Mental Health and Illness Worldwide
Series Editors:
Norman Sartorius · Ee Heok Kua

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Helen Chiu
Kenneth Shulman *Editors*

Mental Health and Illness of the Elderly

Springer

Mental Health and Illness Worldwide

Series Editors
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Most books on mental health and illness are published for readers in North America and Europe, and not much is known about psychiatric practice, services and research in Asia, Africa, and South America. This series will include contributions of clinicians and researchers worldwide. Each volume will cover broad issues including epidemiology, cross-cultural comparison, clinical research, stigma of mental illness, cultural issues in mental healthcare, health economics, innovative services, preventive programs and health service outcome research. The volumes will find a wide readership among psychiatrists, psychologists, sociologists, health policy makers, social workers, health economists, anthropologists and philosophers. It will provide the readers a broader perspective of mental health and illness worldwide and also future research initiatives.

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Helen Chiu • Kenneth Shulman
Editors

Mental Health and Illness of the Elderly

With 25 Figures and 39 Tables

Springer

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ISBN 978-981-10-2412-2 ISBN 978-981-10-2414-6 (eBook)
ISBN 978-981-10-2413-9 (print and electronic bundle)
DOI 10.1007/978-981-10-2414-6

Library of Congress Control Number: 2017943321

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Series Preface

Psychiatry lives exciting and challenging times. Advances of knowledge stemming from basic sciences and epidemiological and clinical research have provided a better understanding of the etiopathogenesis, psychopathology, and natural history of mental disorders. Improved methods of treatment have changed clinical practice and prolonged the life of people with mental illness. Economic consideration and the emphasis on human rights of people with mental illness made a profound impact on the way in which psychiatry is to be practiced.

Regrettably, however, psychiatry is not practiced in the same manner around the world. Undergraduate and postgraduate education in psychiatry varies in content and duration from country to country. Psychiatrists use different doses of medication for the same disorders. The systems of care for people with mental illnesses differ in the organization and content of their interventions. Support to scientific investigations of matters related to psychiatry fluctuates and in many countries amounts to very little. Information about the function of psychiatric services varies in quantity and quality.

The series of seven books on *Mental Health and Illness Worldwide* aims to help in reducing these differences and facilitate international collaboration in psychiatry. We have invited top experts from different countries to edit the volumes, and they have in turn selected authors from different parts of the world. We have also decided to approach the body of psychiatry from a public health and epidemiological perspective rather than have books dealing with different groups of diseases. The series includes books examining and presenting knowledge assembled according to social and public health variables – gender, urbanity, migratory status, age, and education. Each of the volumes has adopted a wide perspective and included chapters based on knowledge stemming from epidemiology, on results of the investigation of cultural issues, on the best of psychopathology, on the results of the investigation of biological factors, mental health care and its innovations, health economics, and experience gained in preventive programs. The volume editors have agreed to aim at producing volumes marked by the balance of information and knowledge from basic social and behavioral sciences and from clinical practice.

The seven volumes of this opus are:

1. Mental Health and Illness of the Elderly
   Editors: Helen Chiu (Hong Kong) and Ken Shulman (Canada).

2. Mental Health and Illness in the City
   Editors (Denmark): Povl Munk-Jorgensen, Niels Okkels, and Christina Kristiansen.
3. Mental Health and Illness of Women
   Editors: Prabha Chandra (India), Helen Herrman and Jane Fisher (Australia).
4. Mental Health and Illness in Rural Communities
   Editor: S. Chaturvedi (India).
5. Mental Health and Illness in Migrant Populations
   Editors: Driss Moussaoui (Africa), Dinesh Bhugra (United Kingdom), and Antonio Ventriglio (Italy).
6. Mental Health and Illness of Children and Adolescents
   Editors: Eric Taylor (United Kingdom), John Wong (Singapore), and Frank Verhulst (Netherlands).
7. Education About Mental Health and Illness
   Editors: Marc Herman (Belgium), Tan Chay Hoon (Singapore), and Edmond Pi (USA).

We were delighted to see that the volume editors have succeeded in recruiting outstandingly knowledgeable authors for the chapters of their books. Most of them have received worldwide recognition for their contributions in their fields of specialization, and all of them have written their texts with authority and excellent judgment concerning the materials to be included.

We believe that these series of books demonstrate the importance and value of interdisciplinary and international collaboration and that it will provide readers a global perspective of mental health and mental illness. We also hope that it will help to make our discipline more homogenous and bring its practitioners worldwide closer together in the pursuit of helping people with mental illness worldwide.

It is our pleasure and a privilege to thank Professor Helen Chiu and Professor Ken Shulman, editors of this volume dealing with Mental Health and Illness of the Elderly – the first of the series – for their hard work and for their insights and dedication to excellence.

Norman Sartorius
Ee Heok Kua

Volume Preface

Remarkable advances have occurred in a number of areas in the field of mental health of the elderly in recent years. These include the progress in nosology and early diagnosis of subtypes of dementia, understanding of common mental health problems in older people, innovative services and treatment, and a move toward prevention of mental disorders. On the other hand, the aging population in many countries of the world, especially the developing countries, coupled with limited resources and services have posed significant challenges to governments and healthcare communities. It is timely for the production of a volume on *Mental Health and Illness of the Elderly*, which is part of a series of volumes on *Mental Health and Illness Worldwide*.

This volume will cover various major issues in the field of mental health in the elderly, including epidemiology, neurobiology and recent advances in dementia, common mental health disorders in the elderly, pharmacotherapy and psychological treatment, services, prevention, and mental capacity. The focus of this volume is on controversies, collaborations, and recent advances. Since collaboration with a wide variety of disciplines, both medical and allied health, is a necessary approach to the multiple comorbidities associated with mental illness in the elderly, this will be one of our themes.

Our hope is that this volume gives the reader a guide to our current state of knowledge and will provide a single resource that reveals important recent developments in research and service delivery. We have highlighted controversies that are of interest to all those who want to improve the lives of elderly people worldwide and their devoted caregivers without whom the "silver tsunami" would be even more overwhelming. We thank the editorial staff at Springer for their diligence and care in making this volume a practical and scholarly contribution to mental health and illness worldwide. Finally, we thank the authors who contributed selflessly to an international perspective on this challenge we all share.

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Series Editor Biography

Professor Norman Sartorius, M.D., M.A., D.P.M., Ph.D., FRC. Psych, obtained his M.D. in Zagreb (Croatia). He specialized in neurology and psychiatry and subsequently obtained a Master's Degree and a Doctorate in Psychology (Ph.D.). He carried out clinical work and research and taught at graduate and postgraduate levels at the University of Zagreb, at the Institute of Psychiatry in London, at the University of Geneva, and elsewhere. Professor Sartorius joined the World Health Organization (WHO) in 1967 and soon assumed charge of the program of epidemiology and social psychiatry. In 1977, Professor Sartorius was appointed Director of the Division of Mental Health of WHO. He was the Principal Investigator of several major international studies on schizophrenia, depression, and of mental and neurological disorders. In 1993, Professor Sartorius was elected President of the World Psychiatric Association (WPA) and served as President-elect and then President until August 1999, after which he was elected President of the European Psychiatric Association. Professor Sartorius is currently the President of the Association for the Improvement of Mental Health Programmes, and he is a member of the Geneva Prize Foundation, having been its President from 2004 to 2008. Professor Sartorius holds professorial appointments at universities in different countries including China, UK, and USA.

Professor Sartorius has published more than 400 articles in scientific journals, authored or coauthored 12 books, and edited more than 80 others. He is the coeditor of three scientific journals and is a member of editorial and advisory boards of many scientific journals. Professor Sartorius is also a corresponding member and fellow of a large number of international organizations and advisory boards. He has several honorary doctorates and is a member of academies of science and of medicine in different countries. He speaks Croatian, English, French, German, Russian, and Spanish.

Dr. Ee Heok Kua is the Tan Geok Yin Professor of Psychiatry and Neuroscience at the National University of Singapore (NUS) and Senior Consultant Psychiatrist at the National University Hospital, Singapore.

He was trained as a doctor at the University of Malaya and received postgraduate training in psychiatry at Oxford University and geriatric psychiatry at Harvard University.

A member of the World Health Organization team for the global study of dementia, he is the previous Head of the Department of Psychological Medicine and Vice Dean, Faculty of Medicine, at NUS, and the Chief Executive Officer and Medical Director at the Institute of Mental Health, Singapore.

His research interest includes depression, dementia, and alcoholism, and he has written 23 books on psychiatry, aging, and addiction. A novel he wrote, *Listening to Letter from America*, is used in a module on anthropology at Harvard University.

The former President of the Pacific-Rim College of Psychiatrists and President of the Gerontological Society of Singapore, he was Editor of the *Singapore Medical Journal* and *Asia-Pacific Psychiatry* journal.

About the Editors

Helen F. K. Chiu is Professor of Psychiatry at the Chinese University of Hong Kong and President of the Hong Kong Psychogeriatric Association; Past President of the Pacific Rim College of Psychiatrists, Past President of the Hong Kong College of Psychiatrists, as well as Past President of the International Psychogeriatric Association. She has been Head of the Department of Psychiatry at the Chinese University of Hong Kong from 1996 to July 2011. Currently, she is Editor of the journal *Asia-Pacific Psychiatry* and sits on the editorial board of several other journals. Dr. Chiu has around 400 papers published in scientific journals.

Dr. Chiu's major research interests are in the field of dementia and suicide. She was awarded a Medal of Honour by the Government of Hong Kong Special Administrative Region in 1999. Further, she has been awarded the Distinguished Service Award by the International Psychogeriatric Association in 2011.

Kenneth Shulman is Professor in the Department of Psychiatry at Sunnybrook Health Sciences Centre, University of Toronto. He graduated from the Faculty of Medicine, University of Toronto, and did postgraduate training in psychiatry at the University of Toronto and specialty training in geriatric psychiatry at the Institute of Psychiatry in London, England. He later completed a Master of Science in Health Policy and Management at the Harvard School of Public Health.

Dr. Shulman was formerly the Director of the Division of Geriatric Psychiatry at the University of Toronto and served as Psychiatrist-in-Chief at Sunnybrook. He was the inaugural recipient of the Richard Lewar Chair in Geriatric Psychiatry. Until 2014, he was Chief of the Brain Sciences Program at Sunnybrook, which facilitates the development of interdisciplinary services, research, and education for disorders of the brain and mind.

His academic interests include bipolar disorder in older adults, the evaluation of the clock-drawing test, pharmaco-epidemiology of mood stabilizers in older adults, as well as the assessment of testamentary capacity.

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Part I

The Global Challenge of Aging Populations

Challenges and Opportunities of Aging Populations Around the World

1

Helen F. K. Chiu and Kenneth Shulman

Keywords
Demographic imperative • Collaboration • Dementia cascade

The demographic imperative and the high prevalence of mental disorders in older adults make the focus of this volume, one of the great public health challenges of the coming generation. Brain disorders associated with psychosocial contributing factors and sequelae make the elderly, and in particular the very old, a most vulnerable population who are growing at the fastest rate. This has the potential for an overwhelming impact on health and social services worldwide. However, this impact may be mitigated by the wide-ranging research, education, and innovative services described in this volume by our internationally representative group of authors, who stand at the vanguard of their respective disciplines.

This volume addresses issues of health, illness, and prevention. Indeed, one of the very unique perspectives in this volume is ▶ Chap. 2, "Successful Aging," which focuses in a refreshingly counterintuitive way on the positive aspects of aging. Moreover, we also have epidemiological, psychological, and sociological contributions that place the older adult in a more holistic context. This interesting perspective on aging is complementary to the overwhelming yet understandable preoccupation with the disorders of later life.

Epidemiological, psychological, and sociocultural factors must be understood in the context of the growing pressure of clinical disorders, such as mood and anxiety disorders (including the risk of suicide), neurodegenerative disorders, delirium, and

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_1

of course the impact of medications on elderly patients, all of which are represented in this volume. These are the traditional "four D's" – depression, delirium, dementia, and drugs. At one time, it was believed that these were entirely distinct syndromes with unique outcomes (Roth 1955). However, recent research, reflected in this volume, shows that the interrelationship of the "four D's" is much more complex and intertwined than originally considered. Depression is a significant risk factor for dementia; delirium is at highest risk in individuals suffering from dementia; schizophrenia and bipolar disorder carry a high prevalence of cognitive impairment in later life; and a multiplicity of drugs profoundly affect the central nervous system and therefore the other three D's. Because of the unique challenge of using drugs in older adults, we have devoted two chapters specifically to pharmacotherapy in mood disorders and in the management of dementia. These chapters complement those highlighting the value of psychological therapies in mood and anxiety disorders and in the management of dementia. This complex interrelationship calls for a more unified approach to disorders of the brain and mind than we have adopted heretofore. We can no longer afford to maintain artificial silos of the traditional medical disciplines and waste the potential of sharing valuable expertise and limited resources by unnecessary duplication and fragmentation of services and training. Accordingly, we also have two chapters that address the common problem of physical comorbidity in older adults – one chapter focusing on mood disorders and the other on dementia. As economic game theory teaches us (Kreps 1990), we (health and social service professionals, patients, and families) are all better off when we share the resources and expertise necessary to understand and manage complex disorders of the brain and mind. One result of this understanding is the recent development of organizational structures that aim to facilitate this kind of integration by bringing together multiple medical and healthcare disciplines under one roof and often under one programmatic structure. The widespread adoption of program management in hospital settings has facilitated this development of integrated medical services under the umbrella of "programs" that include multiple traditional medical departments. An initial exemplar was the approach to major trauma involving multiple medical and surgical disciplines that needed urgent coordination. This approach is reflected in the recent growth of brain health centers, brain sciences centers, and institutes of brain and mind. Our volume reflects the multiple healthcare professionals, medical disciplines, and health and social services involved in such initiatives. In Canada, an educational proposal to the Royal College of Physicians and Surgeons of Canada (RCPSC) mirrors these developments and realities and aims to facilitate the collaboration and integration necessary to address disorders of the brain and mind that impact affect, behavior, and cognition. A training proposal known as a Diploma in "Interdisciplinary Brain Medicine" (IBM) brings together six related but separate medical specialties in the hope of creating a common language and a common set of clinical competencies among psychiatrists, neurologists, geriatric psychiatrists, geriatric medicine specialists, physical medicine, and rehabilitation specialists and even neurosurgeons, who are using new techniques of brain stimulation to address psychiatric and neurological conditions such as

refractory mood disorders, obsessive compulsive disorder, dementias, and familial tremor (Henri-Bhargava et al. 2013).

