1027. Available from https://doi.org/10.1016/j.jpainsymman.2013.06.015.

People v. Olsen, 36 Cal.3d 638 (1984).

Penry v. Lynaugh. 109 S.Ct. 293Y (1989).

Perl, M., & Shelp, E. E. (1982). Psychiatric consultation masking moral dilemmas in medicine. *New England Journal of Medicine*, *307*, 618–621.

Perr, I. N. (1981). Wills, testamentary capacity and undue influence. *Bulletin of the American Academy of Psychiatry and the Law*, *9*, 15–22.

Piaget, J., & Inhelder, B. (1969). *The psychology of the child*. New York: Basic Books.
Platt, A., & Diamond, B. L. (1966). The origins of the "right and wrong" test of criminal responsibility and its subsequent development in the United States: An historical survey. *California Law Review*, *54*, 1227–1258.
President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. (1983). *Deciding to forego life-sustaining treatment*. Washington, DC: Government Printing Office.
Redmond, F. C. (1987). Testamentary capacity. *Bulletin of the American Academy of Psychiatry and the Law*, *15*, 247–256.
Regina v. M'Naghten, 10 Cl. & F, 200, 8 Eng. Rep. 718 (1843).
Roberts, L. W., & Kim, J. P. (2016). Are individuals living with mental illness and their preferred alternative decision-makers attuned and aligned in their attitudes regarding treatment decisions? *Journal of Psychiatric Research*, *78*, 42–47. Available from https://doi.org/10.1016/j.jpsychires.2016.03.004.
Sabatino, C. P., & Basinger, S. L. (2000). Competency: Reforming our legal fictions. *Journal of Mental Health and Aging*, *6*(2), 119–144.
Salend, E., Kane, R. A., Satz, M., & Pynoos, J. (1984). Elder-abuse reporting: Limitations of statutes. *Gerontologist*, *24*, 61–69.
Schloendorff v. Society of New York Hospital, 211 N.Y. 125, 105 NE. 92 (1914).
Shulman, K. I., Cohen, C. A., & Hull, I. (2005). Psychiatric issues in retrospective challenges of testamentary capacity. *International Journal of Geriatric Psychiatry*, *20*, 63–69. Available from https://doi.org/10.1002/gps.1257.
Schurman, R. A., Kramer, P. D., & Mitchell, J. B. (1985). The hidden mental health network. *Archives of General Psychiatry*, *42*, 89–94.
Scitovsky, A. A., & Capron, A. M. (1986). Medical care at the end of life: The interaction of economics and ethics. *Annual Review of Public Health*, *7*, 59–75.
Simon, R. I. (1989). Silent suicide in the elderly. *Bulletin of The American Academy of Psychiatry and the Law*, *17*, 83–95.
Singer, P. A., & Siegler, M. (1990). Euthanasia—A critique. *New England Journal of Medicine*, *322*, 1881–1883.
Sprung, C. L. (1990). Changing attitudes and practices in foregoing life-sustaining treatments. *Journal of the American Medical Association*, *263*, 2211–2215.
Steinbrook, R., & Lo, B. (1984). Decision making for incompetent patients by designated proxy: California's new law. *New England Journal of Medicine*, *310*, 1598–1601.
Stiegel, L. A. (2012). An overview of elder financial exploitation. *Generations*, *36*, 73–80.
Superintendent of Belchertown State School v. Saikewicz, 370 N.E.2d (Mass 1977).
Tarasoff v. Regents of the University of California. 17 Cal.3d 425, 551 P.2d 334 (1976).
Thorogood, A., Deschênes St-Pierre, C., & Knoppers, B. M. (2017). Substitute consent to data sharing: A way forward for international dementia research? *Journal of Law and the Biosciences*, *4*, 133–158. Available from https://doi.org/10.1093/jlb/lsw063.
Thorogood, A., Mäki-Petäjä-Leinonen, A., Brodaty, H., Dalpé, G., Gastmans, C., Gauthier, S., … Bobrow, M. (2018). Consent recommendations for research and international data sharing involving persons with dementia. *Alzheimers & Dementia*, *14*(10), 1334–1343. Available from https://doi.org/10.1016/j.jalz.2018.05.011.
Trollor, J. N., Anderson, T. M., Sachdev, P. S., Brodaty, H., & Andrews, G. (2007). Prevalence of mental disorders in the elderly: The Australian National Mental Health and Well-Being Survey. *The American Journal of Geriatric Psychiatry*, *15*(6), 455–466. Available from https://doi.org/10.1097/jgp.0b013e3180590ba9.
Wanzer, S. H., Federman, D. D., Adelstein, S. J., Cassel, C. K., Cassem, E. H., Cranford, R. E., … Von Eys, J. (1989). The physician's responsibility toward hopelessly ill patients. *New England Journal of Medicine*, *320*, 844–849.
Wells, C. E. (1979). Pseudodementia. *American Journal of Psychiatry*, *136*, 895–900.
WHO, Mental health of older adults. (2017, December 12). Retrieved from https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults.
Veatch, R. M. (1976). *Death, dying, and the biological revolution*. New Haven: Yale University Press.

Further reading

Appelbaum, P. S., & Grisso, T. (1988). Assessing patients' capacities to consent to treatment. *New England Journal of Medicine*, *319*, 1635–1638, erratum 1989, 320, 748.
In re Patrick W, 84 Cal.App.3d 520 (1978), vacated California v. Patrick W, 61 L.Ed.2d 870 (1979), on remand 104 Cal.App.3d 615 (1980), cert. denied 66 L.Ed.2d 824, (1981).
In re Roderick P, 7Cal.3d 801 (1972).
Mental health of older adults. (n.d.). <https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults>.
Thompson v. Oklahoma, 101 L.Ed.2d 702, 108 S.Ct. 2687 (1988).

Chapter 27

The economics of geriatric mental health care

Nicholas T. Bott[1,2]

[1]Clinical Excellence Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States, [2]Department of Psychology, PGSP-Stanford Consortium, Palo Alto University, Palo Alto, CA, United States

Introduction

We are in the midst of an unprecedented acceleration in the aging of populations across the globe. Between 2015 and 2050, the proportion of adults age 60 and over will almost double from 12% to 22%, an absolute increase from ~900 million to over 2 billion (Yasamy, Dua, Harper, & Saxena, 2019). This acceleration is expected to result in substantially increased health care needs, including mental health care for older adults. Globally, 20% of adults over the age of 60 live with a mental or neurological disorder, and these conditions account for 6.6% of all disability-adjusted life years among this age group. Furthermore, these conditions account for 17.4% of Years Lived with Disability globally (Mental Health of Older Adults, 2019). In the United States, the number of older adults currently living with mental health disorders is around 8 million, and this number is expected to increase to around 14 million over the next two decades (Committee on the Mental Health Workforce for Geriatric Populations, Board on Health Care Services, & Institute of Medicine, 2012; US Census Bureau, 2010). Currently, less than 40% of older adults with mental health disorders receive treatment of any kind. Primary care physicians are often the initial —and only— site of treatment, with less than 15% providing minimally adequate mental health care for this population (Wang et al., 2005).

In many respects, the challenges associated with providing mental health care to older adults are similar to those in other age groups. Fundamentally, funding policies and mechanisms have significant downstream effects on care eligibility, the location and context of care, provider incentives and behaviors, and the quality of care itself (Frank & Glied, 2006). It is not an exaggeration to say that state and federal funding policies and mechanisms have created and continue to shape the economy of geriatric mental health care. In the 19th century, locally supported asylums and almshouses provided most of the care for older adults with disabling mental health issues. These structures evolved into state-run—and state-funded—hospital systems in the early- and mid-20th century (Grob, 1987). The advent of Medicare and Medicaid in the 1960s as federally supported social insurance programs further shifted the financial accountability of geriatric mental health care from states to the federal government. The policies surrounding psychiatric care within Medicare and Medicaid further dictated the form of generalized psychiatric mental health care in public and private settings (Lave & Goldman, 1990). The incomplete socialization of geriatric mental health care resulted in a divestment of local dollars and infrastructure for geriatric mental health, narrowing state resources to Medicaid-funded nursing homes (Goldman, Feder, & Scanlon, 1986). This, in combination with limited reimbursement mechanisms for Medicare-based specialty mental health services, further isolated the financing of geriatric mental health care through Medicaid.

The impact of health policy on geriatric mental health

While acceleration of the proportion of the US population over the age of 65 creates the conditions for increased health care utilization and cost, the Baby Boomer generation (born between 1946 and 1964) is also more frequently diagnosed with depression, anxiety disorders, and substance abuse disorders than the preceding generation (The John A. Hartford Foundation, 2011). Higher risk, in combination with increases in longevity and reductions in stigma, all point toward significantly higher numbers of older adults seeking treatment for mental health issues. Currently, almost one in five

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00027-2

older adults in the United States has at least one identified mental health concern, the most prevalent of which are depression, anxiety, and cognitive impairment (State of Mental Health and Aging in America (MAHA), 2019).

The aging of the US population has served as an important catalyst for policy developments in the federal health care system. Perhaps most notably is the passage of the ACA in 2010. The ACA included three major developments: the provision of more affordable health insurance, the expansion of Medicaid for all adults below 138% of the federal poverty line (FPL), and investments in innovative health care delivery models that provide high-value health care. Regarding the first of these developments, passage of the ACA provides tax credits that result in lower costs for health insurance among households with incomes between 100% and 400% of the FPL. In combination with the provision of tax credits, the ACA outlawed the use of preexisting conditions for denial of coverage among payers. While not specifically addressing mental health conditions, the high rates of comorbidity between physical and mental health conditions mean that the elimination of preexisting condition clauses creates the conditions where holistic health care—including mental health care—can take place. Additionally, the ACA eliminated lifetime health care spending caps. The expansion of Medicaid to all adults below 138% of the FPL further assisted in helping to expand health care coverage to the uninsured. To date, 32 states and the District of Columbia have implemented the expansion of Medicaid.

The third major goal of the ACA focused on payment reform in order to incentivize innovative high-value health care delivery models. This goal has provided for innovation that includes mental health care service delivery to older adults. The payment reforms expanded under the ACA focus on shared risk between payers and providers (as opposed to fee-for-service arrangements). These reforms also focused on enhanced care coordination and collaboration with the intent of reducing overutilization and avoidable hospitalizations. One of the delivery models that has continued to see growth and innovation is Medicare advantage (MA) and in many respects, has served as an innovation laboratory for Medicare health care service provision.

Medicare fee-for-service

The Medicare system is a social insurance program that was designed to provide direct medical care benefits for Americans over the age of 65. Enacted in 1965 under Title XVIII of the Social Security Act (SSA O. Health Insurance for the Aged and Disabled, 2019), Medicare was the result of an ongoing national debate regarding national health policy. As a form of public health insurance, Medicare was expanded in 1972 to include younger disabled individuals, as well as older adults who were not Medicare-eligible, provided they paid a monthly coverage premium. The following year, Medicare coverage was extended to individuals with end-stage renal disease (ESRD).

As of 2018, almost 60 million individuals are Medicare beneficiaries, with two-thirds of those beneficiaries enrolled in Medicare fee-for-service ($\sim$40 million) and one-third enrolled in MA ($\sim$20 million) (Total Number of Medicare Beneficiaries, 2019). Of these individuals, 84% are adults over the age of 65. ESRD patients make up approximately 1% of Medicare beneficiaries. Between the years 1991 and 2014, the inflation-adjusted average annual growth rate for Medicare expenditures per enrollee was 5.2%. This is comparable to the 5% average annual growth rate per enrollee in the 1970s and the 5.5% average annual growth rate per enrollee in the 1980s. The average annual growth rate over the past four decades has been 4.9% per year. Put in context, over the same period of time average annual per capita gross domestic product (GDP) has grown 2.1% (Health Care Costs: A Primer—Conclusion, 2014). Whereas in 1965, health care spending accounted for 5% of national GDP, it rose to 15% in 2005 and as of 2017 accounts for 17.9% of national GDP (Centers for Medicare & Medicaid Services, 2018b).

Medicare benefits are almost exclusively limited to acute care services. With respect to mental health care, mental health services are primarily focused on inpatient psychiatric hospitalization, along with physician services associated with hospitalization. Analysis and projections by the Substance Abuse and Mental Health Services Administration (SAMHSA) show an increase in the proportion of Medicare mental health spending as compared with other payers over the past 30 years from 6% in 1986 to 14% in 2014, with a projected 15% share of all mental health care spending in 2020 (Projections of National Expenditures for Treatment of Mental and Substance Use Disorders, 2019). Within Medicare itself, the percentage of costs accounted for by acute psychiatric care has grown from 3.5% in 2003 to 4.5% in 2015. According to 2011 data, 82% of Medicare beneficiaries were at least 65-years-old, and these older adults accounted for 78% of all Medicare spending (Neuman, Cubanski, & Damico, 2015). Forty-one percent of inpatient psychiatric utilization was from older adults, more than half of which are both Medicare and Medicaid eligible (see below) (Medicare Payment Advisory Commission MEDPAC, 2016). The most common diagnosis utilized for these services was psychosis (72.9%). Within the older adult Medicare population, serious mental illness (SMI) and substance use disorder (SUD) are associated with increased health care costs. Utilizing 2010 Medicare claims data, Medicare spend on

older adults with SMI and SUD was $43,792 per beneficiary compared to $8,649 for beneficiaries without SMI or SUD (Medicare Spending for Beneficiaries with Severe Mental Illness and Substance Use Disorder, 2019).

Medicare hospital insurance (Part A)

Medicare hospital insurance, commonly known as Medicare Part A, is available to individuals over the age of 65 and is financed by Social Security payroll taxes paid by employers and employees. Medicare Part A benefits include inpatient hospital care, postacute home health care, short-term skilled nursing facility stays, and hospice care. A standard deductible of $1364 dollars applies to each benefit period or episode of care. With respect to acute inpatient mental health treatment, there is no additional payment for the first 60 days of each benefit period. For days 61−90, there is a $341 copayment for each benefit period, and a $682 copayment for days 91 and beyond until the lifetime limit of 190 days has been reached. In addition to costs associated with inpatient hospital care, Medicare beneficiaries pay 20% of the Medicare-approved amount for mental health services rendered by health care providers during an inpatient hospital treatment.

Supplemental medical insurance (Part B)

Medicare Part B is also described as supplemental medical insurance. Medicare Part B benefits include outpatient hospital care, physician visits, and preventive services. Part B benefits also include lab services, diagnostic services, durable medical equipment (e.g., oxygen), home health care visits, and outpatient mental health care. With respect to mental health care, Medicare Part B benefits include one depression screening per year in a primary care doctor's office, individual and group psychotherapy with physicians or other licensed mental health professionals (clinical psychologists, clinical social workers, clinical nurse specialists, nurse practitioners, and physicians' assistants), family counseling, psychiatric evaluation with medication management, diagnostic tests, a one-time Medicare initiation preventive visit that includes risk factor evaluation for depression, and a yearly wellness visit that includes discussion with a physician about changes in mental health care status. Medicare Part B also covers outpatient mental health services for substance abuse disorders.

Medicare advantage

MA programs represent the fasting-growing form of Medicare fee-for-service in the United States. Approximately one-third of Medicare beneficiaries (∼20 million) are enrolled in MA plans, with enrollment doubling over the past decade (Damico, 2018c). Current Congressional Budget Office estimates project MA enrollment to grow to account for as much as 42% of Medicare beneficiaries by 2028 (Neuman & Jacobson, 2018). Historically, MA was embedded within Part C of Medicare, as a result of the Tax Equity and Fiscal Responsibility Act (TEFRA). TEFRA was passed in 1982 and provided Medicare the ability to contract with privately held capitated, or risk-based, health plans. These plans assume the financial costs associated with the provision of health care for plan enrollees. Rules for implementation of risk-based contracting were finalized within TEFRA in 1985 and MA plans are paid directly by Medicare on a per-member-per-month or PMPM basis. The PMPM cost is determined the prior year and is the result of risk-based cost-forecasting incorporating each beneficiary's health information. MA plan beneficiaries are still required to pay Medicare Part B premiums for physicians' services, but do so through their MA plan policy. In 2018, over half of MA plan beneficiaries paid no additional premiums outside of Part B premiums. The average monthly premium for the remainder was $70 per month (Damico, 2018c).

The early history of MA plans from 1985 to 2003 was largely unsuccessful. Medicare lost money on MA beneficiaries, for a host of reasons, but in large part due to the small market size of MA—only 5% of Medicare beneficiaries enrolled in the early 1990s (Mcguire, Newhouse, & Sinaiko, 2011). In 2003, the Medicare Modernization and Improvement Act (MMA) was passed. While the MMA is most well-known for initiating the Medicare Part D drug benefit, it also had a significant effect on MA. The MMA provided more equitable plan payments for MA plans relative to Medicare fee-for-service. It also created preferred provider organization and special needs programs, which increased enrollment. Finally, risk adjustment methods were updated to provide greater transparency into the expected annualized costs of plan beneficiaries. Beginning in 2004, data were pooled between demographics, ambulatory care, and inpatient diagnoses to create the Medicare Hierarchical Condition Category risk adjustment model (CMS-HCC) (Pope et al., 2004). Conservatively, as much as 10% of the variation in Medicare fee-for-service annual spending was explained with the updated CMS-HCC model. At the same time, risk adjustment models have been shown to underestimate

patients with complex psychiatric illness, such as those seen in safety-net hospitals (Wagner, Almenoff, Francis, Jacobs, & Pal Chee, 2018). As the MA plan market has grown, enrollment has been concentrated in three major health care payers, with over half of MA enrollees in one of three plans. As of 2018, United Healthcare enrolled 25% of all MA beneficiaries, Humana enrolled 17%, and Blue Cross Blue Shield enrolled 13% (Damico, 2018c).

Interestingly, some of the financial stipulations required of MA plans have led to improvements in quality of care in older adults. For example, MA plans are required to limit their beneficiaries' out-of-pocket costs for Medicare services. For 2018, the average MA beneficiary out-of-pocket limit was $5215 (Neuman & Jacobson, 2018). Moreover, in addition to out-of-pocket limits, MA plans are required to use a portion of their marginal profits on "rebate" dollars in order to invest further benefits or return lower premiums to their beneficiaries. In 2018, two-thirds of MA beneficiaries received some form of enhanced benefits, the most common of which are dental care (62%), vision care (77%), and fitness membership benefits (69%) (Damico, 2018c). Overall quality of care among MA plans is mixed, but studies have shown that MA plans outperform Medicare fee-for-service in a number of areas with respect to quality (Newhouse & McGuire, 2014). As of 2018, 74% of all MA plan enrollees are in MA plans with Star ratings of 4 or more (on a scale of 2−5) (Damico, 2018c). Importantly for mental health care specifically, MA plans have been shown to outperform Medicare fee-for-service on preventive and screening services (Gold, 2014; Timbie et al., 2017).

More recently, Centers for Medicare and Medicaid Services (CMS) has provided MA plans the opportunity to offer additional supplementary nondirect medical benefits to their plan beneficiaries. Previously, nondirect medical benefits could not be offered under Medicare. Besides offering further evidence that MA is seen as an innovation test ground, these supplementary benefits are aimed at furthering preventive services and venture into an understanding of health that goes beyond direct medical care. The provision of nondirect medical benefits and services underscores the importance of factors not traditionally linked to health outcomes within Medicare.

Beginning in 2019, MA plans are now permitted to cover a much broader set of services insofar as they are used to diagnose, prevent, or improve the effects of injuries or health conditions or reduce avoidable emergency department visits. These benefits include adult day care services, including transportation to and from the location; home-based palliative care for individuals with life-limiting illnesses and life expectancy greater than 6 months; in-home support services to assist with instrumental activities of daily living and activities of daily living; respite support for caregivers of MA plans, including counseling and training courses caregivers; medically approved non-opioid pain management, standalone memory fitness benefit, home and bathroom safety devices and modifications, transportation, and over-the-counter health-related items and medications.

Another area that has received increased attention over the last several years is the role of social isolation. Social isolation, and the loneliness that often comes as a by-product of this isolation, can have significant health-related consequences including depression and increased risk of cognitive decline. Some MA plans such as CareMore Health provide socialization at clinics as well as through specific social engagement programs to address this issue. Issues such as social isolation form part of a large construct of social determinants of health.

Medicaid and dual-eligible populations

In addition to Medicare, Medicaid is a social insurance program originally enacted by the US Federal government in 1965. Medicaid is a joint federal-state social insurance program that provides financial support for health care services for low-income individuals, including children, expecting women, parents and other related caregivers, disabled individuals, and older adults. As originally enacted, Medicaid required states to provide a minimum set of basic health care benefits in order to receive federal matching funds. As a result of the ACA, beginning in 2014 each state has been given the option to expand eligibility for Medicaid with federal matching funds to all nonelderly adults with income below 138% of the FPL. Analysis of the impact of the ACA Medicaid expansion on health care utilization has shown expansion of insurance coverage, increased access to, and utilization of health care services and improvements in self-reported health. The flow of federal health care resources into expansion states has also risen (Antonisse & Garfield, 2018).