The Challenge of Dementia: Balancing the Search for a Cure and the Need for Care

Dementia and its related conditions is of course most prevalent in the very old, the most rapidly growing segment of the population, especially in developed countries. More recently, this is true even in developing countries as their health services evolve and improve access to healthcare and produce better clinical outcomes. In this volume, two broad approaches are described that balance the wish to find a cure and the need to support caregivers and improve the quality of life for those individuals when primary or secondary prevention is not possible.

Figure 1 reflects the evolution of dementia and its inevitable cascade represented by its most common form, Alzheimer's disease, and its contributing factors. Neurobiologic factors may precede the onset of the clinical manifestations of dementia by 20–30 years. This neurobiologic prodrome may be identified by genetic markers such as apoe4, brain changes on PET scanning, and biomarkers in the cerebrospinal fluid. The clinical prodrome may be manifest by psychiatric disorders such as depression, paranoid symptoms, and subjective cognitive changes until the

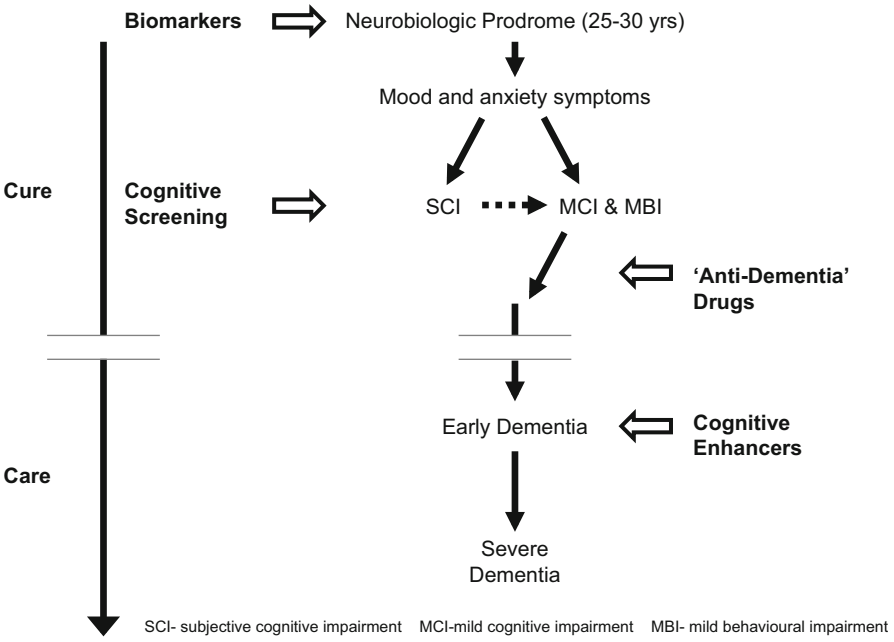

Fig. 1 The dementia cascade

disease progresses toward total disability, dependency, and death. We cannot afford to ignore the search for a cure. Early identification of those biomarkers in the brain, blood, and cerebrospinal fluid will allow us to intervene before the degenerative changes are too advanced to be reversed. Hopefully "anti-dementia" drugs can be developed that have an impact in this early stage of dementia. This in turn raises important bioethical issues. Effective cognitive screening tools include the innovative notion of "mild behavioral impairment" (MBI) as an early manifestation of dementia. At the same time as we search for a cure, we must pay attention to the nature and management of the behavioral and psychological symptoms of dementia (BPSD) and other clinical challenges faced by caregivers worldwide who represent an invaluable resource without whom healthcare systems around the world would buckle under the growing pressure of these disorders.

Other important consequences that reflect the prevalence of mental and neurological disorders in a rapidly growing elderly population include the important impact on mental capacity, as well as the economic impact affecting governments' ability to care for all of its' citizens. Hence, we have devoted separate chapters to issues of mental capacity and its interface with the law and to understanding the basics of health economics, both important areas which are deficient in the training of healthcare professionals and which reflect the interdisciplinary connections that are part and parcel of addressing the needs of older adults.

References

Henri-Bhargava A, Hogan D, Chow T, Black SE, Shulman KI (2013) Enhancing training in dementia and other brain disorders through the creation of a new Royal College Diploma Programme. 7th Canadian conference on dementia, Vancouver, BC, Canada.

Kreps D (1990) Game theory and economic modeling. Oxford University Press, New York. ISBN:0-19-828381-4

Roth M (1955) The natural history of mental disorder in old age. J Ment Sci 101:281–291

Successful Aging

2

Rujvi Kamat, Averria Sirkin Martin, and Dilip V. Jeste

Abstract

Over the course of history, aging has been considered a period of progressive physical, cognitive, and psychosocial declines, yet more recently there is growing evidence that challenges this purely deficit-driven view of aging. In fact, numerous studies have documented improvements in psychological well-being across the life-span, despite age-related declines in physical and cognitive functioning. This subjective well-being in the face of physical limitations is thought to reflect successful aging. Here, we review the definitions, predictors, and biobehavioral mechanisms of successful aging. There are numerous perspectives on what constitutes successful aging and as such a consensus regarding its definition is lacking. Nonetheless, a number of studies have characterized the biologic, environmental, and social determinants of successful aging using often overlapping operational definitions. Of particular interest are positive traits such as resilience and wisdom, which appear to have particular relevance in understanding the counterintuitive relationship between successful aging, even in the presence of poor health status. In addition to characterizing various facets of successful aging, there has been a growing interest in investigating strategies to promote well-being, many of which are discussed here. The ongoing technological revolution has great promise for enabling older adults to age successfully and safely in their own homes and communities despite declines in physical ability.

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_3

Keywords
Resilience • Healthy aging • Wisdom • Positive psychiatry • Well-being

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Introduction

At present there are over 40 million individuals over the age of 65 living in the United States and by 2030 that number is expected to grow to 72 million. Across the literature, this tidal wave of aging baby boomers has been referred to as the "Silver Tsunami" and deemed the number one public health issue faced by the developed world. In line with this rapidly shifting distribution of older adults, disease and disability related to normative and accelerated aging has received much empirical attention. Traditionally, aging has been considered a period of progressive decline in physical, cognitive, and psychosocial functioning. More recently, there is growing evidence to suggest that in contrast to a purely deficit-driven view of aging, older adults often experience increased levels of psychological well-being as they age. In addition, social and emotional functioning not only remains stable but appears to improve with age. Thus, there has been a contradiction between findings that establish a decrease in biological, physiological, and cognitive capacity in older adults and those that demonstrate that older adults are generally satisfied and report high levels of emotional well-being as they age. This contrast has been designated "The Paradox of Aging" and is described as the ability to maintain high levels of well-being and life satisfaction, despite age-related losses in physical and cognitive functioning. Based on this paradox, theories of aging have deviated from unidimensional decline models to focus on life-span developmental models that consider the notion of *successful aging*.

Earlier research on the aging process has concentrated on the way that disease and disability affect older adults. More recently, research has begun to focus on successful aging across multiple domains. Successful aging is thought to be a multidimensional construct that has been defined in numerous ways, often with reference to a variety of factors including, but not limited to, physical health, psychological health, and social health. The construct of successful aging argues against the popular notion that aging invariably involves a decline in functioning; research in this area suggests the presence of various factors that may extend the duration of positive biopsychosocial health and

meaningful experiences as we age. Within this chapter we will discuss definitions of successful aging, components of successful aging, mechanisms underlying successful aging including biological factors, as well as social and environmental factors, and predictors of successful aging.

Definition of Successful Aging

Over the last 50 years, numerous studies have attempted to define successful aging; unfortunately, outside the nonexistence of disability, there still does not appear to be a consensus on the optimum definition of successful aging or the best way to determine if someone is aging successfully. Cicero (106-43 B.C.) a Roman philosopher and statesman was believed to be the first individual to assert the notion of aging successfully through his essay *De Senectute* (44 B.C.) (Baltes and Baltes 1990). In Cicero's work, he was able to exemplify that as one grows older, they do not necessarily decline and can live their life productively and positively. One of the most commonly cited models of successful aging was proposed by Rowe and Kahn (1987); they suggested a three-tier model that integrated freedom from disability along with high cognitive, physical, and social functioning. In their view, successful aging is the opposite end of the continuum from pathological aging, which is characterized by disease and debility. Other definitions suggest that successful aging reflects the degree to which older adults adapt to age-related changes, view themselves as aging successfully, or avoid morbidity until the latest time point before death (see Depp and Jeste 2006 for review). These complementary theories view successful aging from the perspective of life-span development and emphasize psychological, social, and behavioral processes that are involved in adapting to age-related declines, disabilities, and losses. These theories also highlight the relevance of maintaining independence in everyday functioning despite physical limitations.

Given the variability in the definition of the construct of successful aging, it is not surprising that there is a wide range of prevalence estimates of successful aging. Across the literature, the reported proportion of successful agers ranges from 0.4% to 95%. This wide range is likely driven by multiple factors such as differing operational definitions of successful aging, sampling issues, as well as the psychometric properties of the instruments chosen to measure the construct. Furthermore, the prevalence of successful aging may also differ across age groups and settings. For example, in a recent study by Meng and D'arcy (2013), almost 50% of individuals over the age of 50 were classified as aging successfully, whereas only 37.2% of those aged 65 and older were classified as successful agers. The authors also reported that the predicted probability of being a successful ager was 41% for those aged 65–74 years compared to 22% for those aged 85 years and over. Taken together, these data suggest that there is a sizable minority of older adults who demonstrate characteristics of successful aging: a finding that highlights the need to carefully elucidate this construct in aging cohorts.

Further support for the construct of successful aging comes from studies of various disease groups. For example, a study by our group found a linear improvement in various attributes of mental health beginning in young adulthood and progressing into older age. This improvement in well-being was noted despite an accelerated deterioration in physical and cognitive functioning across the same life period (Thomas et al. 2016). These data suggest that it is possible to be happy and subjectively rate oneself as having a good quality of life despite poor physical health. In a study of successful aging in schizophrenia, Cohen et al. (2009) found that in their sample, 13% of older adults with schizophrenia rated themselves as aging successfully. This finding suggests that even in individuals with severe mental illness, subjective successful aging is possible. Similarly, successful aging has also been demonstrated in cohorts of HIV-infected persons. In fact, a recent study found that despite worse physical and mental functioning among HIV+ individuals, their self-rated levels of successful aging were comparable to demographically matched HIV-uninfected individuals (Moore et al. 2013). Across disease groups, evidence supporting the potential for aging successfully highlights the continued need to characterize the components and predictors of this construct.

Components of Successful Aging

Over time there has been an increasing interest in factors that predict successful aging or positive health outcomes in older adults. Although there are multiple definitions of successful aging and diverging estimates of its prevalence, this construct has received increasing empirical attention with numerous studies investigating the nature and predictors of positive states of health and well-being in older adults. As with the definition of successful aging, there is no consensus regarding which components are central to the definition of this construct, nor is there agreement about whether successful aging should be measured objectively by persons other than the individual or be rated subjectively by older adults themselves. Not only is this broad construct defined using diverse parameters, but also across the literature there has been a wide range of suggested designations including "successful aging," "healthy aging," or "aging well." Given these noted discrepancies, there is a clear need to attain consensus to inform and enhance empirical study of this construct. These efforts will also have clinical implications, directly impacting interventions to support successful aging across the life-span. As policy directives mandate investment in health programs that focus on promoting positive health states, there is a growing clinical impetus to better understand the components, mechanisms, and interventions for successful aging.

Biopsychosocial components: A number of biopsychosocial components of successful aging have been identified across cohorts of older adults. However, the manner in which successful aging is operationalized in these studies differs greatly, which impacts the variables that researchers choose to investigate. In the literature regarding successful aging, disability and/or physical functioning (commonly measured by self-reported activities of daily living) is the most frequently discussed

component. Markers of physiological functioning (e.g., physical and cognitive functioning/impairment, illness and health status, longevity, mental health) have also received considerable empirical attention (Cosco et al. 2014).

To complement the data regarding biological components, researchers have examined psychological, social, and environmental variables that may relate to successful aging. These include well-being and life satisfaction, social engagement, personal resources (e.g., level of independence), and extrinsic factors (e.g., environmental and financial resources). For instance, ratings of life satisfaction and well-being, as well as social and productive functioning, are commonly measured components of successful aging (Depp and Jeste 2006). Factors such as hardiness, coping skills, active social participation, number of friendships, and life satisfaction appear to be key psychosocial elements of successful aging. These factors speak to the importance of an individual's perseverance, social engagement, and sense of well-being in promoting positive health states. Similarly, behavioral or physical components of successful aging include participating in healthy behaviors (e.g., exercising) while avoiding poor health habits (e.g., tobacco use).

In addition to objective measures of successful aging (as noted above), understanding older adults' subjective experience of what it means to age successfully is paramount in developing interventions and policy. Self-rated successful aging is a commonly used variable across research studies and has been positively linked to greater physical, mental, and emotional health. A focus group study of older adults' opinions regarding the contributors of successful aging revealed four major factors related to successful aging: attitude/adaptation (e.g., having a positive attitude, realistic perspective, and the ability to adapt to change); security/stability as related to one's living environment, social support, and financial resources; engagement/stimulation (e.g., feeling a sense of purpose in life and being useful to others); and health/wellness. Interestingly, the participants had mixed opinions regarding the necessity of general physical health and wellness for successful aging. Altogether, these data suggest that from the perspective of older adults, psychosocial factors may be more salient components of successful aging as compared to longevity, absence of disease/disability, and independence (Reichstadt et al. 2007).

Clearly, the construct of successful aging is multidimensional, nuanced, and more complex than mere survival. Successful aging may be best thought of as developing and maintaining one's social, cognitive, and emotional functioning. Despite the diversity in how the components of successful aging have been investigated across the literature, there is a growing evidence base regarding the mechanisms underlying successful aging and its various facets.

Mechanisms Underlying Successful Aging

Biological factors: Growing knowledge regarding the biologic mechanisms of normal and pathological aging has sparked an interest in characterizing the genetic, immunologic, and hormonal determinants of successful aging.

Studies in longevity have provided insights into genetic bases of aging outcomes. Different approaches have been used, such as examining predictors of individual life-span, as well as early and late mortality. For example, as noted by Christensen et al. (2006), late deaths (after 90–100 years old) are thought to be indicative of successful aging. There appears to be a familial component to longevity as suggested by the clustering of late deaths in families with many extremely long-living individuals. However, it is unclear whether this reflects a genetic component or environmental impact (e.g., unique environmental exposures during a long life may exert a positive influence on life-span and health at older ages). Data from twin studies indicate that genetic differences account for almost a quarter of the variation in life-span. Interestingly, the magnitude of genetic influences on life-span increases after age 60, suggesting that certain genes may affect longevity especially in older age. Candidate genes associated with longevity include the 641C allele in the APOC3 promoter (with the 641C homozygote status being associated with survival) and microsomal triglyceride transfer protein (MTTP). In the Framingham cohort, PON1 was related to outcomes such as walking speed, living past 65 years of age without chronic illness, and biological age based on osseographic index (Rana 2010). Preliminary data also suggest that IGF1R and HFE, two metabolism-related genes, might be involved in genetic variation in human life-span. Telomere length is another promising predictor of longevity, with findings of longer telomere length being associated with late death in humans. However, these results have not been consistently replicated (Christensen et al. 2006).

The genetic correlates of successful aging have also been explored through the lens of the stress response. Resilience, or resistance to developing psychological disorders despite exposure to trauma or stress, is a key facet of successful aging. The serotonin transporter polymorphism (5-HRRLPR) is a genetic risk factor that is related to the development of depression and anxiety symptomatology in response to stress. As such, it is a promising target for studies investigating the genetic underpinnings of resilience and successful aging. The short form (but not the long form) of this gene is associated with reduced serotonin transcription and reuptake efficiency and appears to play a role in various psychological disorders including depression and anxiety. Interesting, at older ages, the relationship between the 5-HTTLPR s allele and a psychopathologic response to stress is weaker; this raises the question of whether the s allele exerts a detrimental effect on resilience in older adults. In a recent study, O'Hara and colleagues (2012) reported that although the 5-HTTLPR s allele was not associated with lower emotional resilience in older adults, s allele carriers had lower cognitive abilities and self-ratings of successful aging. Their findings suggest that rather than emotional resilience, intact cognition may be more salient with regard to the subjective experience of aging successfully in older s allele carriers.

Biological processes such as apoptosis, neurotoxicity, oxidative stress, and inflammatory dysregulation may occur with greater frequency in older adults and have been shown to play a role in the pathophysiological mechanisms of neurodegenerative diseases such as Alzheimer's disease. There is growing evidence to suggest that in successful biological agers, these processes may be slowed down. This supports the notion that in these older adults, chronological age is not the same

as "biological age" (i.e., physiologically, their functioning is comparable to younger individuals). A recent study of 3,044 older adults suggested that maintaining low levels of systemic inflammation over 5 years may facilitate successful biological aging by mitigating the likelihood of impaired musculoskeletal and respiratory functioning and decreasing the risk of developing diabetes (Akbaraly et al. 2013).

Many studies examining the physiological substrates of aging have focused on the role of stress and stress-related chronic overactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Stress-induced chronic secretion of cortisol appears to damage the hippocampus as well as other brain structures. This is particularly relevant to the aging brain, as hippocampal abnormalities may manifest in impaired learning and consequent declines in everyday functioning. Not only does chronic stress contribute to neuroanatomical abnormalities, but it is also related to shortened telomere length, as well as the upregulation of proinflammatory cytokines. Changes in telomere length and cytokine levels are risk factors for cellular damage in the central nervous system (Eitan et al. 2014). While chronically elevated stress levels have been associated with poor health outcomes in older adults, the same is not true for mild levels of stress. In fact, low levels of stress may produce positive changes in the aging brain. This has been demonstrated in studies examining the effects of physical activity, caloric restriction, and cognitive stimulation; these activities produce low-grade stress, which activates neurotrophic factors such as brain-derived neurotrophic factor (BDNF). BDNF plays an important role in learning and higher-order cognitive functioning; as such, these data suggest that there is a nonmonotonic relationship between stress and cognitive functioning in the elderly that may be modulated by neurobiological changes. In summary, these findings showcase the complexity of the various biologic substrates of aging.

Brain and cognitive reserve: The age-related neurobiological changes described above have notable implications for the construct of brain reserve, which refers to the amount of neural damage that can be tolerated while preserving functioning (Stern 2002). It is thought that structural neural characteristics (e.g., density and number of neurons) determine peak brain volume, which in turn may be associated with brain injury outcomes such that individuals with greater brain volumes are more resistant to neurological insults. As such, greater brain reserve may delay the onset of a host of brain disorders and perhaps slow normal brain aging. The mechanism underlying the acquisition of brain reserve is not fully characterized, but findings from twin studies suggest that brain reserve may be heritable. Thus, it is possible that gene expression may drive neuroarchitectural changes (e.g., cortical thinning, brain shrinkage; Esiri and Chance 2012) and neurobiological changes (e.g., apoptosis) that impact peak brain volume.

Cognitive reserve is related to brain reserve and refers to the ability of the brain to adapt to neural damage via compensation by recruiting alternate brain regions to perform tasks (Stern 2009). The construct of cognitive reserve is thought to underlie the preserved cognition noted in individuals who have significant neuropathological abnormalities postmortem (Snowdon 2003). Compared to brain reserve, cognitive reserve appears to be a modifiable factor. Individuals who participate in cognitively stimulating activities, hold intellectually demanding jobs, and have higher levels of

education typically show greater cognitive reserve (Fratiglioni et al. 2004). In fact, individuals who participate in cognitively enriching physical, mental, or social activities appear to have lower risk of Alzheimer's disease. Relatedly, preliminary evidence suggests that higher cognitive reserve and brain integrity are linked to successful aging. It appears that cognitive reserve may be a neuroprotective factor and promote neural efficiency and neural compensation in the aging brain. Universally, brain and cognitive reserve theories point to the plasticity of aging brains, a particularly salient issue with regard to research into the mechanisms of successful aging. The existing literature suggests that the accumulated effects of exposure to enriching environments over the course of a lifetime impact brain and cognitive reserve in older adults. This relationship between neural, behavioral, and environmental factors appears to impact the trajectory of aging across the life-span. Accordingly, this relationship is of considerable scientific interest and foundational to a multidimensional understanding of successful aging.

Social and environmental factors: A growing body of research suggests that social and environmental variables may have effects on various aspects of successful aging. The impact of these factors may have a direct or indirect influence on aging. For instance, environmental surroundings may influence accessibility to safe areas for physical activity. A lack of exercise, in turn, may predispose individuals to obesity and other health-related issues. Low physical activity and obesity have both been shown to be associated with reduced reports of successful aging (Hodge et al. 2013). The environment (e.g., air quality) may also modulate risk for health conditions such as asthma or respiratory infections. In addition, the environment (i.e., neighborhood) has also been demonstrated to impact access to education (e.g., quality of schools) and quality of nutrition (e.g., food deserts, i.e., urban areas with poor access to fresh, healthy food). Educational resources may drive the extent to which cognitive stimulation is available and the level of cognitive reserve attained, whereas access to primarily unhealthy food vendors may alter risk for chronic, metabolic diseases such as diabetes. In this manner, the environment exerts direct and indirect effects on various components of successful aging. Consistent with this theory, exposure to resource-limited settings in childhood appears to have an impact on adult health. For example, Brandt et al. (2012) found that in a sample of 22,464 European men and women, childhood living conditions were independently associated with elders' odds of aging well even after controlling for demographic variables and later life risk factors. This suggests the importance of examining environmental resources available to an individual across the life-span when investigating predictors of successful aging.

The environment also has a direct impact on social functioning. Many investigators have emphasized the important influence of social factors on the capacity of individuals to age successfully. These include personal characteristics such as race, gender, sexual orientation, and socioeconomic status. The individual's interpersonal environment (e.g., friendships and family structure) also exerts influence on social functioning (Rowe and Kahn 2015). Previous studies have suggested that social connectedness (e.g., the number of close personal contacts or relationships) may predict successful aging and a lack of physical disability. In addition to social

interaction, participation in social activities has been shown to have a beneficial effect on happiness and everyday functioning while reducing risk of mortality (Hodge et al. 2013). Additionally, important social relationships such as family and friends may serve to boost an individual's sense of self-worth and mastery, both of which promote health maintenance and well-being. There are many reasons that may explain the association between social relationships and aging successfully. Supportive social networks may facilitate an individual's efforts to reach health-related goals and promote healthy behaviors (Cherry et al. 2013). It is also thought that the relationship between social functioning and successful aging may be mediated by factors such as cardiovascular health and systemic inflammation. For example, higher levels of social engagement appear to be related to lower C-reactive protein concentrations (Loucks et al. 2006), which signals lower levels of inflammation. These findings, taken in the context of prior studies that demonstrated the relationship between social engagement and coronary heart disease, suggest a biologic mechanism for the negative health outcomes associated with low social integration (Loucks et al. 2006). As a whole, there is growing evidence supporting the notable impact that social and environmental factors encountered throughout the life-span have on successful aging in late life.

Predictors of Successful Aging

Demographic predictors: The identification of the predictors of successful aging has the potential to guide future intervention approaches. As such, a great deal of research has focused on identifying characteristics that are associated with aging successfully. It appears that the subjective experience of well-being is critical for successful aging. In fact, Jeste and colleagues (2013) found that older age was associated with higher self-ratings of successful aging, despite worse physical and cognitive functioning. Their results suggested the role of key mental health factors (e.g., resilience) that may modulate the relationship between age and perceived successful aging. Other demographic variables such as social economic status, level of education, marital status, gender, and ethnicity have also been investigated. There is reason to believe that these factors interact in a complex manner to impact the course of aging. For instance, individuals with higher levels of education may have better employment opportunities and therefore better financial and social status as adults. Higher levels of education and consequent access to improved occupational opportunities may also have a positive effect on health by reducing exposure to hazardous environments and physical strain. Similarly, income appears to be associated with better health in older age; however, it is not clear whether income is a mediator of health rather than a predictor of unhealthy aging (White et al. 2015). Also of interest is the impact of gender on successful aging. Although women typically have longer life expectancies, they have higher rates of illness and disability. The differential rates of healthy aging across genders may be partially driven by socioeconomic differences between men and women, which are possibly a function of educational, occupational, and financial disparities (White et al. 2015).

Cognitive functioning: Cognition is another predictor that has received empirical attention in the successful aging literature. Although it has been investigated as a predictor of successful aging, it has often also been used as a marker of this construct. For example, a number of studies have operationalized successful aging as the absence of moderate to severe cognitive impairments into older age. To date, we know more about the predictors of preserved cognition rather than the various trajectories of cognitive decline and how they are related to healthy aging markers downstream.

It is well known that the lifetime risk of cognitive impairment increases with age; there is growing interest in characterizing the heterogeneity of longitudinal patterns of cognitive changes in adulthood. In fact, there appear to be three subgroups of older adults: one group with long-term maintenance of cognitive function into old age, a second group with mild declines akin to normal aging that do not progress to dementia, and finally a third group with dementia (Barnes et al. 2007). The presence of these varied trajectories raises an interesting question: can modifying key factors earlier in life can alter an individual's course of aging? For this reason, identifying the predictors of intact cognition has been an area of continued empirical study. Preliminary evidence suggests that better physical health, fewer medical comorbidities, engaging in healthy behaviors, and a high level of social engagement are associated with maintenance of optimal cognitive function at a future time point.

With regard to the association between cognition and successful aging, we know that the maintenance of intact cognition in older age is essential to preserving independence and quality of life, avoiding disability, and attaining longevity. It is likely that this relationship is reflective of necessary higher-order cognitive skills that support the execution of complex everyday functioning tasks such as medication management, social participation, and driving. These activities, in turn, contribute to improved health-related quality of life and physical functioning, which are both markers of successful aging. As such, it is not surprising that groups of individuals who show normal aging, mild cognitive impairments, and dementia would also differ on indices of successful aging. While we know that global cognitive functioning is related to successful aging, it is still unclear whether specific domains of cognition are differentially important for aging successfully. For example, it may be the case that preserved executive functioning and memory are more salient in terms of maintaining a robust quality of life into older age, while declines in processing speed or motor functioning can be compensated for, to some extent, and have a lesser detrimental effect on markers of successful aging. This issue has received limited empirical attention and warrants a closer analysis given the implications for developing interventions to target specific cognitive domains.

Physical functioning: In addition to demographic variables and cognition, much attention has been devoted to health-related predictors. Markers of physical functioning such as the absence of arthritis and hearing problems, hypertension, and medical comorbidities appear to be strong predictors of aging successfully. This relationship likely reflects the positive impact of the absence of disability on maintenance of independence in activities of daily living and robust quality of life, which in turn is associated with greater subjective experience of successful aging

(Montross et al. 2006). In addition to health-related predictors, lifestyle factors such as preserved daily functioning, physical activity level, and being a nonsmoker are also related to aging successfully.

It has long been known that engaging in multiple unhealthy behaviors (e.g., lack of exercise, smoking) is associated with a higher risk of early mortality, chronic disease, and cognitive impairment. The critical question is whether participation in healthy behaviors has a protective effect on the course of aging. Recent studies have demonstrated that engaging in healthy behaviors (e.g., increased physical activity, consumption of nutrient dense food) is associated with greater odds of aging successfully. In a large cohort of the British men and women, never smoking, moderate use of alcohol, daily consumption of fruits and vegetables, and participating in some physical activity predicted how successfully the participants aged over a 16-year time period (Sabia et al. 2012). Healthy behaviors impacted all four aspects of successful aging that were examined (i.e., cognitive, mental, respiratory, and cardiovascular health). These findings indicate the positive impact of modifying lifestyle variables, not only to reduce mortality and morbidity but also to improve quality of life in older adults (Jeste et al. 2015).

Participation in leisure activities is related to physical health and is a predictor of well-being. Leisure is typically defined as an enjoyable activity performed in one's free time; leisure activities may include physical activities like walking, cognitive activities like crossword puzzles, creative activities such as painting, or passive activities such as watching television. It may also include social activities such as spending time with friends. Many studies have demonstrated the negative impact that physical illness has on leisure activities, but there is a growing interest in characterizing the benefits of continued leisure participation into older age. Montross and colleagues (2006) found that the number of close friends, as well as frequency of reading, listening to the radio, and visiting family, was associated with self-ratings of successful aging, thus highlighting the relationship between leisure activities and subjective well-being.

These findings are complemented by prospective studies of older adults, which have shown that engaging in various leisure activities such as visiting restaurants or playing cards is associated with positive outcomes such as lower mortality, morbidity, and increased longevity. It has been theorized that the playfulness that stems from leisure activities buffers against sadness and stress. Additionally, the social support obtained by participating in group leisure activities may provide older adults with a rich, protective feeling of belonging and increased resilience when coping with age-related stressors (e.g., losing a spouse; Son et al. 2007). Hutchinson and Nimrod (2012) demonstrated that older adults were more likely to seek out leisure activities depending on (1) their beliefs in personal responsibility for their health, (2) their beliefs in personal abilities to care for their health, (3) acceptance of their health, and (4) their history of participating in leisure activities. The authors found that even older adults with chronic conditions were motivated to find ways in which they could compensate for their physical limitations and continue to participate in leisure activities. The level of participation was associated with markers of successful aging such as maintaining engagement with life. Altogether, these data support

the important role that preserved physical functioning, whether through leisure or healthy behaviors, can play in promoting successful aging.