Currently, Medicaid provides for the health care of 7 million older adults (Centers for Medicare & Medicaid Services, 2018a). In addition to paying Medicare premiums for older adults below 138% of the FPL, Medicaid also provides health benefits to older adults including transportation costs to a physician, vision care, dental care, and in some cases home health care, durable medical equipment, and mental health care needs including acute psychiatric hospitalization, psychosocial rehabilitation services, and psychotropic medications. The 2017 breakdown of Medicaid spending on long-term services and supports (LTSS) included 53.8% spending on home health and personal care, 36.4% on nursing facilities, 7.8% on intermediate care facilities for the intellectually disabled, and 2% on mental health facilities

(Distribution of Fee-for-Service Medicaid Spending on Long Term Care, 2018). Perhaps most importantly, Medicaid covers the costs of nursing home care and other LTSS. This is crucial when considering that one-third of adults over 65 need nursing home care.

The terms "dual eligible," or "duals" refer to individuals who meet eligibility criteria for Medicare and who are also eligible for some amount of Medicaid benefits. As of 2013, 92% of dual-eligible individuals were also older adult Medicaid beneficiaries, and duals represent one-fifth of all Medicare beneficiaries (Dual Eligibles as a Percent of Total Medicare Beneficiaries, 2018). Duals have received increasing interest over the past decade because they represent a subpopulation with high medical expenditures. The approximately 12 million Americans included in this category have lower incomes, are sicker, and have higher levels of comorbidity and disability, often including mental illness. As a result of this increased medical complexity, the costs of care for these individuals is almost four times higher than nondual-eligible Medicare beneficiaries (Dual-eligible beneficiaries of Medicare and Medicaid: Characteristics, health care spending, and evolving policies, 2019). In terms of overall cost, as of 2012, while duals made up 20% of all Medicare beneficiaries and 15% of all Medicaid beneficiaries, they accounted for one-third of the total spending for both Medicare and Medicaid (People Dually Eligible).

Forty-one percent of dual-eligible individuals have at least one mental health diagnosis, with almost half of all duals utilizing LTSS (Better Care for People Dually Eligible for Medicare and Medicaid and Health Affairs, 2019). One of the significant factors that challenges the efficient and effective provision of medical care in this population, including mental health care, is the reality that the dual-eligible population is receiving care from two separate payers (Glazer & McGuire, 2002). The lack of coordination between these two payers has led to numerous challenges. The current Administrator of the CMS, Seema Verma, has included lack of coordination, increased care fragmentation, misaligned incentives for payers and providers, and inefficiencies at the administrative and programmatic levels (Better Care for People Dually Eligible for Medicare and Medicaid and Health Affairs, 2019). One of the enduring challenges of health care generally, and mental health care specifically, is that disintegrated care leads to suboptimal outcomes across measures of cost, quality and patient experience (Care for Dual Eligibles, 2019; Minnesota Managed Care Longitudinal Data Analysis, 2016). This reality is particularly present in the treatment of mental health conditions.

Currently, 37 states and the District of Columbia have provided letters of intent indicating a desire to participate in care coordination alignment initiative. CMS has worked with and approved plans in 15 states aimed at deploying innovative care designs to improve Medicare and Medicaid patient coordination. An important component of these care designs is the integration of disparate aspects of health care including primary care, behavioral and mental health, acute care, and LTSS. One such Medicaid-specific model is Medicaid-financed Specialty Home Care. This model focuses on care coordination for individuals with multiple chronic conditions including mental health conditions. One such program demonstrated improvements in general health including blood pressure, cholesterol, and fasting glucose among individuals with SMI (Bartels, Gill, & Naslund, 2015).

Private insurance and out-of-pocket payments

Historically, and in large measure to this day, the US health care delivery system has organized itself around fee-for-service medical care. In this arrangement, health care services are paid for on a service unit basis, agnostic to the quality, cost, or outcomes associated with that unit of health care service. This arrangement results in incentivization for increased health care utilization, since provider revenues increase as the number of health care services provided increases. This incentivization is further catalyzed by the fact that insurance plans often pay for these services on behalf of their customers, who are the patients. Because patients are not solely responsible for the full cost of health care service utilization, the fee-for-service arrangement often leads to overutilization of health care providers and services. This is made clear when one examines the per capita increases in health care costs in the United States relative to GDP. In 2017, health care costs of $3.5 trillion represented 17.9% of GDP. By 2027, that percentage is projected to rise to 19.4% (Sisko et al., 2019).

Out-of-pocket costs among Medicare beneficiaries have continued to grow. In 2013, these costs accounted for 41% of per capita Social Security income with greater shares among older beneficiaries. Current projections estimate a full 50% of average Social Security income to be spent on out-of-pocket health care costs by 2030 (Damico, 2018a). With respect to mental health care costs, Medicare claims data from 2017 found that 3% of PMPM costs were spent on non-serious and persistent mental health conditions, 10% of PMPM costs were spent on serious and persistent mental health conditions, and 11% of PMPM costs were spent on treatment for SUDs. Including all beneficiaries' health care costs,

2% of the average PMPM costs were spent on behavioral health–related care (Potential Economic Impact of Integrated Medical-Behavioral Healthcare, 2017). The breakdown out-of-pocket costs associated with Medicare Parts A and B include:

Medicare Part A	Medicare Part B
Part A deductible: $1364 in 2019	Part B deductible: $185 in 2019
Days 1–60 of inpatient psychiatric care: $0 per day	20% of Medicare-approved amount of health care provider services
Days 61–90 of inpatient psychiatric care: $341 per day	~20% copayment for outpatient mental health services
>90-day inpatient psychiatric care: $682 per day up to 60 days	~20% coinsurance for outpatient mental health services

Given the potential for high out-of-pocket costs, nearly 30% of Medicare enrollees purchase Medigap supplemental insurance policies to cover out-of-pocket costs associated with Medicare Parts A & B services (Medigap Enrollment and Consumer Protections Vary Across States, 2019). Medigap policies are overwhelmingly utilized by older adults, with uptake variation across states. As with most policies, there are 10 Medigap plan offerings that provide unique sets of benefits. Some are high deductible plans, with others offering more comprehensive coverage (Medigap Enrollment and Consumer Protections Vary Across States, 2019). Monthly premiums for Medigap policies range from $100 to over $250. Outside of Medigap policies, 30% of Medicare beneficiaries utilize employer-sponsored insurance, 22% utilize Medicaid, and nearly 20% have no supplemental coverage (Damico, 2018b).

Another out-of-pocket cost for some older adults is long-term care (LTC) insurance. Beginning in 1974, LTC insurance arose out of a perceived market gap to further protect aging adults in the event that a serious illness or disability resulted in functional impairment and the loss of independence. Importantly, while these policies provided coverage for conditions such as dementia, coverage for psychiatric illness was much more limited. This market was unregulated until the late 1980s when the National Association of Insurance Commissioners released the Long-Term Care Insurance Model Act in 1987 and the Long-Term Care Insurance Model Regulation in 1988. These regulations reigned in a number of the ill-gotten gains over the first decade of the LTC insurance market, which often took advantage of customers. Major areas of reform included the prohibition of post-claim underwriting and post-claim policy cancellation, disclosure of policy replacement to mitigate rampant commissions, disclosure of LTC policy suitability to customers to mitigate the sale of overly comprehensive policies, and market-wide standardization of policy benefit triggers to ensure customers received adequate benefits from their policies. Despite the early success of LTC insurance policies, payers found themselves under water with claims in large part due to the number of older adults living longer with chronic and disabling conditions and very few policy lapses. Today, the LTC insurance market is much smaller and smarter than in decades past. Traditional LTC insurance policies are rare; most have been replaced by life insurance "hybrid" policies that include a LTC rider. Such policies allow the policyholder to draw on tax-free death benefits if they have a serious illness or condition including the need for longer-term care. Unfortunately, coverage for mental health conditions remains sparse among these hybrid solutions.

Policy and infrastructure innovation

There are a number of recent innovations that provide hope for higher-value geriatric mental health care. Some of these innovations are the result of changes in policy, with others the result of novel infrastructure. Increasingly, the challenges in providing better mental health care for older adults are not due to a lack of effective treatments. In fact, a strong body of research has demonstrated common elements among a diverse set of evidence-based treatments for mental health and substance use issues among older adults. In 2012, the committee on the Mental Health Workforce for Geriatric Populations concluded that a combination of systematic outreach and diagnosis, patient and family education and self-management support, provider accountability for outcomes, and close follow-up and monitoring to prevent relapse are the key ingredients for addressing the most common mental health and substance use issues in the older adult population (Committee on the Mental Health Workforce for Geriatric Populations, Board on Health Care Services, & Institute of Medicine, 2012). The remaining challenge has to do with the implementation of policy and infrastructure to support the dissemination of this evidence base. To that end, elements of the ACA and innovations within the MA space continue to support the effective dissemination of high-value care models that address the mental health concerns of older adults.

Quality standards reporting—While not a specific program, the ACA's creation of increased quality standards for behavioral health care provides greater transparency through required data submission and sharing. These data are used

to provide incentives or penalties based on care performance. For example, a 2% penalty is assessed on psychiatric hospitals failing to submit data on time.

Medicare annual wellness visit (AWV)—The Medicare AWV was developed as a preventive measure that can include a depression screen and appropriate referrals to mental health care professionals. Research to date has shown that beneficiaries that utilize the AWV saw a 5.7% reduction in annual health care costs compared to those that did not utilize an AWV (Beckman et al., 2019). Still, according to 2014 data, only 16% of Medicare beneficiaries utilized an AWV (Tao, 2017). While this is an increase from 2011 utilization of just 7.5%, the potential value of this preventive service remains highly underutilized.

Accountable care organizations (ACOs)—ACOs promote the integration of mental health and primary health care through provider bonus eligibility when more efficient and effective care can be demonstrated. Four million Medicare beneficiaries currently participate in ACOs (Gold, 2014). One of the shortcomings of current ACO regulations is the meager commitment to mental health care. Screening, documentation, and care planning for depression is the only mandated ACO quality measure that explicitly addresses mental health. Perhaps not surprisingly, the majority of ACOs do not have formal relationships with mental health care providers. Still operating within a fee-for-service payment arrangement, the lack of meaningful reimbursement for service providers that help provide care coordination and integration results in less than fully integrated mental health care.

Patient-centered medical home (PCMH)—While not new, the popularity of PCMHs increased substantially with the passage of the ACA, as PCMHs were identified as a strategic model for higher-value care. PCMHs hold to five core pillars of care: comprehensive, patient-centered, coordinated, accessible, high quality, and safety (Defining the PCMH, 2019). These pillars support the integration of mental health and primary care in older adult populations, and the ACA provides increased federal monetary support for PCMHs that increase the amount of care coordination—including the embedding of a mental health provider, care management, and clinical information technology (Kessler et al., 2014).