Mental health functioning: The role of sustained positive mental health in aging successfully is also of great interest, as it is a potentially modifiable factor. There appears to be an association between age and depressive symptoms. Older adults often experience clinically significant depressive symptomatology, even though they may not meet criteria for major depressive disorder. Often, these nonmajor forms of depression are classified as "subthreshold depression" or "subsyndromal depression." The prevalence of subthreshold depression ranges from 8.8% to 21.3% (Vahia et al. 2010). Subthreshold depression is associated with numerous negative outcomes. These include increased healthcare utilization, risk of future major depressive disorder, suicide, disability, as well as declines and overall functioning and health-related quality of life (Vahia et al. 2010). In cohorts of older adults, higher prevalence of depressive symptoms also appears to be associated with increased incidence of cognitive impairment (i.e., both mild cognitive impairment and dementia; Goveas et al. 2016).

With regard to successful aging, one study showed that in a group of older women, subthreshold depression was associated with lower scores on various markers of successful aging. The components of successful aging examined in this study included optimism, resilience, health-related quality of life, and subjective cognitive difficulties (Vahia et al. 2010). There was a stair-step relationship between depression and successful aging such that the nondepressed group had the highest scores on markers of successful aging, the group with subthreshold depression had intermediate scores, and the depressed group showed the lowest rates of successful aging. The above finding that individuals with subthreshold depression have higher levels of disability and are aging less successfully than individuals who do not demonstrate any depressive symptoms has significant clinical implications. While subthreshold depression is considered prevalent in older adults, it frequently goes unrecognized by clinicians, and, consequently, individuals do not receive the treatment they need to alleviate their mood symptoms. Vigilant detection and management of mild depressive symptomatology is crucial for overall health in older adults and has the potential to reduce morbidity and improve the likelihood of aging successfully.

In addition to depression, resilience is another aspect of mental health functioning that is closely associated with successful aging. Resilience is conceptualized as an internal psychological resource or the "ability to bounce back from the variety of challenges that can arise in life" (Campbell-Sills and Stein 2007; p. 1026). It is theorized as comprising the characteristics of equanimity (i.e., a balanced perspective of life), meaningfulness (i.e., a sense of purpose in life), perseverance, existential aloneness (i.e., recognizing one's unique path and accepting one's life), and self-reliance (Wagnild 2003). Across cohorts of different ages and disorders, resilience has been found to be a buffering factor that protects against psychological distress. In a large, community-based study of self-rated successful aging, the positive effect of resilience on successful aging was comparable to that of physical health (Jeste et al. 2013). This suggests that increasing resilience may be as effective as physical health with regard to facilitating

successful aging. Similarly, higher levels of resilience have also been reported to protect against the negative influence of new medical disorders in older adults (Manning et al. 2014). Not only does resilience protect against declines in physical health, there is some evidence to suggest that high levels of resilience contribute to longevity; in fact, centenarians have been shown to be more resilient than any other age group (Zeng and Shen 2010).

The construct of resilience has particular relevance in understanding the counter-intuitive relationship between health status and self-reported successful aging. Across studies, researchers have found that regardless of suboptimal health status, older adults often report that they are aging successfully. (This concept was briefly noted earlier in the chapter and is coined *The Paradox of Aging*.) Over the past two decades, there has been a growing effort to characterize the moderators of this unexpected relationship; resilience appears to be a central factor. One study demonstrated that in older adults, resilience influenced the role perceived stress played in the relationship between mental health status and self-rated successful aging (Moore et al. 2015). The authors found that higher levels of resilience appeared to have an intervening role on perceived stress, reducing the strength of the relationship between poor mental health and decreased levels of self-rated successful aging. Clinically, these findings suggest that experiencing high levels of stress can have a detrimental effect on physical health and indirectly decrease subjective well-being. In addition, these data highlight the important role of resilience as a moderator of poor health status and psychological well-being. Resilience has also been linked to higher cognitive functioning and more positive views of aging. Accordingly, increasing one's ability to adjust and adapt to stressful situations (increase resilience) may have an impact on both physical and mental health. Such interventions may target goals such as increasing social connectedness, increasing a sense of mastery, and promoting spiritual grounding.

Positive traits: As evidenced by the growing interest in characterizing the role of resilience in promoting well-being, the focus of research is now shifting from deficit models focused on mental illness toward strength-based models focused on mental health as predictors of successful aging. As such, constructs such as optimism, spirituality, and wisdom are getting closer empirical attention. Optimism refers to an individual's expectation of positive outcomes across different situations and over time. Multiple studies have shown that optimism is associated with reduced number and intensity of physical symptoms, lower depressive symptoms, and better post-surgical outcomes. In older adults, data supporting the relationship between optimism and positive outcomes are mixed. Brenes and colleagues (2002) demonstrated that pessimism (i.e., the expectation that things will consistently go badly) but not optimism was correlated with daily activities such as walking, climbing stairs, and lifting. This study suggests that pessimism and optimism are two orthogonal dimensions, not just polar opposites of the same trait. It also suggests that pessimists may choose less adaptive coping strategies or behaviors (e.g., seek treatment less often or not adhere to treatment). In contrast, Bowling and Iliffe (2011) found that an individual's level of optimism as well as perceived self-efficacy predicted ratings of quality of life at a 7–8-year follow-up. Comparing these two contrasting findings

raises the possibility that older adults who are optimistic about future outcomes may not necessarily engage in specific health-promoting behaviors, but they may continue to perceive themselves as having a high level of well-being despite physical difficulties associated with aging. On the other hand, individuals who take a pessimistic view may engage in less healthy behaviors that lead to poor health outcomes and worse quality of life as they age.

Similar to the buffering role of resilience and optimism in moderating stress, religious involvement has also been shown to facilitate adjustment to stressful situations. Participating in active spiritual coping strategies such as private prayer has been associated with greater levels of optimism and may result in improved quality of life (Ai et al. 2010). Religiosity and spirituality appear to promote a sense of purpose, value, and meaningfulness in older adults, all of which are important aspects of well-being (Lawler-Row and Elliott 2009). Independent of demographic factors (e.g., age, gender), religious participation, social support, and spirituality or existential well-being (not necessarily tied to an organized religion or practice) predicted health outcomes in a study of older adults (Lawler-Row and Elliott 2009). The authors also found that individuals with higher levels of existential well-being had lower rates of depression and higher levels of subjective well-being. These data suggest that having a sense of purpose and meaning that comes from spirituality and religious practice may positively contribute to physical and mental health. Whether the relationship is mediated by social support or engaging in healthy behaviors or some other aspects remains to be fully characterized.

Wisdom, which in folk psychology is thought to increase with age, has also been examined in the context of successful aging. Wisdom is a holistic, multidimensional trait thought to encompass knowledge, good decision-making abilities, and also prosocial values and actions. Specifically, the subcomponents of wisdom include:

(1) Social decision-making and pragmatic knowledge of life as related to social reasoning, ability to give good advice, life knowledge, and life skills
(2) Prosocial attitudes and behaviors such as empathy, compassion, warmth, and a sense of fairness
(3) Reflection and self-understanding, which encompasses introspection, insight, intuition, and self-awareness
(4) Acknowledging and coping with uncertainty
(5) Emotional homeostasis, i.e., affect regulation and self-control (Bangen et al. 2013)

Biological studies of wisdom suggest that aspects of this construct (e.g., pragmatic life knowledge, emotional homeostasis, and processing ambiguity) may be subserved by brain regions associated with emotionality and immediate reward dependence (e.g., prefrontal cortex, anterior cingulate cortex, and amygdala; see Meeks and Jeste 2009 for review). Importantly, the relative weighting of the different subcomponents of wisdom may depend on the individual's culture (e.g., depending on the cultural context, the importance of introspection or social decision-making may vary). In older adults, wisdom appears to be related to multiple positive states including better physical health, greater quality of life, and better quality of social

relationships (Ardelt 1997; Ardelt and Edwards 2001). Wise elders identify the importance of recognizing the physical declines that accompany old age and yet continuing to engage with life. As such, wisdom may promote successful aging by facilitating the acceptance of the realities of aging and mortality while continuing to live a meaningful life (Ardelt et al. 2013).

This review of the literature regarding the varied predictors of successful aging clearly demonstrates the complex relationships among these factors. For example, participating in leisure activities may exert a positive influence on aging by boosting resilience (a positive psychological trait), building cognitive reserve through engagement, and/or by promoting physical activity and thus improving physical health. These complex interactions have not yet been disentangled, and future research should clarify the associations among these variables and their relative influence on successful aging.

Strategies and Interventions to Promote Successful Aging

While much of the research in the area of successful aging has focused on the underlying factors that promote this construct, a growing body of work has begun to assess interventions to improve upon the typical trajectory of aging. A major limitation in examining the evidence base regarding the effectiveness of various successful aging strategies is the lack of consensus regarding the definition of successful aging. Taking this into consideration, Harmell et al. (2014) defined a "successful aging strategy" as an intervention or potentially modifiable characteristic that is intended to enhance the functioning of normally aging older adults. Numerous strategies for successful aging have received empirical attention, and they are described below.

Physical activity: The benefits of physical activity in aging cohorts have been long established, with longitudinal studies demonstrating that greater exercise participation predicts lower risk of mortality, disability, cardiovascular disease, osteoporosis, and certain types of cancer. As such, the American College of Sports Medicine recommends at least 30 min of exercise 5 days/week to obtain health benefits. Not only is physical activity associated with improved health, it is also a predictor of better cognitive outcomes. Research findings have shown a relationship between higher levels of physical activity and lower levels of cognitive impairment concurrently and also at an 18-month follow-up (Harmell et al. 2014). Additionally, physical exercise also appears to enhance emotional functioning in older adults. Overall, there is substantial support to suggest that physical activity across the lifespan has beneficial effects on various facets of successful aging.

Numerous randomized controlled studies have examined the effectiveness of increasing physical activity on a variety of markers of successful aging in older adults. The exercise modalities studied have included aerobics, strength training, and resistance exercises. In a recent study, Klusmann and colleagues (2012) demonstrated that engagement in physical exercise reduced dissatisfaction in a cohort of older women. This is a promising finding that supports participation in new physical

activity programs as a strategy to positively modulate negative mood. Similarly, moderate exercise in mid- and late life may reduce the risk of mild cognitive impairment and dementia (Ahlskog et al. 2011).

Exercise appears to have the most prominent benefit on executive functioning and verbal memory; however, it remains to be seen how long these effects persist and whether there is a dose effect with regard to benefit in other cognitive domains. There is also evidence suggesting that exercise results in neuroanatomical changes such that sustained aerobic activity over 6 months was shown to increase gray and white matter volume in previously sedentary older adults (Colcombe et al. 2006). It is likely that exercise improves brain functioning by promoting neurotrophic factors and reducing inflammation as well as oxidative stress. With regard to the antidepressant effect of exercise, it has been theorized that exercise may increase levels of neurotransmitters such as serotonin and norepinephrine, boost dopaminergic activity, and elevate endogenous opioids. From a psychological perspective, exercise is thought to boost a sense of mastery and self-efficacy. It may also improve mood and psychological functioning via behavioral activation.

Although there is growing empirical and clinical attention to the benefits of physical activity for older adults, this segment of the population continues to have low rates of physical exercise. Indeed, older adults have unique barriers (e.g., pain, fear of injury or falls, lack of a peer group to exercise with) that lower their participation in physical activity. These issues warrant consideration prior to implementing public health interventions to increase physical activity in older adults. Another issue that must be addressed in future research pertains to improving the adherence of older adults to exercise and sustainment over time. Addressing these barriers has implications for how physical activity may be deployed as an intervention for successful aging in the future.

Dietary change: Diet and nutrition-based interventions are the most frequently studied strategies for extending the life-span in animal models of aging. In humans, studies have demonstrated that high calorie diets and obesity are risk factors for dementia. As such, it is not surprising that there has been an increase in the empirical attention given to dietary interventions. Of note, the findings supporting the use of dietary supplements have been mixed. For example, diets supplemented with folic acid, omega-3 fatty acids, and antioxidants have been associated with better cognitive functioning, while other supplements such as ginkgo biloba and vitamin D have not shown significant benefit for cognition. On the other hand, dietary patterns such as the Mediterranean diet, which includes high consumption of fruits and vegetables, high ratio of polyunsaturated to saturated fats, and foods with low glycemic load, have been shown to be associated with reduced depressive symptoms and lower risk for cognitive impairment.

Based on findings from animal research that support the relationship between caloric restriction and longevity, small trials among humans involving reduced caloric intake compared to baseline have shown improvements in markers such as blood pressure, cholesterol levels, body mass index, and triglycerides (Bordone and Guarente 2005). It is thought that caloric restriction reduces oxidative stress produced by energy metabolism and also changes insulin sensitivity. Furthermore,

caloric restriction may trigger the release of neurotrophic factors such as BDNF that are positively associated with longevity. The exact mechanism through which dietary changes impact successful aging is yet to be characterized, and it is very likely that other factors such as genetic makeup and gut microbiota will play a role in explaining this complex relationship between diet and aging outcomes.

Cognitive stimulation: The growing evidence regarding neuroplasticity being preserved as people age has driven the development of cognitive interventions to delay or slow the progression of cognitive decline. Consequently, older adults are increasingly being encouraged to engage in cognitively stimulating activities such as reading, solving crossword puzzles, and playing board games. In individuals without cognitive impairment, there does appear to be a positive effect of cognitive interventions on cognitive functioning (Vahia et al. 2010). Reijnders and colleagues (2013) reviewed 35 cognitive intervention studies and found that cognitive training in older adults with or without cognitive impairment can be effective in improving objective cognitive functioning. The authors reported a varied range of approaches that were used in these studies, including computerized training, teaching memory strategies, training metacognitive skills, or promoting selective attention skills. Overall, they found improvements in the domains of memory, executive functioning, processing speed, attention, and fluid intelligence. As a result of these interventions, participants' subjective cognitive complaints also appeared to decrease.

Investigators have also explored computerized approaches to improve cognition; however, the results supporting this modality are mixed. In some studies computerized training via videogame-like platforms appeared to have a beneficial effect on multitasking and processing speed, although in others such an approach did not improve visuospatial navigational skills or memory (Pieramico et al. 2014).

Despite these interesting preliminary findings, a major gap in the literature is whether these improvements on laboratory measures of cognition generalize to real-world settings where individuals must execute everyday functioning tasks that tap multiple aspects of these cognitive domains. Another concern is the rapid increase in commercially available products that claim to improve cognition in older adults; many of these tools lack rigorous empirical studies regarding their validity, reliability, and efficacy. Taken as a whole, there are some important issues that are yet to be thoroughly examined in the context of cognitive interventions. First, we need to increase our understanding of the causal effects of these cognitively stimulating activities on slowing or delaying cognitive decline. Second, future research should investigate what types of cognitive activities have the best cognitive outcomes, and relatedly, what frequency of interaction is necessary for cognitive gains. Finally, the mechanisms of the interventions and stimulating activities, whether through structural changes in the brain or alteration in neural activity and circuits, should be characterized.

Social engagement: Across the life-span, social engagement has been found to have positive effects on health and well-being. Social engagement can be defined as being socially and emotionally connected with others such as family members, friends, or the community (e.g., fellow religious organization members). A recent meta-analysis found that social engagement was a strong protective factor for multiple levels of health (i.e., physical, mental, emotional; Holt-Lunstad et al. 2010).

The level of social engagement appears to have a positive effect on health-related quality of life (Cherry et al. 2013). Promoting social engagement and reducing social isolation have been the target of multiple intervention studies. Across studies, different approaches have been including improving social skills, enhancing social support, and facilitating access to peer groups. An important issue to consider when implementing such social engagement interventions is environmental barriers (e.g., limited mobility, transportation resources) that older adults encounter. A novel intervention program called *The Seniors Centre Without Walls* targets the social needs of older adults who are socially isolated due to financial, geographical, or physical restrictions (Newall and Menec 2013). As part of this program, older adults participate in a phone conference, which is facilitated by a leader who provides general aging-related educational information. The conference provides the participants with an avenue to connect with others in the community and make new friends. Participation in this program was associated with increased happiness and lowered loneliness and depression. These findings suggest that even remote or non-face-to-face approaches to social interaction can have a beneficial effect on aspects of successful aging.

Given the strong relationship between environmental and social factors and successful aging, it is critical that these variables be considered when planning and developing communities for older adults. As such, there is a growing interest in establishing community-wide projects to change built (physical) and social environments so that older adults do not encounter barriers to social participation (Scharlach and Lehning 2013). These modifications may include establishing transportation assistance, providing sidewalk benches, creating community senior centers, and hosting social, cultural, or recreational events. Such approaches are critical to building age-friendly cities that promote active aging and enhance quality of life by providing resources for health, social participation, and security to older adults. The development of age-friendly cities reflects a large-scale intervention aimed at providing resources to individuals across the life-span that target critical facets of successful aging (Jeste et al. 2016).

Technology: Another avenue to address the social and environmental aspects of successful aging may be through technology. The ongoing technological revolution shows promise with regard to transforming experience of aging by addressing key social and environmental issues that are salient to older adults. For instance, new computer-based technologies have the potential of helping older adults communicate with relatives and friends who live far away, thus enhancing their social functioning. Another approach to maintaining existing social ties and engagement is by enabling older adults to age safely and successfully in their own homes. Novel technologies such as sensors and monitors are also being used to ensure that older adults can continue to live safely in their own homes despite declines in physical ability. An important issue, of course, is whether older adults can or will adapt to these new technologies. Early data suggest that older adults do in fact adopt novel information and communication technologies and they are increasingly proficient in using these services. These are promising findings that support the development and deployment of exciting new technological approaches to promote well-being in older adults.

Conclusion

In this chapter, we have attempted to deconstruct the various components of successful aging and the underlying mechanisms of successful aging including biological, social, and environmental factors and reviewed predictors of successful aging and various strategies that may increase the likelihood of aging successfully. At present, there is no consensus regarding the definition of successful aging, nor is there a gold-standard measure to assess this construct. Nonetheless, researchers agree that this multidimensional concept that includes physical, cognitive, social, and psychological well-being warrants close attention. The mechanisms of successful aging appear to be reciprocal in nature, and there is a great need to study the interplay between the observable environmental and biological substrates. The predictors of aging successfully also have a complex relationship with one another and various facets of this construct. Further disentangling these relationships has the potential to inform future interventions to promote successful aging across the life-span.

Cross-References

► Depression in Late Life: Etiology, Presentation, and Management
► Sociology of Aging

References

Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC (2011) Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc 86(9):876–884

Ai AL, Ladd KL, Peterson C, Cook CA, Shearer M, Koenig HG (2010) Long-term adjustment after surviving open heart surgery: the effect of using prayer for coping replicated in a prospective design. The Gerontologist 50(6):798–809

Akbaraly TN, Hamer M, Ferrie JE, Lowe G, Batty GD, Hagger-Johnson G, . . . Kivimäki M (2013) Chronic inflammation as a determinant of future aging phenotypes. Can Med Assoc J 185(16): E763–E770

Ardelt M (1997) Wisdom and life satisfaction in old age. J Gerontol Ser B Psychol Sci Soc Sci 52 (1):P15–P27

Ardelt M, Edwards CD (2001) Old age wisdom: a powerful predictor of aging well across race and gender. Gerontologist 41:216–217

Ardelt M, Landes SD, Gerlach KR, Fox LP (2013) Rediscovering internal strengths of the aged: the beneficial impact of wisdom, mastery, purpose in life, and spirituality on aging well. In: Sinnott JD (ed) Positive Psychology. Springer, New York, pp 97–119

Baltes PB, Baltes MM (1990) Psychological perspectives on successful aging: the model of selective optimization with compensation. Success Aging: Perspect Behav Sci 1(1):1–34

Bangen KJ, Meeks TW, Jeste DV (2013) Defining and assessing wisdom: a review of the literature. Am J Geriatr Psychiatry 21(12):1254–1266

Barnes DE, Cauley JA, Lui LY, Fink HA, McCulloch C, Stone KL, Yaffe K (2007) Women who maintain optimal cognitive function into old age. J Am Geriatr Soc 55(2):259–264

Bordone L, Guarente L (2005) Calorie restriction, SIRT1 and metabolism: understanding longevity. Nat Rev Mol Cell Biol 6(4):298–305

Bowling A, Iliffe S (2011) Psychological approach to successful ageing predicts future quality of life in older adults. Health Qual Life Outcomes 9(1):1

Brandt M, Deindl C, Hank K (2012) Tracing the origins of successful aging: the role of childhood conditions and social inequality in explaining later life health. Soc Sci Med 74(9):1418–1425

Brenes GA, Rapp SR, Rejeski WJ, Miller ME (2002) Do optimism and pessimism predict physical functioning? J Behav Med 25(3):219–231

Campbell-Sills L, Stein MB (2007) Psychometric analysis and refinement of the connor–davidson resilience scale (CD-RISC): validation of a 10-item measure of resilience. J Trauma Stress 20(6):1019–1028

Cherry KE, Walker EJ, Brown JS, Volaufova J, LaMotte LR, Welsh DA,. . . Wood RH (2013) Social engagement and health in younger, older, and oldest-old adults in the Louisiana healthy aging study. J Appl Gerontol 32(1):51–75

Christensen K, Johnson TE, Vaupel JW (2006) The quest for genetic determinants of human longevity: challenges and insights. Nat Rev Genet 7(6):436–448

Cohen CI, Pathak R, Ramirez PM, Vahia I (2009) Outcome among community dwelling older adults with schizophrenia: results using five conceptual models. Community Ment Health J 45(2):151–156

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, . . . Kramer AF (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol Ser A: Biol Sci Med Sci 61(11):1166–1170

Cosco TD, Prina AM, Perales J, Stephan BC, Brayne C (2014) Operational definitions of successful aging: a systematic review. Int Psychogeriatr 26(03):373–381

Depp CA, Jeste DV (2006) Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. Am J Geriatr Psychiatry 14(1):6–20

Eitan E, Hutchison ER, Mattson MP (2014) Telomere shortening in neurological disorders: an abundance of unanswered questions. Trends Neurosci 37(5):256–263

Esiri MM, Chance SA (2012) Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease. Alzheimers Res Ther 4(2):1

Fratiglioni L, Paillard-Borg S, Winblad B (2004) An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 3(6):343–353

Goveas JS, Rapp SR, Hogan PE, Driscoll I, Tindle HA, Smith JC,. . . Ockene JK (2016) Predictors of optimal cognitive aging in 80+ women: the Women's Health Initiative Memory Study. J Gerontol Ser A: Biol Sci Med Sci 71(Suppl 1):S62–S71

Harmell AL, Jeste D, Depp C (2014) Strategies for successful aging: a research update. Curr Psychiatry Rep 16(10):1–6

Hodge AM, English DR, Giles GG, Flicker L (2013) Social connectedness and predictors of successful ageing. Maturitas 75(4):361–366

Holt-Lunstad J, Smith TB, Layton JB (2010) Social relationships and mortality risk: a meta-analytic review. PLoS Med 7(7):e1000316

Hutchinson SL, Nimrod G (2012) Leisure as a resource for successful aging by older adults with chronic health conditions. Int J Aging Hum Dev 74(1):41–65

Jeste DV, Savla GN, Thompson WK, Vahia IV, Glorioso DK, Martin AVS, . . . Kraemer HC (2013) Association between older age and more successful aging: critical role of resilience and depression. Am J Psychiatry 170(2):188–196

Jeste DV, Palmer BW, Rettew DC, Boardman S (2015) Positive psychiatry: its time has come. J Clin Psychiatry 76(6):675–683

Jeste DV, Blazer DG II, Buckwalter KC, Cassidy KL, Fishman L, Gwyther LP, Levin S, Liu KJ, Lustig T, Phillipson C, Rao R, Rosenbloom S, Schmeding E, Vega W, Avanzino JA, Glorioso DK, Feather J (2016) Age-friendly communities initiative: why is it important for geriatric psychiatry? Am J Geriatr Psychiatry 24:1158–1170. (in press)

Klusmann V, Evers A, Schwarzer R, Heuser I (2012) Views on aging and emotional benefits of physical activity: effects of an exercise intervention in older women. Psychol Sport Exerc 13(2):236–242

Lawler-Row KA, Elliott J (2009) The role of religious activity and spirituality in the health and well-being of older adults. J Health Psychol 14(1):43–52
Loucks EB, Berkman LF, Gruenewald TL, Seeman TE (2006) Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. American J Cardiology 97(7):1010–1016
Manning LK, Carr DC, Kail BL (2014) Do higher levels of resilience buffer the deleterious impact of chronic illness on disability in later life? The Gerontologist 56(3):514–524
Meeks TW, Jeste DV (2009) Neurobiology of wisdom: a literature overview. Arch Gen Psychiatry 66(4):355–365
Meng X, D'arcy C (2013) Successful aging in Canada: prevalence and predictors from a population-based sample of older adults. Gerontology 60(1):65–72
Montross LP, Depp C, Daly J, Reichstadt J, Golshan S, Moore D,. . . Jeste DV (2006) Correlates of self-rated successful aging among community-dwelling older adults. Am J Geriatr Psychiatry 14(1):43–51
Moore RC, Moore DJ, Thompson WK, Vahia IV, Grant I, Jeste DV (2013) A case-controlled study of successful aging in older HIV-infected adults. J Clin Psychiatry 74(5):417–423
Moore RC, Eyler LT, Mausbach BT, Zlatar ZZ, Thompson WK, Peavy G,. . . Jeste DV (2015) Complex interplay between health and successful aging: role of perceived stress, resilience, and social support. Am J Geriatr Psychiatry, 23(6):622–632
Newall NE, Menec VH (2013) Targeting socially isolated older adults a process evaluation of the senior centre without walls social and educational program. J Appl Gerontol. doi:10.1177/0733464813510063
O'Hara R, Marcus P, Thompson WK, Flournoy J, Vahia I, Lin X,. . . Jeste DV (2012) 5-HTTLPR short allele, resilience, and successful aging in older adults. Am J Geriatr Psychiatry 20(5):452–456
Pieramico V, Esposito R, Cesinaro S, Frazzini V, Sensi SL (2014) Effects of non-pharmacological or pharmacological interventions on cognition and brain plasticity of aging individuals. Front Syst Neurosci 8:153
Rana B (2010) Molecular genetic building blocks of successful cognitive and emotional aging. In: Colin DVJ, Depp A (eds) Successful cognitive and emotional aging. American Psychiatric Publishing, Washington, DC, pp 215–241
Reichstadt J, Depp CA, Palinkas LA, Jeste DV (2007) Building blocks of successful aging: a focus group study of older adults' perceived contributors to successful aging. Am J Geriatr Psychiatry 15(3):194–201
Reijnders J, van Heugten C, van Boxtel M (2013) Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. Ageing Res Rev 12(1):263–275
Rowe JW, Kahn RL (1987) Human aging: usual and successful. Science 237(4811):143–149
Rowe JW, Kahn RL (2015) Successful aging 2.0: conceptual expansions for the 21st century. J Gerontol Ser B Psychol Sci Soc Sci 70(4):593–596
Sabia S, Singh-Manoux A, Hagger-Johnson G, Cambois E, Brunner EJ, Kivimaki M (2012) Influence of individual and combined healthy behaviours on successful aging. Can Med Assoc J 184(18):1985–1992
Scharlach AE, Lehning AJ (2013) Ageing-friendly communities and social inclusion in the United States of America. Ageing Soc 33(01):110–136
Snowdon DA (2003) Healthy aging and dementia: findings from the Nun Study. Ann Intern Med 139(5_Part_2):450–454
Son JS, Kerstetter DL, Yarnal CM, Baker BL (2007) Promoting older women's health and well-being through social leisure environments: what we have learned from the Red Hat Society®. J Women Aging 19(3–4):89–104
Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychologia Soc 8(3):448–460
Stern Y (2009) Cognitive reserve. Neuropsychologia 47(10):2015–2028

Thomas ML, Kaufmann CN, Palmer BW, Depp CA, Martin AS, Glorioso DK, . . . Jeste DV (2016) Paradoxical trend for improvement in mental health with aging: a community-based study of 1,546 adults aged 21–99 years. J Clin Psychiatry (in press)

Vahia IV, Meeks TW, Thompson WK, Depp CA, Zisook S, Allison M,. . . Jeste DV (2010) Subthreshold depression and successful aging in older women. Am J Geriatr Psychiatry 18(3):212–220

Wagnild G (2003) Resilience and successful aging: comparison among low and high income older adults. J Gerontol Nurs 29(12):42–49

White G, Singh T, Caine K, Connelly K (2015) Limited but satisfied: low SES older adults experiences of aging in place. Paper presented at the Pervasive Computing Technologies for Healthcare (PervasiveHealth), 2015 9th International Conference on

Zeng Y, Shen K (2010) Resilience significantly contributes to exceptional longevity. Curr Gerontol Geriatr Res, vol. 2010, Article ID 525693, 9 pages. doi:10.1155/2010/525693

Sociology of Aging

3

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Abstract

The relevance of social factors and not only biological and psychological factors is now considered to be a truism in present-day psychiatry. Aging is certainly related to physiological changes the body goes through during the life course but is also influenced by the social norms and expectations pertaining to different periods in the individuals' life. The purpose of this chapter is to address both empirical data and theoretical background studied in the sociology of aging. This discipline seeks to understand the social aspects in the process of aging and the challenges encountered as seniors grow older. Different sociological aspects are relevant for psychiatrists; this chapter is written by clinicians, and the emphasis will be placed on sociological subjects relevant to geriatric psychiatrists in particular.