Independence at home—Independence at home is a payment incentive model that uses home-based primary care teams to provide primary care services to chronically ill patients in the home. Independence at home aims to improve health outcomes and reduce Medicare expenditures. This model has demonstrated efficacy in chronically ill populations and under Medicaid section 1915i, individual states can choose to extend home- and community-based services to special populations, including older adults with mental health conditions. These services can include health monitoring and health promotion, case management, psychosocial rehabilitation, clinical services, and behavioral supports.

Program for all-inclusive care of the elderly (PACE)—PACE programs provide all-inclusive care for older adults aged 55 and older, who need nursing care assistance and are able to live independently at the time of enrollment. PACE programs provide care across the continuum of needs for its enrollees, including adult day care, primary and specialty medical care, home health care, prescription drugs, social services, respite care, as well as hospital and nursing home care. PACE programs utilize capitation based upon Medicare rates, with 90% of enrollees dually eligible for both Medicare and Medicaid. Analysis of mental health services in PACE programs has demonstrated the value of mental health integration within comprehensive care programs. On Lok Lifeways, one of the most well-known PACE programs nationally, introduced embedded psychologists, psychiatrists, social workers, and marriage and family therapists into their program in 2005. The addition of these services resulted in a reduction of psychiatric inpatient utilization from 129.4 days per 1000 patients in 2004 to 23.6 days per 1000 patients in 2007 (Ginsburg & Eng, 2009).

Conclusion

Financing of health care for older adults in the United States is accomplished through a combination of public (Medicare and Medicaid) and private insurance and out-of-pocket expenditures by individuals. Over a third of the US population annually receives some form of health care through a public insurance program, and as of 2016 Medicare benefit payments reached $675 billion, accounting for 15% of the federal budget (National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Care Services, & Committee on Health Care Utilization and Adults with Disabilities, 2018). Nine percent (~7.4 million) of Medicaid enrollees are older adults, and as of 2014 Medicaid benefit payments to adults 65 and over accounted for 21% of all Medicaid payments, totaling $96.4 billion (Medicaid Enrollees by Enrollment Group, 2017). Current projections estimate health spending to grow 0.8 percentage points faster than GDP though 2027, resulting in an overall share of GDP of 19.4%.

The next two decades will see an unprecedented rise in the number of older adults in the United States and a concomitant rise in the mental health needs of this population. Despite the reality of these numbers, geriatric mental health needs require more visibility. The lack of understanding regarding age-related mental health vulnerabilities and the minimal education most providers receive regarding the heterogeneity and acuity of geriatric mental health conditions result

in persistent under-identification and delayed treatment initiation of mental health disorders. While the sheer number of older adults may bring more awareness, ageist preconceptions persist regarding mental health conditions such as late-life cognitive decline and depression. These preconceptions will continue to stymie much-needed progress in the access and support for geriatric mental health care. Within fee-for-service Medicare, the limits of mental health care coverage and high associated co-payments continue to prevent adequate inpatient mental health care. Coverage gaps for outpatient mental health care services remain a major impediment for older adults in need of mental health care, and the current coverage offerings for these gaps remains out of financial reach for a large number of older adults. Medicaid spending is expected to see an unprecedented rise in cost over the next decade, with projections of 6% per year, largely driven by the changing enrollment mix. Not surprisingly, older adults with multiple comorbidities, including cognitive impairment and dementia, will drive utilization of LTSS and home and community based services , for which Medicaid is the primary payer.

At the same time, there is evidence that growing awareness of the financial benefits—in terms of lower health care utilization—associated with investment in geriatric mental health care is providing much-needed innovation in addressing the mental health challenges of this group. With 10,000 baby boomers aging into Medicare a day, the political benefits of support from the older adult population will likely serve as an important catalyst for continued policy development. Early analysis of the effects of the ACA has demonstrated some of the benefits of focused policy improvements in care coordination, expanded Medicaid eligibility, and the removal of preexisting condition restrictions for coverage. Similarly, the expansion of MA plans has helped to create a larger market for Medicare-eligible older adults. Risk-based, capitated payment, which serves as a hallmark of MA plans, has underscored the importance of care coordination, patient engagement, and holistic health care benefits, including mental health care. Nevertheless, the size and acceleration of the aging population should remain sobering indicators that the current structures to pay for and service the mental health care needs of our aging population remain inadequate.

References

Antonisse, L., & Garfield, R. (2018). March 28 SAP, 2018. *The effects of Medicaid expansion under the ACA: Updated findings from a literature review* [Internet]. The Henry J. Kaiser Family Foundation. [cited June 2, 2019]. Available from: <https://www.kff.org/medicaid/issue-brief/the-effects-of-medicaid-expansion-under-the-aca-updated-findings-from-a-literature-review-march-2018/>.

Bartels, S. J., Gill, L., & Naslund, J. A. (2015). The Affordable Care Act, accountable care organizations, and mental health care for older adults: Implications and opportunities. *Harvard Review of Psychiatry*, *23*(5), 304–319.

Beckman, A. L., Becerra, A. Z., Marcus, A., DuBard, C. A., Lynch, K., Maxson, E., et al. (2019). Medicare annual wellness visit association with healthcare quality and costs. *The American Journal of Managed Care*, *25*(3), e76–e82.

Better care for people dually eligible for Medicare and Medicaid. Health Affairs [Internet]. [cited May 18, 2019]. Available from: <https://www.healthaffairs.org/do/10.1377/hblog20190423.701475/full/>.

US Census Bureau. (2010). *The older population in the United States: 2010 to 2050* [Internet]. [cited May 19, 2019]. Available from: <https://www.census.gov/library/publications/2010/demo/p25-1138.html>.

Care for dual eligibles. Health Affairs [Internet]. [cited May 18, 2019]. Available from: <https://www.healthaffairs.org/do/10.1377/hpb20120613.634976/full/>.

Centers for Medicare & Medicaid Services. (2018a). *Medicaid report* [Internet]. [cited June 2, 2019]. Available from: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ActuarialStudies/MedicaidReport.html>.

Centers for Medicare & Medicaid Services. (2018b). *Historical* [Internet]. [cited May 18, 2019]. Available from: <https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nationalhealthaccountshistorical.html>.

Committee on the Mental Health Workforce for Geriatric Populations, Board on Health Care Services, & Institute of Medicine. (2012). *The Mental health and substance use workforce for older adults: In whose hands?* [Internet]. In: Eden, J., Maslow, K., Le, M., & Blazer, D. (Eds.), Washington, DC: National Academies Press (US). [cited May 19, 2019]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK201410/>.

Damico, A. (2018a). *Jan 26 KSP, 2018. Medicare beneficiaries' out-of-pocket health care spending as a share of income now and projections for the future* [Internet]. The Henry J. Kaiser Family Foundation. [cited June 5, 2019]. Available from: <https://www.kff.org/medicare/report/medicare-beneficiaries-out-of-pocket-health-care-spending-as-a-share-of-income-now-and-projections-for-the-future/>.

Damico, A. (2018b). *Sources of supplemental coverage among Medicare beneficiaries in 2016* [Internet]. The Henry J. Kaiser Family Foundation. [cited June 5, 2019]. Available from: <https://www.kff.org/medicare/issue-brief/sources-of-supplemental-coverage-among-medicare-beneficiaries-in-2016/>.

Damico, A. (2018c). *A dozen facts about Medicare advantage* [Internet]. The Henry J. Kaiser Family Foundation. [cited June 1, 2019]. Available from: <https://www.kff.org/medicare/issue-brief/a-dozen-facts-about-medicare-advantage/>.

Defining the PCMH. PCMH Resource Center [Internet]. [cited June 7, 2019]. Available from: <https://pcmh.ahrq.gov/page/defining-pcmh>.

Distribution of dfee-for-service Medicaid spending on long term care. (2018). [Internet]. The Henry J. Kaiser Family Foundation. [cited June 7, 2019]. Available from: <https://www.kff.org/medicaid/state-indicator/spending-on-long-term-care/>.

Dual eligibles as a percent of total Medicare beneficiaries. (2018) [Internet]. The Henry J. Kaiser Family Foundation. [cited June 2, 2019]. Available from: <https://www.kff.org/medicaid/state-indicator/duals-as-a-of-medicare-beneficiaries/>.

Dual-eligible beneficiaries of Medicare and Medicaid: Characteristics, health care spending, and evolving policies, Congressional Budget Office [Internet]. [cited May 18, 2019]. Available from: <https://www.cbo.gov/publication/44308>.

Frank, R. G., & Glied, S. (2006). Changes in mental health financing since 1971: Implications for policymakers and patients. *Health Affairs*, *25*(3), 601–613.

Ginsburg, I. F., & Eng, C. (2009). On-site mental health services for PACE (program of all-inclusive care for the elderly) centers. *Journal of the American Medical Directors Association*, *10*(4), 277–280.

Glazer, J., & McGuire, T. G. (2002). Multiple payers, commonality and free-riding in health care: Medicare and private payers. *Journal of Health Economics*, *21*(6), 1049–1069.

Gold, M. (2014). November 06 GCP, 2014. *What do we know about health care access and quality in Medicare advantage versus the traditional Medicare program?* [Internet]. The Henry J. Kaiser Family Foundation. [cited June 7, 2019]. Available from: <https://www.kff.org/medicare/report/what-do-we-know-about-health-care-access-and-quality-in-medicare-advantage-versus-the-traditional-medicare-program/>.

Goldman, H. H., Feder, J., & Scanlon, W. (1986). Chronic mental patients in nursing homes: Reexamining data from the National Nursing Home Survey. *Psychiatric Services*, *37*(3), 269–272.

Grob, G. N. (1987). *Mental illness and American society, 1875–1940. c1983.*

Health care costs: A primer—Conclusion [Internet]. (2012). The Henry J. Kaiser Family Foundation. [cited May 18, 2019]. Available from: <https://www.kff.org/report-section/health-care-costs-a-primer-2012-conclusion/>.

Kessler, R., Miller, B. F., Kelly, M., Graham, D., Kennedy, A., Littenberg, B., et al. (2014). Mental health, substance abuse, and health behavior services in patient-centered medical homes. *Journal of the American Board of Family Medicine*, *27*(5), 637–644.

Lave, J. R., & Goldman, H. H. (1990). Medicare financing for mental health care. *Health Affairs*, *9*(1), 19–30.

Mcguire, T. G., Newhouse, J. P., & Sinaiko, A. D. (2011). An economic history of Medicare part C. *The Milbank Quarterly*, *89*(2), 289–332.