The sections in this chapter review the process of aging, the biological facts, the cultural attitudes, and the social implications, including distinctive social situations in elderly individuals, such as the differences in men/women, retirement, potential dependency, and problems related to caregivers or to economic difficulties. The aging in the population is approached to explain demographic

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_4

changes, including those related to marital status, migration, educational level, or socioeconomic status. Furthermore, this chapter reviews some specific challenges for the elderly, including the ageism, abuse, and stereotypes, and analyzes classical sociological theories of aging. This chapter ends by portraying potential guidelines for actions on aging.

Keywords

Sociology • Aging • Theories • Geriatric psychiatry • Ageism • Stereotype • Elderly

Contents

Introduction

The Relevance of the Sociology of Aging in Geriatric Psychiatry

The relevance of social factors and not only biological and psychological factors is now considered to be a truism in present-day psychiatry. There is substantial evidence that social problems serve as risk factors for mental health disorders and as contingencies that influence the course and outcome of psychiatric disturbances and determine to some extent the use of mental health services (George 2009). This may be particularly pertinent in elderly patients. Aging is certainly related to physiological changes the body goes through during the life course but is also influenced by the social norms and expectations pertaining to different periods in

the individuals' life. Life expectancy has increased in recent years, particularly in Western countries, as the result of medical advancements but also as a result of social advances that made possible a health improvement. The purpose of this chapter is to address both empirical data and theoretical background studied in the discipline sociology of aging, which seeks to understand the social aspects in the process of aging and the challenges encountered as seniors grow older (Harris 2007). It is pertinent here to remember the unique place psychiatry occupies in scientific medicine, as was described brightly by Jaspers: Psychiatry needs the "natural sciences" but also the "sociocultural sciences," including sociology (Jaspers 1997). This is the beauty of the discipline, but it is also a challenge. More recently, in the Johns Hopkins Hospital "Perspectives of Psychiatry," McHugh and Slavney (1998) have convincingly argued about the need of models strongly influenced by the Jasperian tradition, to accompany the "medical" or "disease" model.

This chapter is written by clinicians, and the emphasis will be placed on sociological subjects relevant to clinicians, to geriatric psychiatrists in particular. Indeed, they should be interested in the social aspects of aging in relation to psychopathological disturbances. Together with the biological processes, they should be concerned with the social problems encountered in this period of life and their potential to cause or be the consequence of psychiatric disturbances. In fact, from the sociological field, it has been discussed how both economic and social hardships contribute to different health outcomes and potentiate the risk of poor health when combined (Ahnquist et al. 2012). Even from the positivist view and the biological perspective, the influence of environmental factors in conditions with strong genetic background is now acknowledged. Clinicians should also be aware of the attitudes and beliefs about the aging process, because of the potential implications for mental health.

The Process of Aging: Biological Facts

Social Implications and Cultural Attitudes

Stages of Aging

There is no generalized acceptance to define old age. The World Health Organization acknowledges that 65 years old is the commonly accepted definition in most advanced nations, but it suggests a limit somewhere between 50 and 55 years old for developing nations (WHO 2012). In any case, the limits of grouping the elderly according to chronological age are obvious. A crucial aspect to consider here is the component of social construction in the way individuals and nations define who is elderly; the shared meaning of the concept is created through interactions among people in society and may therefore vary in different cultures. This is exemplified by the cliché that you are only as old as you feel. Still, it is obvious that both from the physical and the psychological point of view, the life experience of a 65-year-old is very different from that of a 90-year-old. In relation to this, it is now common to

Table 1 Biological changes in the old age

Some functional physiological changes (Wide individual differences)	Morfological and functional brain and CNS changes
↓ Function in organs/systems, generalized	↓ Weight
↓ Vitality, progressive	↓ Volumen (atrofy)
↓ Ability to cope with stress	Fibrosis
→ Frailty/vulnerability	Rigidity cerebral arteries
	↓ 0_2 and glucose consumption
	↓ Motor efficiency
	Changes in sleep pattern

divide the elderly population into three subgroups: the young-old (approximately 65–74 years), the middle-old (ages 75–84 years), and the old-old (over age 85 years).

It also influences the view on the dichotomy of the so-called Third Age and Fourth Age, although both are subject to important variation and evolution. The former, generally defined as the span of time between the ages of 65 and 80+, has been considered by many to be the "golden years" of adulthood. Following retirement and the beginning of age-imposed physical, emotional, and cognitive limitations, there is a period with fewer responsibilities (e.g., career and family rearing) than before, and, particularly with reasonable financial resources, this may be a period of good physical and psychological health, with the potential for self-fulfillment and accomplishment. On the contrary, in the so-called Fourth Age, it is more typical to find biological and functional decline, including a period when most individuals experience non-pathological cognitive decline. The preservation of functional capacity is more difficult, and the probability of having multi-morbidity increases substantially, although older adults may display an adaptive potential to solve problems and regulate emotions (Blanchard-Fields 2009).

Biological and Psychological Changes in the Elderly

The term "senescence" refers basically to the biological aging, the gradual decay in function living organisms go through. Inevitable biological changes occur in old age. Table 1 summarizes some commonly described in humans, although the specific changes are a matter of controversy and it is obvious that there are wide individual differences. It is important to recognize that changes take place, and adaptation is necessary.

While the psychological changes in the elderly are also a matter of controversy, particularly because the literature often emphasizes the negative kind of changes, there are modifications in both cognitive style and copying style requiring adaptation. It is commonly accepted that the elderly are more introspective and reflexive, may have important health concerns, and are certainly aware that death is approaching. However, acceptance and resignation are psychological resources that may serve adaptation purposes. From the psychodynamic perspective, Erikson has described in older adults what he calls the "maturity" phase, a period of wisdom,

Table 2 The components of frailty

Nutritional status	Weight loss
Energy	Exhaustion
Physical activity	Leisure time activity, decreased
Mobility	Gait speed, slow
Strength	Grip strength, decreased
Psycho-social	Vulnerability, social disengagement

reflection on life, and the sense of fulfillment, although psychosocial conflict may also arise in the form of regret and despair.

In relation to the biological changes, it is also an inevitable consequence of aging; at some point poor physical health may be accompanied by poor psychological health. "Frailty" is a modern medical term to describe the vulnerable situation the oldest adults may reach at some point. This concept has grown in importance in medicine and is now a priority because of a need for a better understanding of the health and functional status of older persons and a need to prevent or at least delay the onset of late-life disability and its adverse consequences. While there is no consensus regarding the definition of frailty (Romero-Ortuno and O'Shea 2013), several biological domains are commonly included in the concept (Table 2), which is widely accepted in the medical field. A crucial point is that this construct identifies a phenotype of older persons at elevated risk for numerous adverse outcomes (Rodriguez-Mañas et al. 2013). Nevertheless, "frailty" also implies a psychosocial vulnerability and should also be a matter of social concern. The dynamic concept of frailty developed by Rockwood recognizes a complex interplay of assets and deficits, "medical" and "social," that maintain or threaten independence (Rockwood et al. 1994).

Sociological Implications of Changes in Old Age

Since chronological age does not necessarily coincide with health status, it is difficult to decide at a population level when social alert should start, but the biological alert might begin in those individuals aged 75 years or more, and particularly in those 85 years or more, in relative coincidence with the "Fourth Age," a time of frailty and vulnerability but also of "social disengagement." It is at this point when families and the care system must be prepared to cope, not only with the medical side of the problem but also with the social side. Attitudes and habits may importantly influence the possibilities given to the elderly, but also individuals themselves may strongly influence the limits they impose on themselves. In undesirable cases, an "auto-stereotype" could result with the restriction in activities that is not supported by the biological state of the individual (Stuckelberger et al. 2012).

Distinctive Social Situations in Elderly Individuals

Particular situations occur in old age are susceptible to become challenges for the elderly discussed in this sector.

Gender Differences

As a result of demographic changes described in the following section, there is a clear imbalance in the sex ratio of men to women in the population, which is increasingly skewed toward women as people age (WHO 2003). The differences in life expectancy may have important social implications, since the old-old population is the cohort with the greatest needs for care, and therefore women are more affected. Moreover, an economic imbalance may exist. Women have less retirement benefits because many did not work outside the household, and the ones having been employed may have earned less on average than men.

In relation to this, it is inevitable to consider the potential implications for psychiatry. Older women report higher levels of psychiatric symptoms, especially depressive symptoms, than do men (De la Cámara et al. 2008), although there is some conflicting data related to the differences by sex in the incidence of major depression among older adults (Schoevers et al. 2000).

Retirement

An achievement of Western civilization is the fact that most people in developed countries now have the expectation that at some point in the aging experience they will stop working and enjoy a retirement plan and some kind of pension. The main challenge of pension policies is to combine adequacy and financial sustainability (Zaidi 2008). Still, most adults expect an enjoyable life without the daily duties and to be involved in activities for which they had no time before. Nonetheless, substantial differences are observed among individuals, which are partially explained by social roles and social factors. Some individuals reach retirement age finding it difficult to adapt to new activities, new routines, and new social roles. Since both roles and social factors change over time, and across setting and social context, the meanings of retirement or the value given to work are social constructs that vary importantly in individuals and in different cultures. This may explain some empirical observations, including controversial data in relation to higher levels of psychological distress at the time of retirement, especially in men (Vo et al. 2015).

Gender differences have likewise been observed in relation to psychological reactions following retirement, and some authors have documented higher levels of distress in men, when compared with women (Vo et al. 2015). While the gender differences in relation to work and occupation are changing drastically, until now men seem to be influenced more than women by traditional expectations of being seen as the main providers and the ones for whom work achievements were considered to have overriding importance (Vo et al. 2015).

Healthy aging programs are now directed at preparing adults for the time of retirement, and maintaining an active life is proposed by most programs. An example of this is the "University for the experimented," a very successful initiative in the University of Zaragoza to help the elderly maintain an active intellectual life (www.uez.unizar.es). Authors in different countries, including the European countries, now argue that it is important for the country's economy, but also for

individual's satisfaction, to extension working life in order to adjust to a longer-life course and similarly to the changing perceptions of the elderly (Zaidi 2008; Biggs et al. 2013).

Potential Dependency

Some people are particularly concerned about old age and would embark on cosmetic remedies, or even in medical or surgical remedies, to avoid the natural effects of age. Most are aware of the risk of becoming dependent, and some of them are similarly concerned. Dependency changes through the phases of the life course are certainly common in old age, as has been well documented by epidemiological research. Quintanilla (2006) found disability in instrumental activities of daily living (ADLs) in 18.4% of adults aged 55 years or more, 12.8% for basic ADLs, and 19.8% for social ADLs, proportions that increased considerably in the older olds. In fact, cultural values and norms profoundly influence views on the life course and on the experience of dependency. Among the social values, family support is crucial in aging, influencing the actual experience of care, but also the individuals' satisfaction (Edmonson 2013).

Since dependency is also a form of social perception, it may require objective measures in its assessment. To rely only on the chronological age of individuals, no matter where the cutoff point is placed, or only on the employed status of individuals, would be incomplete. A considerable proportion of older individuals remain independent following retirement age and are involved in family affairs such as caring for the sick or the children, which allows other family members to be financially productive, or are involved in nonpaid activities external to the family such as volunteer associations, often satisfactory for the individual and fruitful for the community (Edmonson 2013).

The healthcare system needs to be aware of the dependency condition. Several authors have suggested the importance of new public policies to face this problem and have offered potential solutions such as the provision of incentives to family members so that they would care for their own elderly family members (Zaidi 2008). An example of public policy is the dependency law passed by the socialist government in Spain with the explicit objective to help financially all the elderly in situations of documented dependency. However, doubts have emerged because the help never reached all the target population, as a consequence of the economic recession after the law was adopted in 2006 (Jiménez et al. 2016).

Caregivers

In relation to dependent individuals, family caregivers are fundamental, and this notion applies to any country (Edmonson 2013). Caregivers can provide real help, and can be rewarding. However, real difficulties for them are frequent, and provisions in welfare states, such as the incentives to younger family members to take care of their own older family members, may be crucial for facilitating the process (Zaidi 2008). This is particularly relevant in view of recent social movements, mainly because of the transition of women to the work force. Relatedly, the migration phenomenon, a partial result of globalization and the need for

many young and adult people to move to seek employment in other regions/countries, even overseas, has resulted in many elderly parents being deprived of care in their homeplace.

Economic Difficulties and Socioeconomic Status

Socioeconomic status (SES) has been shown to be associated with healthy aging and increased life expectancy (Donkin et al. 2002). Conversely, socioeconomic disadvantage in older people tends to marginalize them and may eventually breed ill health. Together with major changes in social institutions, such as the family, and in the economy, increasing demands for public and government care in older individuals come from ill health, including from psychiatric conditions such as dementia and depression. Universal health insurance is being debated as one remedy for such health inequalities. Moreover, in this situation, the great majority of patients and their families will need social care support, with inevitable economic implications.

The need for social care support is observed in Western countries, but in fact also in developing countries experiencing population aging, although at a different pace. Social care policies are quite different across countries and sometimes across the same country, and cultural norms strongly influence the demand (Edmonson 2013). Still, state policy has to face the reality of the increasing demand for care, and under the name "political economy of old age" (Estes 1991), the discussion is how the economic resources should be distributed, since this will have crucial effects on the lives of older people.

Welfare states provide the older degrees of protection unknown until recently. Nevertheless, a generalized problem is the sustainability of the system, and to some extent most countries have the private sector and the civil society involved. A crucial problem the pension policies have to face is to balance suitability and financial sustainability. The idea is to prevent the real possibility of poverty in older people, but the system has still to be economically solid (Zaidi 2008).

Some implications may be derived from this section in view of the biological facts of the aging process and the challenging social factors reviewed. It is commonly suggested that each improvement in education, income, occupation, or wealth is associated with better health outcomes. In the context of industrialization, advantages and disadvantages may be tied with the SES status (Adler and Stewart 2010). However, to disentangle the components of SES status may be intricate, since factors such as income, occupation, or education are all involved. The general view is that individuals with low socioeconomic status, compared with their counterparts, have less information related to health and are less involved in active behaviors promoting health, are exposed to more physical hazards and environmental risk factors, and experience more stressful events and may have a worse adaptation to them.

Psychological discomfort and/or psychiatric disturbance among the elderly, and similarly general health disorders, have often been associated with SES, which is an independent predictor of both disease risk and mortality. In other studies, stressful life events and lack of perceived social support have been strongly related to risk of depression among all age groups (George 2009).

It is important that both preventive plans and interventions at the individual or public health levels take into account this kind of information.

Aging in the Population: Demographic Changes with Social Implications

Aging Demographics

The aging of the population is a global phenomenon with strong social implications (Hooyman and Asuman Kiyak 2013; Romero-Ortuno and O'Shea 2013). It occurs both in developed and in developing countries, although rates are different. In general, it reveals a demographic change from high-fertility rural agrarian societies to low-fertility urban industrialized societies. The largest proportion of the elderly are in industrialized countries, where life expectancy and the median age have increased dramatically in recent years. In Europe, the elderly population is expected to increase to 30% of the population over the next 30 years (Zaidi 2008).

The social implications of this phenomenon are derived from different factors. First, the majority of the elderly, including in the oldest age groups, live in non-institutionalized settings. This has clear implications for families and for developing special support systems. Second, the highest proportion of disability and poor health are concentrated in the oldest old; the potential social consequences seem to be obvious, but more realistic perspectives derive from recent empirical data showing that the association between chronological age and poor health status and/or frailty is not direct and may be very variable (Romero-Ortuno and Kenny 2012). Third, a crucial problem to face, related to global aging, may be the fact that fewer workers are available to support the increasing proportion of the elderly. Fourth, are the social repercussions derived from the imbalance in the sex ratio of men to women, described in the previous section.

Age Itself: A Potential but Controversial Risk Factor

Age itself is a risk factor for some physical and psychiatric disorders with great social implications. On the physical side, the increased prevalence of conditions such as hypertension and cardiovascular disorders or diabetes has been documented (Lobo-Escolar et al. 2008). Similarly, in relation to psychiatric disorder, it is clear that age is the main risk factor for highly disabling conditions such as dementia in general and Alzheimer's disease and vascular dementia in particular (Lobo et al. 2011). Disability due all such conditions is an inevitable corollary, resulting in the "frailty" problem described in the previous section. However, the potential of social factors in the etiology of these conditions should not be minimized. For example, it is now clear that poor education is a risk factor for Alzheimer's disease (Lobo et al. 2011), and, on the contrary, an active lifestyle is protective (Marioni et al. 2015).

The association between age and psychiatric disorder in conditions such as depression are complex and often inconsistent across studies, therefore suggesting that social factors may be more relevant. Contrary to some generalized views, we found that the great majority of the elderly population (65+ years) is in reasonably good mental health, particularly among the younger old strata. For example, we have documented that the prevalence of psychiatric disorder in the general population of the elderly is 11.8%, meaning that the great majority do not have diagnosable psychiatric condition, although they may have isolated symptoms (Lobo et al. 1995). The prevalence of disorder in younger adults is not very different. In relation to depressive symptoms, some reports suggest that older adults, especially the very old, usually report levels of symptoms equal to or higher than those reported by younger and middle-aged adults (Schieman et al. 2002). In contrast, some studies of psychiatric disorders suggest lower current and lifetime prevalence among older compared to younger adults for conditions other than most neurocognitive disorders (Robins et al. 1984). Moreover, in support of the hypothesis of the influence of social and environmental factors associated with depression in the elderly, we reported in the EURODEP studies wide cross-cultural differences of prevalence in European cities, using standardized assessment methods and criteria (Copeland et al. 2004).

While biological factors in aging emerge from an internal, developmental program, differences observed across age groups in different sociocultural settings suggest the influence of social and/or environmental changes external to the individual, factors that may vary substantially over time and across cohorts of older adults.

Specific Demographic Changes

Demographic factors have consistently been associated with mental disturbance in older adults (George 2009). However, the nature of this association is far from clear, and a causal relationship cannot always be established. For example, the nature of differences in the prevalence of mental disturbances such as depression or Alzheimer's disease in men compared with women has not been clarified. A higher prevalence of both conditions among women has been reported (De Pedro-Cuesta et al. 2009), and social factors such as education, marital status, and economic or social stress may be at play. Some authors have suggested that demographic factors may act as proxies for other social factors (Letenneur et al. 2000).

Marital Status

Marital status has been associated with depression in older adults, and symptoms of depression have been found to be more frequent among unmarried individuals (Cairney and Drause 2005). Specific factors intrinsic to the married state have been considered to explain the nature of the association, and multivariate methods

suggest that aspects such as social support or social stress may explain the association (George 2009).

Migration

Psychological distress and/or psychiatric disturbance among immigrants have often been reported in the literature. Still, the nature of the association has not been clarified (Butler et al. 2015). Different social factors have to be considered. In the migration process, individuals often lose economic resources and certainly prestige and social power. They may have new financial burdens related to restrictions for medical care in countries such as the USA, and the role of older adults in the new situation may be related to home care or care of the children, at the cost of losing autonomy and opportunities they had in their homeland. Marginalization of the elderly immigrant may be a real issue in such circumstances.

Educational Level

Considerable evidence indicates that early events and achievements have persistent effect on psychiatric status throughout adulthood. Education is most strongly related to psychiatric morbidity in later life. Among older adults, low levels of education are strongly associated with high levels of depressive symptoms, and they have also been found to be a significant predictor of incident cases of major depression and of Alzheimer's disease (Koster et al. 2006; Lobo et al. 2011).

Cultural Attitudes Vary

Cultural attitudes and values profoundly influence the views on different aspects of aging, including dependency and demand of services. Similarly, expectations about behaviors in older people may differ due to cultural factors, leading to the consideration of some pathological behaviors regarded as normal in other cultures. The marks of growing into adulthood are often a source of pride, but, in some cultures and specifically in developed countries, marks of natural aging can lead to awkwardness or shame. When discussing myths and stereotypes, cultural attitudes may cause the elderly to feel embarrassment and may influence the milieu, eventually leading to marginalization (Stuckelberger et al. 2012). It is both the subjective feeling of the individual and the social environment that are influenced (Bytheway 2011).

Implications for psychiatry could be derived following the review of this section. Prevention planning must consider the vast demographic changes documented recently and the ones predicted for the coming decades. From the social perspective, it is not only aging that matters, since the associated social phenomena, including demographic changes and cultural attitudes, have been shown to influence health and disease, including mental conditions. The available information may be useful for planning social care and prevention. It is also clear that new research is essential to improve this information.

Specific Challenges for the Elderly: Ageism, Social Challenges, Implications for Geriatric Psychiatry

Introduction

In the process of aging, biological changes described in previous sections pose challenges for the individual, as reviewed when describing the "frailty" construct. Other challenges derive from the psychosocial perspective, including dependence, marginalization, or the negative side of retirement. We now describe several other threats described by sociologists, namely, "ageism," abuse, or stereotypes.

Ageism

The subject of so-called ageism is a crucial one in the field of the sociology of aging, with important implications for the field of geriatric psychiatry. The term was coined by Robert Butler (1975) and refers to the "systematic stereotyping and discrimination against people because they are old" (Edmonson 2013). This phenomenon may result in "social exclusion" and discrimination, with all the negative implications for the individual and for the group of excluded individuals.

Age discrimination for older adults may be more common than suspected. As an example of the usefulness of empirical studies in this field, Rippon et al. (2014) documented the phenomenon of "perceived age discrimination" in a sample of 7,500 individuals of the English Longitudinal Study of Ageing (ELSA). They found that more than one third of those aged 65 and over experienced age discrimination. The ageism phenomenon is obviously influenced by cultural factors, and in this particular social environment, the researchers found that age discrimination was associated with higher education, lower levels of household wealth, and being retired or not employed. Empirical studies of this sort may direct preventive policies.

Socially excluded individuals find obstacles for activities regarded as normal in a given society, and different authors have described the phenomenon in different populations, such as the institutionalized populations. The applicability of this concept in care homes and in institutionalized psychiatric older populations is apparent. Edmonson has suggested that the risk of social exclusion can derive from healthcare settings themselves (Edmonson 2013). Although the care itself is not intended to disempower individuals, Faulkner (2001) has suggested that individuals in such situation may develop "learned helplessness" when deprived of control. It is therefore advisable to stimulate social participation, particularly in long-term institutions. In other examples of empirical studies in the field, Ishii and Tado'oka (2015) have observed that subjects who had no previous experience living with older adults may be more vulnerable to ageism in times of adverse circumstances.

Abuse

Abuse and mistreatment of the elderly is a well-known phenomenon, often reported in the literature, and the significance of the sociocultural aspects merits some emphasis. There is relevant information suggesting that elderly abuse is more common than documented in the literature, so that reporting is much lower than prevalence. In addition, different types of studies have described the negative outcome of abused individuals, with important health implications (Burnett et al. 2016).

Many factors have been discussed to interpret the origins of this phenomenon. The systematic review by Johannesen and LoGiudice (2013) is noteworthy in this respect. These authors concluded that the etiology of abuse is multifactorial. Some factors are related to older persons themselves, and a considerable number of features have been described: cognitive impairment, behavioral problems, psychiatric illness, psychological problems, functional dependency, poor physical health or frailty, low income or wealth, trauma or past abuse and ethnicity. Other factors depend on the perpetrator and include caregiver burden or stress and psychiatric illness or psychological problems. And some factors are more environmental, such as problematic interpersonal relationships or family disharmony and low social support. In a different, systematic review of community studies, Johannesen and LoGiudice (2013) concluded that the highest risk of abuse in the elderly was associated with interpersonal relationships, such as family disharmony and poor or conflictual relationships, and with environmental factors, specifically to low levels of social support. Nonetheless, there is no consensus on this subject, and the emphasis of authors commenting on the issue of ageism is placed on environmental causes, specifically on the social attitudes, rather than the interpersonal difficulties (Biggs and Haapala 2013).

At the level of individuals, both clinicians and administrators must be alert in view of the frequency of the phenomenon of abuse and the negative implications for individuals and for groups such as the institutionalized elderly. Preventive measures of abuse should be based on documented risk factors such as the ones described here, and adequate professional training seems to be essential. Furthermore, this literature suggests the importance of new studies to document the origins of abuse and the efficacy of intervention programs.

Stereotypes

While there is no generalized acceptance of the meaning of the term stereotype, it relates to ideas or beliefs that can be adopted about specific types of individuals or about their way of doing things, ideas that do not necessarily reflect reality. The concept also reflects the characteristics that are attributed to a group of individuals, in this particular case to the old. One frequent example is to view the elderly as lonely, although this is heavily influenced by cultural views (Yang and Victor 2011).

Negative stereotypes are germane in this chapter. Cultural stereotypes may be and frequently are incorporated by individuals, resulting in a self-definition that has an impact on the function of that person, who eventually might lead to behavioral and/or health difficulties. Specifically, negative attitudes toward older people may adversely influence the functioning of individuals and result in negative "auto-stereotypes."

Stories, images, and symbols give clues to the way the elderly perceive who they are and how they are seen by others. It is not surprising that jokes and cartoons often reveal negative views of old people ("humor reveals socially unacceptable images of ageing") (Polanski 2014).

Ideas, images, and meaning of old age vary across cultures and across time. It is not surprising that more recent studies have found cross-cultural differences in the stereotypes of the elderly, supporting the influence of societal norms and values (Edmonson 2013). The changing nature of stereotypes has similarly been documented (Chen 2015), but other studies using information from newspapers and magazines show that various stereotypes, and specifically those with unfavorable connotations, may be lasting (Polanski 2014). Negative age stereotypes have been detected in modern social networks which are expected to improve intergeneration communication, such as Facebook.

A central issue in this chapter is that social and cultural ideas about aging impact older individuals and can strongly influence their behavior. The perception of old-age cues by individuals may come from retirement norms, professional decisions at the time of employment, or interpersonal cues in the way the older individual is addressed by family or other members. In relation to this, it is relevant to mention that a negative view on the health of aging individuals is not necessarily supported by data. In the Zaragoza Study of dementia and depression in the elderly, and contrary to some expectations, we observed that the prevalence of general psychological morbidity in a representative sample of the population was ~12%, a frequency not substantially different from that observed in the population of non-elderly adults (Lobo et al. 1995).

Some authors have described different ways in which stereotypes influence individuals and have given examples of negative consequences (Levy 2009). A "psychological" pathway includes, for example, the generation of expectations in such a way that eventually act as self-fulfilling prophecies. A "behavioral" pathway might be exemplified by practices related to health: the elderly incorporating the stereotype that health problems are an inevitable consequence of aging might behave as if healthy practices are pointless. In the "physiological" pathway, autonomic nervous system disturbances might result in cases of negative age stereotypes, as shown by abnormal cardiovascular response to stress.

There are ways to fight negative stereotypes. Some studies suggest beneficial effects on physical and/or mental health by resisting negative age stereotypes or maintaining an optimistic attitude (Wurm and Benyamini 2014). Such a positive attitude could result in an increased life expectancy (Levy et al. 2002). It is in this context that Moody (1988), has argued in favor of the notion that gerontology should offer an "emancipatory

discourse," with a positive idea of aging as a movement toward freedom beyond domination (autonomy, wisdom, transcendence).

Early information about myths and stereotypes is important in this respect, since people rarely understand ageism and its negative implications until they reach old age themselves.

Sociological Theories of Aging: Implications

Introduction

Sociologists have tried to understand the meaning of aging itself and to what extent present concepts are influenced by culture and the social factors in a given time (Table 3). Starting in the second half of the past century, movements were observed to base their theories on a modern scientific basis. We have already discussed the issues of "ageism" and of "stereotypes," strongly influenced by underlying sociological factors. We have described in the previous sections the many faces of aging and the influences of biological, psychological, and social factors. It is not surprising therefore to consider aging a multifaceted process with many theories of aging and contradictory views that have emerged in the field (Settersten and Angel 2011; Edmonson 2013).

Some Sociological Theories

In the "disengagement" theory (Havighurst et al. 1963), a crucial factor was considered to be the "functioning" of the individual, which varies along the lifetime. Aging in this view means a separation from the productive social role, having strong implications at the time of retirement, leading to potential marginalization of individuals. Criticism of this theory has also emerged. While, the negative side of retirement may certainly be true in some cases, we have also discussed in previous sections that it may be a very happy and productive period of life for other individuals.