Medicaid enrollees by enrollment group [Internet]. (2017). The Henry J. Kaiser Family Foundation. [cited May 18, 2019]. Available from: <https://www.kff.org/medicaid/state-indicator/distribution-of-medicaid-enrollees-by-enrollment-group/>.

Medicare Payment Advisory Commission (MEDPAC). (2016). *A data book: Health care spending and the Medicare program.*

Medicare Spending for Beneficiaries with Severe Mental Illness and Substance Use Disorder. The SCAN Foundation, Aging and Long Term Care with Dignity and Independence [Internet]. [cited June 7, 2019]. Available from: <https://www.thescanfoundation.org/medicare-spending-beneficiaries-severe-mental-illness-and-substance-use-disorder>.

Medigap Enrollment and Consumer Protections Vary across States. The Henry J. Kaiser Family Foundation [Internet]. [cited June 5, 2019]. Available from: <https://www.kff.org/medicare/issue-brief/medigap-enrollment-and-consumer-protections-vary-across-states/>.

Mental health of older adults [Internet]. [cited May 19, 2019]. Available from: <https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults>.

Minnesota managed care longitudinal data analysis [Internet]. (2016). ASPE. [cited May 18, 2019]. Available from: <https://aspe.hhs.gov/pdf-report/minnesota-managed-care-longitudinal-data-analysis>.

National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Care Services, & Committee on Health Care Utilization and Adults with Disabilities. (2018). *Changing patterns of health insurance and health-care delivery* [Internet]. National Academies Press (US); [cited May 18, 2019]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK500098/>.

Neuman, P., Cubanski, J., & Damico, A. (2015). Medicare per capita spending by age and service: New data highlights oldest beneficiaries. *Health Affairs*, *34*(2), 335–339.

Neuman, P., & Jacobson, G. A. (2018). Medicare advantage checkup. *The New England Journal of Medicine*, *379*(22), 2163–2172.

Newhouse, J. P., & McGuire, T. G. (2014). How successful is Medicare advantage? *The Milbank Quarterly*, *92*(2), 351–394.

People Dually Eligible *for Medicare and Medicaid.* Centers for Medicare & Medicare Services.

Pope, G. C., Kautter, J., Ellis, R. P., Ash, A. S., Ayanian, J. Z., Iezzoni, L. I., et al. (2004). Risk adjustment of Medicare capitation payments using the CMS-HCC model. *Health Care Financing Review*, *25*(4), 119–141.

Potential economic impact of integrated medical-behavioral healthcare: Updated projections for 2017—Milliman Insight [Internet]. [cited June 5, 2019]. Available from: <http://www.milliman.com/insight/2018/Potential-economic-impact-of-integrated-medical-behavioral-healthcare-Updated-projections-for-2017/>.

Projections of national expenditures for treatment of mental and substance use disorders, 2010–2020. SAMHSA Publications [Internet]. [cited June 2, 2019]. Available from: <https://store.samhsa.gov/product/Projections-of-National-Expenditures-for-Treatment-of-Mental-and-Substance-Use-Disorders-2010-2020/SMA14-4883>.

Sisko, A. M., Keehan, S. P., Poisal, J. A., Cuckler, G. A., Smith, S. D., Madison, A. J., et al. (2019). National health expenditure projections, 2018–27: Economic and demographic trends drive spending and enrollment growth. *Health Affairs.*, *38*(3), 491–501.

Social Security Act: Title XVIII—Health insurance for the aged and disabled [Internet]. [cited May 18, 2019]. Available from: <https://www.ssa.gov/OP_Home/ssact/title18/1800.htm>.

State of mental health and aging in America (MAHA). (2019). Alzheimer's Disease and Healthy Aging Data Portal, CDC [Internet]. [cited June 2, 2019]. Available from: <https://www.cdc.gov/aging/agingdata/data-portal/mental-health.html>.

Tao, G. (2017). Utilization pattern of other preventive services during the US Medicare annual wellness visit. *Preventive Medicine Reports*, *10*, 210–211.

The John A. Hartford Foundation. (2011). *Annual report* [Internet]. [cited June 1, 2019]. Available from: <https://www.johnahartford.org/ar2011/>.

Timbie, J. W., Bogart, A., Damberg, C. L., Elliott, M. N., Haas, A., Gaillot, S. J., et al. (2017). Medicare advantage and fee-for-service performance on clinical quality and patient experience measures: Comparisons from three large States. *Health Services Research*, *52*(6), 2038–2060.

Total number of Medicare beneficiaries [Internet]. (2019). The Henry J. Kaiser Family Foundation. [cited May 18, 2019]. Available from: <https://www.kff.org/medicare/state-indicator/total-medicare-beneficiaries/>.

Wagner, T. H., Almenoff, P., Francis, J., Jacobs, J., & Pal Chee, C. (2018). Assessment of the Medicare advantage risk adjustment model for measuring Veterans Affairs hospital performance. *JAMA Network Open*, *1*(8), e185993.

Wang, P. S., Lane, M., Olfson, M., Pincus, H. A., Wells, K. B., & Kessler, R. C. (2005). Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 629–640.

Yasamy, M. T., Dua, T., Harper, M., & Saxena, S. *Mental health of older adults, addressing a growing concern.* [cited May 18, 2019]. Available from: <https://www.academia.edu/36124304/Mental_Health_of_Older_Adults_Addressing_a_Growing_Concern>.

Chapter 28

The future of mental health and aging

Nathan Hantke[1,2], Ruth O'Hara[3,4,5], Sherry A. Beaudreau[3,4,6] and Amit Etkin[3]

[1]Department of Neurology, Oregon Health and Science University, Portland, OR, United States, [2]Mental Health and Neuroscience Division, VA Portland Health Care System, Portland, OR, United States, [3]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States, [4]Sierra Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, United States, [5]Stanford/VA Alzheimer's Center, Palo Alto, CA, United States, [6]School of Psychology, University of Queensland, Brisbane, QLD, Australia

Introduction

Until 1978, only one medical department offered specialized training in geropsychiatry (Cohen, 1992). This humbling fact sets the stage for appreciating the substantial growth in services for older adults and the increase in understanding of the complicated nature of treating mental health in older adults. Predicting the future of mental health care for older adults for the next several decades feels akin to reading science fiction predictions of the future from the 1950s; well-intentioned yet accurately impossible. This being said, research relevant to mental health care, including geriatric mental health, has undergone a wholesale shift since the last edition of this book nearly 30 years ago, which came prior to the introduction of contemporary neuroimaging, genetic, and molecular biological methods. Exciting growth in technology has accelerated our understanding of how the brain operates and how dysfunction in neural circuitry can contribute to late-life mental health symptoms. Clinical neuroscience, neurobiology, neuroimaging, and genetic techniques have arrived at the forefront of the field, resulting in several remarkable discoveries. For example, the utility of traditional diagnostic categories for uncovering distinct biological mechanisms has been questioned. There are more neural similarities than differences among adult psychiatric disorders, suggesting shared neural substrates across psychopathology (Goodkind et al., 2015). Geriatric mental health research has also begun to identify shared neural substrates across psychiatric symptoms and disorders, many of which mirror what has been found in younger and middle-aged adults, but some findings that are unique to older populations (Andreescu & Reynolds, 2011; Andreescu, Sheu, Tudorascu, Walker, & Aizenstein, 2014). Similar results have emerged from psychiatric genetics (Brainstorm et al., 2018). These findings and related discoveries have dramatically shifted our understanding of what mental illness truly is and creates a question of how we should diagnostically define it across the adult life span. In line with these advances, the National Institute of Mental Health (NIMH) has advanced a conceptual framework, the Research Domain Criteria (RDoC), for grounding an understanding of psychiatric disorder with respect to underlying brain dysfunction (Insel et al., 2010). This framework, now nearly a decade old, continues to undergo its own evolution.

Regardless of age, the increasing appreciation of taking a neurobiological approach to understanding mental illness represents a significant paradigm shift from previous, clinical symptom-based definitions of mental illness. Our emerging understanding of how deficits in the brain networks that support cognitive and emotional regulatory functions can result in functional impairment has broad conceptual and treatment implications (Etkin, Gyurak, & O'Hara, 2013). One such study on this topic found that networks involved in cognitive control, an ability vital in successful daily functioning and predictive of socio-occupational stability, are disrupted across a broad spectrum of psychopathology regardless of diagnosis (McTeague et al., 2017). In other words, this finding implicates specific neural circuitry dysfunction (i.e., multiple-demand network) that may explain why adults of all ages with mental illness are prone to difficulty in managing daily activities and cognitive deficits. Conversely, recent research suggests the presence of neurophysiological subtypes of depression, defined by distinct patterns of dysfunctional connectivity between the frontostriatal and limbic networks, with differing clinical symptom profiles (Drysdale et al., 2017). Taken in context, these findings (along with others), suggest transdiagnostic neural commonalities within mental illness, yet distinct clinical subtypes—neither of which align with current clinical nosology.

Handbook of Mental Health and Aging. DOI: https://doi.org/10.1016/B978-0-12-800136-3.00028-4

Understanding the brain functional connectome (i.e., how the regions of the brain communicate as a large network) is integral in understanding this proposed transdiagnostic, neurobiological approach to geriatric mental illness and mental illness more broadly. Importantly, it also allows us to understand where and how dysfunction may occur that manifests as clinical symptoms. Understanding the individualized nature of the brain's functional connectome likely requires an individual-tailored brain mapping approach, which may be part of the reason for the limited specificity seen in group-level neuroimaging findings (Kaufmann et al., 2018). Recent research lends credence to the importance of an individual-based understanding of brain connectivity and its involvement in understanding late-life mental health disorders. Research by Kaufmann and colleagues (2018) indicates that the brain connectome increases in stability during development, peaks in early adulthood, and decreases in stability as individuals age (Kaufmann et al., 2018). However, delayed connectome stabilization is associated with preclinical signs of mental illness, including schizophrenia spectrum disorders, with weaker connectome distinctiveness being associated with greater clinical symptom burden (Kaufmann et al., 2017, 2018). Findings such as these regarding brain connectome stability, connectomic "brain age" as compared to chronological age [e.g., schizophrenia as a disorder of accelerated brain aging (Eyler & Jeste, 2018; Kirkpatrick, Messias, Harvey, Fernandez-Egea, & Bowie, 2008)], and life span developmental changes lend themselves to the growing appreciation of the neural circuity involved in late-life mental health symptoms and terms such as precision psychiatry as applied to geriatric mental health, which we will discuss below.

Large-scale projects are currently underway in an attempt to better understand the brain functional connectome. Historically, however, they have focused on younger populations. The Human Connectome Project (HCP), for example, was an NIH-funded consortium included multiple sites obtaining neuroimaging of healthy young adults aged 22−35 in order to characterize the structure, function, and connectivity of the brain (Harms et al., 2018). More recently, such efforts have been extended to understanding individuals across the life span. Projects such as the Lifespan Human Connectome Project are attempting to expand upon the findings of the HCP. The goal of this new ambitious project is to collect a large, normative dataset of brain, cognitive, and biometric data in an older adult sample to inform our understanding of how the brain changes with age (Bookheimer et al., 2019). This proposed sample of over 1200 cross-sectional and 600 longitudinal participants will be characterized by factors already associated with cognitive decline in older adults, such as cerebrovascular risk factors, genetic status, level of physical activity, and mental health (Bookheimer et al., 2019; Harms et al., 2018). Such data may reveal interacting factors associated with healthy aging and those associated with the onset of a neurodegenerative process. Important within the context of mental health, these data may also inform us of factors associated with late-onset mental health symptoms, including changes in network function that may guide future projects.

The growing appreciation for the role of neural networks in cognition and mental illness has significant potential for understanding etiology and guiding individually tailored treatment. This chapter will briefly review several key concepts within the emerging field, including the current state of repetitive transcranial magnetic stimulations (rTMS), the foundation of precision psychiatry, and how innovations in technology are guiding treatment in older adults.

Conceptualizing geriatric mental health within neural circuitry

The field of mental health, including the field of geriatric mental health, has been entrenched for the past century in the view of mental health disorders as discrete entities with unique symptoms. The Diagnostic and Statistical Manual of Mental Disorders (DSM) was first published in 1952 and grounded within the framework of diagnosing a mental disorder based upon clinical presentation instead of etiology. Intuitively, the system appears relatively straightforward in clinical terms, and echoes in a certain sense the patient's interaction with the clinician: a patient presents to clinic with a cluster of symptoms, a diagnosis is made based upon this clinical presentation, and treatment is administered with the goal of normalizing these symptoms. Yet, this conceptualization has become problematic as our understanding of mental health has expanded over the past 70 years, as well as based on basic clinical grounds alone. Implicit in the current diagnostic system is the assumption that individuals with similar symptoms should be diagnosed with the same disorder, and symptoms for these disorders are mutually exclusive. However, depressive disorders and anxiety disorders are considered distinct diagnoses, despite their frequent cooccurrence (Mineka, Watson, & Clark, 1998). Similarly, two patients may be diagnosed with depression and yet share few symptoms. Further, and relevant to older adults, this classification system assumes a fixed diagnostic threshold throughout life. Evidence suggests, however, that older adults often have subthreshold anxiety and depressive symptoms (Beekman, Copeland, & Prince, 1999; Gallo & Lebowitz, 1999; Miloyan, Byrne, & Pachana, 2015), which would not meet DSM diagnostic criteria and yet are still associated with substantial functional impairment—perhaps the most important indicator of a need for mental health treatment. As such, the current DSM/international classification of diseases (ICD) classification system continues to be a source of

controversy within the field of geriatric mental health, especially as our understanding of associated neural circuitry has moved at a remarkable pace.

Clark and colleagues (2017) attempted to synthesize these concerns by classifying mental health into four primary issues: determining the *etiology* of a mental health disorder, using *categories versus dimensions* as a way of classifying symptoms, determining the *thresholds* of when to classify a cluster of symptoms as a disorder, and appreciating *comorbidity* across mental health disorders (Clark, Cuthbert, Lewis-Fernandez, Narrow, & Reed, 2017). Current research suggests that mental health disorders at any age are likely the result of the interplay of multiple factors, including genetics, psychosocial variables, and other causal factors. Therefore, determining the etiology of specific mental health disorders has thus far been a difficult task. In addition, creating arbitrary boundaries for what is a mental health disorder and what differentiates one disorder from another based on clinical presentation is inherently complicated and likely varies within individuals over time. In response, recent research has started focusing on integrating breakthroughs in basic and translational science into our conceptual understanding of what is a mental health disorder and how neural circuitry is related to clinical symptoms (Clark et al., 2017).

There is growing evidence of common neural circuit dysfunction (in particular, highlighting the dorsal anterior cingulate and insula) across mental health disorders and symptoms, including in older adults, further obscuring the boundaries between disorders (Goodkind et al., 2015). Even clinical presentation may not be particularly dichotomizing; recent research in younger and older adults suggests that worry and rumination reflect differing cognitive strategies of neuroticism, despite being more being associated with different diagnoses, anxiety and depression, respectively (Merino, Senra, & Ferreiro, 2016). Reflective of the growing intersection between neurobiology and the conceptualization of mental health disorders that by and large generalizes across the life span, the field is predominantly moving toward the appreciation of psychopathology being a product of dysfunction in neural circuitry, as compared to conceptualizing mental health strictly on clinical presentation (Lilienfeld & Treadway, 2016).

The increased understanding of the role of large-scale brain circuitry in clinical symptoms further guides this movement and is equally relevant to geriatric mental health (Williams, 2016). Dr. Leanne Williams in her 2016 publication proposed a refined taxonomy for anxiety and depression, focused on putative biotypes of neural circuit dysfunction applicable to adults across the developmental life span (Williams, 2016). She proposed eight phenotypes for depression and anxiety associated with specific network dysfunction: rumination, anxious avoidance, negative bias, threat dysregulation, anhedonia, context insensitivity, inattention, and cognitive dyscontrol. Theoretically, hyper- or hypoaction of these proposed circuits may be associated with clinical presentation and importantly, treatment response. Findings from prior studies have found patterns of neural activation associated with treatment response to specific psychotropic medications, suggesting possible utility of such an approach with both adult and geriatric mental health patients (Dunlop & Mayberg, 2014; Williams et al., 2015). While these models are still highly speculative, the potential ability for a provider to identify and target specific dysfunctional brain circuits has the ability to revolutionize geriatric mental health care, if these areas of research come to fruition.

Consistent with the increased appreciation of a dimensional approach to understanding mental illness and associated neural circuitry, the NIMH initiated the RDoC project in 2009. This strategic shift was conceived as a research-related initiative, with the goal of studying mental disorders based on dimensions of observable and neurobiological measures (Cuthbert, 2015). More specifically, RDoC is a programmatic initiative to fund grants, contracts, early-phase trials, and similar activities to establish research to guide future conceptualizations of mental illness. Though applicable to psychopathology across the adult life span, RDoC is especially relevant to geriatric mental health, in which vast heterogeneity in neurological system functions has been documented in older adults and proposed to underlie some mental health syndromes such as depression (Eyre et al., 2016; Li, Ma, Yu, He, & Li, 2014; Zhu, Li, Wang, & Li, 2014).

Unlike ICD and DSM, RDoC frames mental health in terms of neuroscience- and behavioral science−based dimensions that cut across traditional diagnostic categories (Clark et al., 2017). The significance of pushing away from understanding mental health purely within clinical symptoms and instead anchoring mental health disorders as sets of dysfunctions in brain circuitry, especially in older populations, cannot be understated. RDoC is also intended to be a living program of research that can be adapted and refined, as our appreciation of the interplay between the many factors involved in mental illness is elucidated. Importantly, the hope is that this growth will guide our understanding of the neural basis of psychopathology across the adult life span to lead to the development of more focused treatments or interventions.

RDoC is currently constructed as six domains: negative valence systems, positive valence symptoms, cognitive systems, social processes, arousal and regulatory systems, and sensorimotor systems. Each domain is then further broken down into constructs and subconstructs, such as acute threat or "fear" within the negative valence systems domain. More and more investigations, including those in geriatric mental health (Beaudreau et al., 2017; Namaky et al., 2017),

are being published that examine RDoC constructs. Generally, these constructs are studied via specified units of analysis, which include genes, molecules, cells, circuits, physiology, behaviors, self-reports, and behavioral tests (e.g., Go/No-Go task). Recent review articles have translated the RDoC constructs into clinical terms, paving the way for practitioners to understand these constructs within more familiar psychiatric terms (e.g., positive valence systems equating to drive and effort allocation) (Yager & Feinstein, 2017).

As applied to the two most common mental health symptoms and disorders, anxiety and depression, the RDoC framework has particularly guided recent developments in geriatric mental health research. A critical review identified several domains as relevant to geriatric anxiety disorders including physiological systems [i.e., hypothalamic-pituitary-adrenal axis (HPA-axis)] and genetic factors (i.e., genetic risk factors for HPA-axis dysregulation). The review also described plausible neurobiological pathways underlying negative and positive valence systems in older adults with high anxiety, such as an impaired ability to suppress negative thoughts via the lateral prefrontal cortex. In addition, cognitive systems are described in terms of several studies with either community-dwelling older adults or samples of older adults with a late-life anxiety disorder, in which high anxiety has associated lower performance in domains of executive functions, such as set-shifting, categorization, and in inhibitory control, and in immediate memory (Bower, Wetherell, Mon, & Lenze, 2015).

Regarding depression, negative emotion verbal memory biases have been associated with both older adults with depression and in older adults with amnestic mild cognitive impairment in a single domain (Mah, Anderson, Verhoeff, & Pollock, 2017). The complexity of these different RDoC and their interface with geriatric depression has led to hypothesized depressive subtypes with different behavioral, genetic, and neurobiological underpinnings (Rutherford, Taylor, Brown, Sneed, & Roose, 2017).

Taking our knowledge of the functional connectome and neurobiology and directly translating it into clinical care for geriatric patients potentially represents the next significant step in mental health treatment. Across the adult life span, pioneering work within psychiatry has elucidated circuitry involved in adaptive and maladaptive behavior, and modulation of these projections has resulted in changes in clinical behavior (Deisseroth, 2014; Williams, 2016). Connectome-guided deep brain stimulation (DBS) is being utilized for treatment-resistant major depression, and findings within optogenetics and TMS suggest potential for symptom-guided, neural projection−based interventions (Deisseroth, 2014; Riva-Posse et al., 2018; Zhou et al., 2018).

Perhaps most saliently, however, a shift from clinical phenomenology to a transdiagnostic, mechanistic, individually robust neurocircuitry-based definition heralds the potential for brain biomarker tests for diagnostic, prognostic, or treatment-selection purposes. This approach, often termed precision or personalized medicine, follows the highly successful evolution of other fields along similar lines over the past few decades. For example, in oncology it is rare for a new medication to be developed in absence of a "companion diagnostic"—that is, a test that identifies individuals with a particular tumor or somatic genetic characteristics that would endow then particularly sensitive or resistant to a medication, based on a specified mechanism of action. In psychiatry, this may take the form of brain imaging−based tests. Already in Alzheimer's disease, magnetic resonance imaging and positron emission tomography scans are in use. Because of its utility as a brain imaging modality, as well as both ease of administration and low cost, it is possible that electroencephalography may provide such a test. Such tests would be building on decades of neuroimaging research in psychiatry. Additionally, substantial attention has been put toward development of smartphone-based biomarkers, such as patterns of typing that may indicate different levels of cognitive dysfunction. Such smartphone work, while promising, remains early in its development. Nonetheless, the potential ease and passivity of such biomarker collection and quantification hold great promise in general. Within geriatric populations, however, some additional caution must be had as the prevalence of smartphone use is lower in older individuals, who may also not use their smartphones as routinely as younger individuals may. Nonetheless, it is likely that the next evolution in neurocircuitry characterization, using brain imaging or behavioral tools, will be toward the level of robust characterization of signals from individuals in order to aid the clinician in diagnosing, treating, and monitoring their patients.

Repetitive transcranial magnetic stimulation

Complementary to the concept of neurocircuitry-based reformulation and characterization of mental illness is the idea that treatment ought to likewise target neurocircuity. The most tractable such approach at present involves repetitive rTMS. This method involves pulsing a strong electromagnet at a particular temporal pattern over a cortical target under the coil. As such, factors such as where in the brain is targeted, as well as the details of the pulse pattern, are modifiable and help to tie together the quantification of circuit dysfunction to its remediation through neurostimulation (which induces neuroplasticity). One rTMS protocol, involving stimulation of the left prefrontal cortex with a "high frequency"

protocol composed of repeated 10 Hz stimulation bursts, garnered Food and Drug Administration clearance first in 2008. Multiple follow-on clearances have been granted since then for related TMS machines, and more recently clearance was also given for a medial prefrontal stimulation protocol for obsessive–compulsive disorder. Clinical trial evidence suggests that left prefrontal 10 Hz rTMS is effective for geriatric depression (Kaster et al., 2018) as well as vascular depression, a common etiology for depression in late life (Jorge, Moser, Acion, & Robinson, 2008). Given the positive clinical findings in geriatric populations, which mirror those in younger populations, rTMS therefore holds great promise as a therapeutic tool for pushing neuroimaging-based insights into the therapeutic arena. Also, while far less developed, other methods for noninvasive brain stimulation such as transcranial direct or alternating current, or even ultrasound, may become useful as their evidence base develops.

Treatment innovation through technology

Novel treatment approaches for geriatric mental health care are only of utility if they are available to older patients who need them. Patients who live a considerable distance from medical centers or have medical-related limitations that make travel difficult may not be able to receive these innovative services, leaving a significant percentage of older adults without access to specialty care. An estimated 5.6–8 million American older adults are living with a mental health disorder and yet have difficulty with access to adequate care (Committee on the Mental Health Workforce for Geriatric Populations, Board on Health Care Services, & Institute of Medicine, 2012). Fortunately, the integration of technology into mental health services is rapidly decreasing this gap in service. The expansion of telehealth services via online videoconferencing has increased access to care and convenience while decreasing health care–related costs. Gould and colleagues discuss in their chapter innovative ways technology is currently being utilized to improve access to care, as medication management, cognitive assessment, and psychotherapy intervention are increasingly being offered via telehealth. In addition to access to care, technology may serve a purpose in decreasing social isolation. Subjective, but not objective, social isolation in older adults is associated with higher levels of psychological distress (Taylor, Taylor, Nguyen, & Chatters, 2018). There is growing evidence that older adults who utilize video chat have a lower risk of developing depression than those who do not, presumably by decreasing subjective social isolation (Teo, Markwardt, & Hinton, 2019). In theory, clinicians may consider encouraging adjunct video chat with family members in addition to face-to-face social interactions as a way to decrease risk for future depressive episodes (Teo et al., 2015).

In their chapter in the current book, Seelye and colleagues discuss the role of technology in the assessment of daily functioning in older adults. Recent studies have examined older adult daily activity by utilizing continues metrics, with interesting findings (Kaye et al., 2014). For example, in one study changes in everyday computer use (e.g., taking longer to complete online surveys) predicted conversion to mild cognitive impairment prior to diagnosis (Seelye et al., 2018). Similarly, changes in the sophistication of Internet search terms used by older adults may indicate cognitive dysfunction. A recent study showed that older adults with higher cognitive functioning used more unique terms when conducting Internet searches as compared to those with worse cognitive function, suggesting the presence of subtle changes in fluency and word-finding often associated with cognitive decline (Austin, Hollingshead, & Kaye, 2017). The goal of monitoring older adult functioning via unobtrusive ambient metrics is twofold: to allow care providers the ability to make tailored accommodations that allow patients to live in their home longer, and to monitor for subtle changes in function that are not easily captured in clinic. Most clinicians can relate to the difficult position of talking with a patient who is reporting memory decline in their daily life yet perform within normal limits on exam. Increasing the sensitivity of our measures may help clinicians more accurately predict who will experience cognitive decline and lead to earlier interventions. Importantly, these research efforts are working toward bridging the ever-present gap between clinic-based assessment and external validity.

Summary

Many of the predictions about geriatric mental health care made in the last edition of this book have come to fruition over the past 30 years. Automated medication dispensers, smart homes, technology-driven interventions, and telehealth are now commonplace within mental health care for older adults (Cohen, 1992). Unfortunately, other predictions, such as refined pharmacological interventions for Alzheimer's disease and affordable health care, are still lacking. Innovations in technology have facilitated growth in the field of geriatric mental health in ways Dr. Cohen (1992) would have been very unlikely to predict. Appreciation of how large regions of the brain communicate as a network and how dysfunction within these networks results in psychiatric and cognitive symptoms has the potential to revolutionize the way the field conceptualizes, diagnoses, and treats mental illness in older adults. In an effort to integrate this

scientific progress into the concept of mental illness, the NIMH initiated the RDoC project (Cuthbert, 2015). Expanding upon the DSM-5 (APA, 2013), RDoC proposes the examination of mental health in terms of neuroscience- and behavioral science–based dimensions that cut across problematic traditional diagnostic categories. Treatments that utilize a connectome-based approach to mental illness, such as rTMS and DBS, have found early success in the treatment of refractory psychiatric symptoms and have strong implications for the future delivery of mental health treatments for older patients.

Dissemination of mental health care has also benefited greatly from advancements in technology. Access to health care continues to improve and integration of service and technology has allowed clinicians to provide services to patients unable to attend clinic due to physical distance or medical concerns. The potential impact of this technology use in addressing geriatric mental health barriers is substantial. Predicting which older adults will experience healthy aging and which will experience cognitive decline continues to remain an elusive endeavor. Neuroimaging initiatives, such as the Lifespan Human Connectome Project, hold potential insights into the aging process and cognitive decline, as do machine learning models that can accommodate what is likely a multifactorial process (Bookheimer et al., 2019). Monitoring the daily activities of older adults also holds potential for predicting on an individual basis future cognitive status (Kaye et al., 2014).

The ability for clinicians to provide personalized medicine will likely only increase as the field continues to make advances in understanding the relationship between neural circuitry and geriatric mental health. Yet, if the past 30 years is any indication of what the future portends, geriatric mental health care will likely pivot and evolve in unpredictable and exciting directions.

References

American Psychiatric Association (APA). (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Publishing.

Andreescu, C., & Reynolds, 3rd, C. F. (2011). Late-life depression: evidence-based treatment and promising new directions for research and clinical practice. *The Psychiatric Clinics of North America*, *34*(2), 335–355, vii–iii. Available from https://doi.org/10.1016/j.psc.2011.02.005.

Andreescu, C., Sheu, L. K., Tudorascu, D., Walker, S., & Aizenstein, H. (2014). The ages of anxiety—Differences across the lifespan in the default mode network functional connectivity in generalized anxiety disorder. *International Journal of Geriatric Psychiatry*, *29*(7), 704–712. Available from https://doi.org/10.1002/gps.4051.

Austin, J., Hollingshead, K., & Kaye, J. (2017). Internet searches and their relationship to cognitive function in older adults: Cross-sectional analysis. *Journal of Medical Internet Research*, *19*(9), e307. Available from https://doi.org/10.2196/jmir.7671.

Beaudreau, S. A., Hantke, N. C., Mashal, N., Gould, C. E., Henderson, V. W., & O'Hara, R. (2017). Unlocking neurocognitive substrates of late-life affective symptoms using the research domain criteria: Worry is an essential dimension. *Frontiers in Aging Neuroscience*, *9*, 380. Available from https://doi.org/10.3389/fnagi.2017.00380.

Beekman, A. T., Copeland, J. R., & Prince, M. J. (1999). Review of community prevalence of depression in later life. *The British Journal of Psychiatry*, *174*, 307–311. Available from https://doi.org/10.1192/bjp.174.4.307.

Bookheimer, S. Y., Salat, D. H., Terpstra, M., Ances, B. M., Barch, D. M., Buckner, R. L., … Yacoub, E. (2019). The Lifespan Human Connectome Project in aging: An overview. *NeuroImage*, *185*, 335–348. Available from https://doi.org/10.1016/j.neuroimage.2018.10.009.

Bower, E. S., Wetherell, J. L., Mon, T., & Lenze, E. J. (2015). Treating anxiety disorders in older adults: Current treatments and future directions. *Harvard Review of Psychiatry*, *23*(5), 329–342. Available from https://doi.org/10.1097/hrp.0000000000000064.

Brainstorm, C., Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., … Murray, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*(6395). Available from https://doi.org/10.1126/science.aap8757.

Clark, L. A., Cuthbert, B., Lewis-Fernandez, R., Narrow, W. E., & Reed, G. M. (2017). Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest*, *18*(2), 72–145. Available from https://doi.org/10.1177/1529100617727266.

Cohen, G. D. (1992). *The future of mental health and aging*. *Handbook of mental health and aging* (2nd ed.). San Diego, CA: Academic Press.

Committee on the Mental Health Workforce for Geriatric Populations., Board on Health Care Services., & Institute of Medicine. (2012). In J. Eden, K. Maslow, M. Le, & D. Blazer (Eds.), *The mental health and substance use workforce for older adults: In whose hands?* Washington, DC: National Academies Press (US).

Cuthbert, B. N. (2015). Research Domain Criteria: toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience*, *17*(1), 89–97.

Deisseroth, K. (2014). Circuit dynamics of adaptive and maladaptive behaviour. *Nature*, *505*(7483), 309–317. Available from https://doi.org/10.1038/nature12982.

Drysdale, A. T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., … Liston, C. (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, *23*(1), 28–38. Available from https://doi.org/10.1038/nm.4246.

Dunlop, B. W., & Mayberg, H. S. (2014). Neuroimaging-based biomarkers for treatment selection in major depressive disorder. *Dialogues in Clinical Neuroscience*, *16*(4), 479–490.

Etkin, A., Gyurak, A., & O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in Clinical Neuroscience*, *15*(4), 419–429.

Eyler, L. T., & Jeste, D. V. (2018). Aging of the body and the brain in schizophrenia. *Schizophrenia Research*, *196*, 1–3. Available from https://doi.org/10.1016/j.schres.2017.11.036.

Eyre, H. A., Yang, H., Leaver, A. M., Van Dyk, K., Siddarth, P., Cyr, N. S., ... Lavretsky, H. (2016). Altered resting-state functional connectivity in late-life depression: A cross-sectional study. *Journal of Affective Disorders*, *189*, 126–133. Available from https://doi.org/10.1016/j.jad.2015.09.011.

Gallo, J. J., & Lebowitz, B. D. (1999). The epidemiology of common late-life mental disorders in the community: Themes for the new century. *Psychiatric Services*, *50*(9), 1158–1166. Available from https://doi.org/10.1176/ps.50.9.1158.

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., ... Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*, *72*(4), 305–315. Available from https://doi.org/10.1001/jamapsychiatry.2014.2206.

Harms, M. P., Somerville, L. H., Ances, B. M., Andersson, J., Barch, D. M., Bastiani, M., ... Yacoub, E. (2018). Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. *NeuroImage*, *183*, 972–984. Available from https://doi.org/10.1016/j.neuroimage.2018.09.060.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., ... Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, *167*(7), 748–751. Available from https://doi.org/10.1176/appi.ajp.2010.09091379.

Jorge, R. E., Moser, D. J., Acion, L., & Robinson, R. G. (2008). Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Archives of General Psychiatry*, *65*(3), 268–276. Available from https://doi.org/10.1001/archgenpsychiatry.2007.45.

Kaster, T. S., Daskalakis, Z. J., Noda, Y., Knyahnytska, Y., Downar, J., Rajji, T. K., ... Blumberger, D. M. (2018). Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: A prospective randomized controlled trial. *Neuropsychopharmacology*, *43*(11), 2231–2238. Available from https://doi.org/10.1038/s41386-018-0121-x.

Kaufmann, T., Alnaes, D., Brandt, C. L., Bettella, F., Djurovic, S., Andreassen, O. A., & Westlye, L. T. (2018). Stability of the brain functional connectome fingerprint in individuals with schizophrenia. *JAMA Psychiatry*, *75*(7), 749–751. Available from https://doi.org/10.1001/jamapsychiatry.2018.0844.

Kaufmann, T., Alnaes, D., Doan, N. T., Brandt, C. L., Andreassen, O. A., & Westlye, L. T. (2017). Delayed stabilization and individualization in connectome development are related to psychiatric disorders. *Nature Neuroscience*, *20*(4), 513–515. Available from https://doi.org/10.1038/nn.4511.

Kaye, J., Mattek, N., Dodge, H. H., Campbell, I., Hayes, T., Austin, D., ... Pavel, M. (2014). Unobtrusive measurement of daily computer use to detect mild cognitive impairment. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*, *10*(1), 10–17. Available from https://doi.org/10.1016/j.jalz.2013.01.011.

Kirkpatrick, B., Messias, E., Harvey, P. D., Fernandez-Egea, E., & Bowie, C. R. (2008). Is schizophrenia a syndrome of accelerated aging? *Schizophrenia Bulletin*, *34*(6), 1024–1032. Available from https://doi.org/10.1093/schbul/sbm140.

Li, R., Ma, Z., Yu, J., He, Y., & Li, J. (2014). Altered local activity and functional connectivity of the anterior cingulate cortex in elderly individuals with subthreshold depression. *Psychiatry Research*, *222*(1-2), 29–36. Available from https://doi.org/10.1016/j.pscychresns.2014.02.013.

Lilienfeld, S. O., & Treadway, M. T. (2016). Clashing diagnostic approaches: DSM-ICD versus RDoC. *Annual Review of Clinical Psychology*, *12*, 435–463. Available from https://doi.org/10.1146/annurev-clinpsy-021815-093122.

Mah, L., Anderson, N. D., Verhoeff, N., & Pollock, B. G. (2017). Negative emotional verbal memory biases in mild cognitive impairment and late-onset depression. *The American Journal of Geriatric Psychiatry*, *25*(10), 1160–1170. Available from https://doi.org/10.1016/j.jagp.2017.05.005.

McTeague, L. M., Huemer, J., Carreon, D. M., Jiang, Y., Eickhoff, S. B., & Etkin, A. (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *The American Journal of Psychiatry*, *174*(7), 676–685. Available from https://doi.org/10.1176/appi.ajp.2017.16040400.

Merino, H., Senra, C., & Ferreiro, F. (2016). Are worry and rumination specific pathways linking neuroticism and symptoms of anxiety and depression in patients with generalized anxiety disorder, major depressive disorder and mixed anxiety-depressive disorder? *PLoS One*, *11*(5), e0156169. Available from https://doi.org/10.1371/journal.pone.0156169.

Miloyan, B., Byrne, G. J., & Pachana, N. A. (2015). Threshold and subthreshold generalized anxiety disorder in later life. *The American Journal of Geriatric Psychiatry*, *23*(6), 633–641. Available from https://doi.org/10.1016/j.jagp.2014.08.010.

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Clinical Psychology*, *49*(1), 377–412.

Namaky, N., Beltzer, M. L., Werntz, A. J., Lambert, A. E., Isaacowitz, D. M., & Teachman, B. A. (2017). Moderators of age effects on attention bias toward threat and its association with anxiety. *Journal of Affective Disorders*, *216*, 46–57. Available from https://doi.org/10.1016/j.jad.2016.10.048.

Riva-Posse, P., Choi, K. S., Holtzheimer, P. E., Crowell, A. L., Garlow, S. J., Rajendra, J. K., ... Mayberg, H. S. (2018). A connectomic approach for subcallosal cingulate deep brain stimulation surgery: Prospective targeting in treatment-resistant depression. *Molecular Psychiatry*, *23*(4), 843–849. Available from https://doi.org/10.1038/mp.2017.59.

Rutherford, B. R., Taylor, W. D., Brown, P. J., Sneed, J. R., & Roose, S. P. (2017). Biological aging and the future of geriatric psychiatry. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *72*(3), 343–352. Available from https://doi.org/10.1093/gerona/glw241.

Seelye, A., Mattek, N., Sharma, N., Riley, T., Austin, J., Wild, K., ... Kaye, J. (2018). Weekly observations of online survey metadata obtained through home computer use allow for detection of changes in everyday cognition before transition to mild cognitive impairment. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*, *14*(2), 187–194. Available from https://doi.org/10.1016/j.jalz.2017.07.756.

Taylor, H. O., Taylor, R. J., Nguyen, A. W., & Chatters, L. (2018). Social isolation, depression, and psychological distress among older adults. *Journal of Aging and Health*, *30*(2), 229–246. Available from https://doi.org/10.1177/0898264316673511.

Teo, A. R., Choi, H., Andrea, S. B., Valenstein, M., Newsom, J. T., Dobscha, S. K., & Zivin, K. (2015). Does mode of contact with different types of social relationships predict depression in older adults? Evidence from a nationally representative survey. *Journal of the American Geriatrics Society*, *63*(10), 2014–2022. Available from https://doi.org/10.1111/jgs.13667.

Teo, A. R., Markwardt, S., & Hinton, L. (2019). Using skype to beat the blues: Longitudinal data from a national representative sample. *The American Journal of Geriatric Psychiatry*, *27*(3), 254–262. Available from https://doi.org/10.1016/j.jagp.2018.10.014.

Williams, L. M. (2016). Precision psychiatry: A neural circuit taxonomy for depression and anxiety. *The Lancet Psychiatry*, *3*(5), 472–480. Available from https://doi.org/10.1016/s2215-0366(15)00579-9.

Williams, L. M., Korgaonkar, M. S., Song, Y. C., Paton, R., Eagles, S., Goldstein-Piekarski, A., … Etkin, A. (2015). Amygdala reactivity to emotional faces in the prediction of general and medication-specific responses to antidepressant treatment in the randomized iSPOT-D trial. *Neuropsychopharmacology*, *40*(10), 2398–2408. Available from https://doi.org/10.1038/npp.2015.89.

Yager, J., & Feinstein, R. E. (2017). Potential applications of the National Institute of Mental Health's Research Domain Criteria (RDoC) to clinical psychiatric practice: How RDoC might be used in assessment, diagnostic processes, case formulation, treatment planning, and clinical notes. *The Journal of Clinical Psychiatry*, *78*(4), 423–432. Available from https://doi.org/10.4088/JCP.15nr10476.

Zhou, C., Zhang, H., Qin, Y., Tian, T., Xu, B., Chen, J., … Xie, P. (2018). A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *82*, 224–232. Available from https://doi.org/10.1016/j.pnpbp.2017.11.012.

Zhu, X., Li, R., Wang, P., & Li, J. (2014). Aberrant functional connectivity of the hippocampus in older adults with subthreshold depression. *PsyCh Journal*, *3*(4), 245–253. Available from https://doi.org/10.1002/pchj.60.

Author Index

Note: Page numbers followed by "*f*" and "*t*" refer to figures and tables, respectively.

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

Subject Index

Note: Page numbers followed by "*f*" and "*t*" refer to figures and tables, respectively.

B

C

D

E

F

M

N

O

P

T

U

V

W

Handbook of
MENTAL HEALTH AND AGING
THIRD EDITION

Edited by
NATHAN HANTKE, AMIT ETKIN AND RUTH O'HARA

The ***Handbook of Mental Health and Aging***, Third Edition provides a foundational background for practitioners and researchers to understand mental health care in older adults as presented by leading experts in the field. Wherever possible, chapters integrate research into clinical practice. The book opens with conceptual factors, such as the epidemiology of mental health disorders in aging and cultural factors that impact mental health. The book transitions into neurobiological-based topics such as biomarkers, age-related structural changes in the brain, and current models of accelerated aging in mental health. Clinical topics include dementia, neuropsychology, psychotherapy, psychopharmacology, mood disorders, anxiety, schizophrenia, sleep disorders, and substance abuse. The book closes with current and future trends in geriatric mental health, including the brain functional connectome, repetitive transcranial magnetic stimulation (rTMS), technology-based interventions, and treatment innovations.

Key Features:

- Identifies factors influencing mental health in older adults
- Includes biological, sociological, and psychological factors
- Reviews epidemiology of different mental health disorders
- Supplies separate chapters on grief, schizophrenia, mood, anxiety, and sleep disorders
- Discusses biomarkers and genetics of mental health and aging
- Provides assessment and treatment approaches

ELSEVIER
ACADEMIC PRESS
An imprint of Elsevier
elsevier.com/books-and-journals

ISBN 978-0-12-800136-3