Table 3 Sociological theories relevant in Geriatric Psychiatry

"Agesim" and stereotypes
"Social exchange" theory
"Disengagement" theory
"Activity" theory
"Continuity" theory
"Modernization" theory
"Age stratification" theory
"Social labeling" theory
"Symbolic interactionism" theory
"Buffering/stress" model

An other classical theory, the "activity theory," carries more positive implications: it underlines the social role aged individuals may develop (James et al. 2006). A good example in present day in Spain is the fact that 17% of grandmothers provide intensive care to grandchildren in times of limited welfare support and drastic changes in the women's role, many of them now maintaining jobs while at the same time preserving the mother's role (Glaser et al. 2013).

It is also well known in this country that in the present circumstances of unemployment, a considerable proportion of young or even adult individuals with children are living at the cost of the grandparent's pension. Specifically, a recent report found that 80% of grandparents help financially their families, a percent that was 20% in 2010 (EDUCO 2015).

Related to this is the "exchange" theory (Dowd 1980) describing the interactions of the elderly with society and the assets they provide for mutual satisfaction. According to this, it is important in older adults to achieve a balance between their contributions to society and the costs of their support. Efforts should be directed toward increasing older people's resources so that they are valued by society. They prefer to give money, time, caregiving, or other resources in exchange for services. Important variations are observed across cultures, but according to this theory, the way in which older adults are engaged in society diverges with the nature of their power resources, such as their material possessions, knowledge, and social authority.

The "continuity" theory in aging emphasizes the importance for individuals of maintaining links with past personal and social experiences as a way to prevent the negative psychosocial aspects of senescence. In societies where the position of individuals on the social scale is strongly dependent on their work and occupation, the risk of excluding the elderly would be particularly high (Gilleard and Higgs 2000).

Some theories have stirred considerable controversy, for example, the "modernization" theory (Cogwill and Jolmes 1972) studying the transition from a "traditional" to a "modern" society. This theory tries to identify the social variables contributing to social progress, to describe the process of change, and to identify the adaptation to that change. The theory argues that modernization is necessary, since traditional societies will develop as they adopt modern practices, and reflected by higher standards of living. The critics of the theory, argue that it lacks adequate empirical support; sees non-modernized societies as inferior even if they have the same standard of living as western societies; and ignores the fact that the division between traditional and modern is arbitrary. An important aspect of modernization is the advent of new technologies. For some, recent technical advances and new skills, accessible to the younger generations, have considerable risk of stimulating ageism. However, critics of this position underline the fact that this situation cannot be generalized, since older generations are increasingly active in modern technologies and may in some circumstances be responsible for their knowledge and experience. An important criticism comes from the general view that the traditional family continues to be crucial in supporting the oldest adults, although important variations are observed across cultures.

In the "age stratification" theory (Riley et al. 1999), a central idea is that ideological pressure may be placed on individuals for directing their behavior, with expected roles dependent on the age "strata." In terms of pressure on the individual, the power of political and economic forces is often quite considerable. The "political economy of old age," may exclude the elderly as a potential outcome, in response to the political ideas and the state of the economy. On the contrary, strong social politics may provide a welfare state, providing regulations such as the dependency law in Spain although it turned out to be a regulation difficult to fulfill in practice.

The "symbolic interactionism" theory (Blumer 1969) emerged in the past century. The nucleus of this approach is that behaviors of people toward things or others are based on the meaning those things have for them. In this particular case, behaviors toward the elderly will be determined by the meaning given to the construct of old age. This meaning emerges out of the social interaction of individuals with other individuals and with society. Behaviors toward the elderly, therefore, are mediated by the meaning of this construct and are influenced by social interactions. Therefore, interpretation of the meaning may be crucial when addressing problems of the elderly.

The **buffering/stress model** is well known in psychiatry and undoubtedly has a social perspective (Brown and Harris 1989). Old age might be a period of particular stress, as explained in previous sections. It is a time of frequent losses, including retirement, loss of occupational prestige and low income, often loss of friends and of driving, etc. of particular importance is the loss of a spouse, often with dramatic consequences. Different studies have shown that bereavement is a strong predictor of psychiatric disorder in the elderly.

The buffering/stress model emphasizes the importance of both the vulnerability to stressful events and the ability to cope and solve them and the high risk of developing disorders such as depression. Nevertheless, authors such as Brown and Harris (1989) have underlined the relevance of aspects such as the meaning of the lost object, aside from the loss itself. Moreover, in the case of the elderly, not only isolated losses should be considered, but aggregated life events.

Notwithstanding the above, some studies could not confirm that some specific losses in the elderly are associated with psychiatric morbidity and specifically with depression. For example, some authors did not observe an increased risk of psychiatric disorders following retirement (Midanik et al. 1995). From the perspective of the buffering/stress model, some reasons related to vulnerability and ability to cope could explain this fact. For example, learning to copy with adversity with a better psychological adaptation could make individuals more resilient. Copeland et al. (1987) suggested the possibility that stressful life events could be lived in later life as inevitable and without the possibility of change, but may not necessarily be painful or unpleasant. Conversely, early, adverse experiences in childhood may have persistent effects on an individual's vulnerability to psychiatric disorders, particularly depression, during adulthood, suggesting that childhood adversities could interact with recent stressors to increase the likelihood of depression

(George 2009). Similarly, the lack of a confidante relationship would increase the vulnerability to stress and poor health in the aged (Murphy 1982). Studies related to this model bring to light the significance of jointly investigating biological and social factors as a comprehensive model of the etiology of mental illness.

Clinical psychiatrists, because of their medical background, are generally more familiar with the natural and biological sciences. However, as Jaspers taught, psychiatry needs the humanistic and sociocultural sciences. It is true that clinical psychiatrists facing the influenced reality of severely ill patients, and by empirical data coming from the so-called "evidence-based" medicine, may find abstruse some of the sociological theories discussed in this chapter. Still, all these theories have a causality side that may help to understand the social origins of the attitudes and behaviors observed in the clinics. These theories have in addition an underlying prescriptive side, where clinicians interested in a holistic view of individual patients and their social environment could find some guidance for their professional activities. The theories discussed here may stimulate clinical enquiries with individual patients, and with groups or categories of geriatric psychiatry patients. In addition, they should certainly stimulate **multidisciplinary work and multidisciplinary team interventions with geriatric patients, focused not only on biological aspects but also considering their psychosocial and environmental dimensions.** The theories likewise have a heuristic potential for stimulating hypotheses to be tested, in particular in epidemiological enquiries.

Toward Guidelines for Actions on Aging

The analysis of the previous sections indicates some potential guidelines to direct the Actions on Aging, including the organization of social services. The following areas are important to consider (Zaidi 2008; Edmonson 2013; Romero-Ortuno and O'Shea 2013):

- Education on aging for youth and the promotion of preventive measures such as a healthy lifestyle during early stages of the life course.
- Public policies to facilitate progress in factors such as education, gender roles, housing standards, transport, and social attitudes intended to postpone disability.
- Promotion of healthy aging and fit people. Frail people are vulnerable and healthy aging improves their status. This may be associated with a longer life.
- Active aging, which is receiving considerable support in Western nations, since this contributes to the well-being of society. This is crucial, and all key stakeholders, including the public sector and the private sector, should be involved to find ways to keep old people active.
- Employment for old people. Innovative actions and policies have been developed in different countries in this direction. The underlying idea is that the use of their competence and experience and making them useful, is a way to reduce ageism in Western societies.

- The role of information and communication technologies (ICT) has been controversial. Some studies have detected a "digital divide" between the younger and the older generations, including some negative attitudes toward technologies in the old. Nonetheless, more older adults adopt ICTs in trying to fit in with new developments. Some recent studies conclude with a positive view of projects that facilitate these advances to older individuals (Wu et al. 2015).
- Protection policies need a review. There is a tendency in Western countries to implement new retirement policies intended to prolong the active employment of older workers while reducing the burden on their state pension programs, although this has found some resistance.
- Early identification of problems such as frailty, with the goal of developing instruments and methods for its early identification, as a way to minimize the risk of age discrimination.
- Access to social care policies. Social care policies, and access to social care, vary widely across different countries and/or across different regions in the same country. This subject becomes crucial in areas such as the dementia and depression in the elderly, since the great majority of affected individuals and families will need social care support. In view of the relevance of this subject and the paucity of methods to address the problem, the IDEAL Consortium has developed a simple, staging instrument to document care needs in individuals with dementia (Semrau et al. 2015).
- Home-based care. To reduce the burden of healthcare professionals working at acute hospitals and the costs involved and to meet the demand of older people, home care programs have been developed. Ideally, these programs should offer "multidisciplinary care" to meet the reality of health problems in the elderly. Family physicians are usually involved in the initial screening.
- Medical education should change present teaching systems, since they are not yet prepared to meet the needs of the elderly with multi-morbidity, both physical and psychiatric, as well as the associated social problems.
- Health service use. Research in this area has shown that this is a function not only of disease characteristics, but is often determined by different social factors (George 2009). For example, older individuals have a lower probability of receiving mental health treatment in the presence of psychiatric disorder. Social support is a very significant enabling factor in psychiatric disorders and determines the need to take into account not only formal services provided by professional providers but also informal services provided by family and friends.
- International initiatives. A 2008 review of the Madrid International Plan of Action on Ageing was adopted by the United Nations in a political declaration in 2002. It urged action in terms of national policies and practices to promote the health, employment, and human rights of older adults globally. It called for more attention to disease prevention; for the reduction of health and economic disparities that are intensified in old age; for promoting the empowerment and decision-making of elders, with positive incentives for working longer; and for identifying ways for their contribution to social and economic progress. Similar initiatives have been taken in countries like the United Kingdom (Department-of-Health 2010).

Conclusion

This chapter has addressed empirical data and the theoretical background in the discipline sociology of aging. This information should help in understanding how social factors, together with the inevitable biological changes, may affect the elderly. Psychiatrists and geriatric psychiatrists in particular may find some help in the information discussed here. They should be prepared to face the differences observed in men and women; the potential advantages or challenges related to retirement; and the difficulties that may be encountered in relation to stress on potential dependency, the caregivers, or the economic difficulties in old age. Psychiatrists should be aware of the demographic changes in the population and the implications in relation to migration, educational level, or socioeconomic status. Efforts to highlight social issues such as ageism and other stereotypes should help them understand the difficulties some old individuals experience. Indeed, geriatric psychiatrists should be vigilant with regard to abuse of the elderly. The practical clinician may find some of the sociological theories in vogue abstruse, but still these could be illuminating in order to understand what is at stake with individuals or populations. Finally, this chapter reviews potential guidelines for action on aging, recommended by experts in the field; this information should be particularly helpful for those geriatric psychiatrists with administrative responsibilities.

Cross-References

- ▶ Challenges and Opportunities of Aging Populations Around the World
- ▶ Dementia and Caregiving
- ▶ Depression in Late Life: Etiology, Presentation, and Management
- ▶ Elderly Services, Community Care, and Health Economics of Service
- ▶ Epidemiology of Mental Disorders (Including Cross-Cultural Comparisons)
- ▶ Psychological Interventions for Older Adults: Evidence-Based Treatments for Depression, Anxiety, and Carer Stress
- ▶ Successful Aging

References

Adler NE, Stewart J (2010) Health disparities across the lifespan: meaning, methods, and mechanisms. Ann N Y Acad Sci. Feb;1186:5–23

Ahnquist J, Wamala SP, Lindstrom M (2012) Social determinants of health – a question of social or economic capital? Interaction effects of socioeconomic factors on health outcomes. Soc Sci Med. Mar;74(6):930–939

Biggs S, Haapala I (2013) Elder mistreatment, ageism, and human rights. Int Psychogeriatr 25:1299–1306

Biggs S, Fredvang M, Haapala I (2013) Not in Australia. Migration, work and age discrimination. Australas J Ageing 32:125–129

Blanchard-Fields F (2009) Flexible and adaptive socio-emotional problem solving in adult development and aging. Restor Neurol Neurosci 27:539–550
Blumer H (1969) Symbolic interactionism: perspective and method. Prentice-Hall/University of California Press, Englewood Cliffs/Berkeley
Brown GW, Harris T (1989) Life events and illness. Un-win Hyman, London
Burnett J, Jackson SL, Sinha AK, Aschenbrenner AR, Murphy KP, Xia R, Diamond PM (2016) Five-year all-cause mortality rates across five categories of substantiated elder abuse occurring in the community. J Elder Abuse Negl 28:59–75
Butler M, Warfa N, Khatib Y, Bhui K (2015) Migration and common mental disorder: an improvement in mental health over time? Int Rev Psychiatry N27(1):51–63
Bytheway B (2011) Unmasking age: the significance of age for social research. The Policy Press, Bristol
Cairney J, Drause N (2005) The social distribution of psychological distress and depression in older adults. J Aging Health 17:807–835
Chen CH (2015) Advertising representations of older people in the United Kingdom and Taiwan: a comparative analysis. Int J Aging Hum Dev 80:140–183
Cogwill D,O, Jolmes LD (eds) (1972) Ageing and modernization. Appleton-Century-Crofts, New York
Copeland JR, Dewey ME, Wood N, Searle R, Davidson IA, McWilliam C (1987) Range of mental illness among the elderly in the community. Prevalence in Liverpool using the GMS-AGECAT package. Br J Psychiatry 150:815–823
Copeland JR, Beekman AT, Braam AW, Dewey ME, Delespaul P, Fuhrer R, Hooijer C, Lawlor BA, Kivela SL, Lobo A, Magnusson H, Mann AH, Meller I, Prince MJ, Reischies F, Roelands M, Skoog I, Turrina C, deVries MW, Wilson KC (2004) Depression among older people in Europe: the EURODEP studies. World Psychiatry 3(1):45–49
Department-of-Health (2010) A vision for adult social care: capable communities and active citizens. Social Care Policy, United Kingdom
De la Cámara C, Saz P, López-Antón R, Ventura T, Día JL, Lobo A (2008) Depression in the elderly community: I. Prevalence by different diagnostic criteria and clinical profile. Eur J Psychiatry 22(3):131–140
De Pedro-Cuesta J, Virués-Ortega J, Vega S, Seijo-Martínez M, Saz P, Rodríguez F, Rodríguez-Laso A, Reñé R, de las Heras SP, Mateos R, Martínez-Martín P, Manubens JM, Mahillo-Fernandez I, López-Pousa S, Lobo A, Reglà JL, Gascón J, García FJ, Fernández-Martínez M, Boix R, Bermejo-Pareja F, Bergareche A, Benito-León J, de Arce A, del Barrio JL (2009) Prevalence of dementia and major dementia subtypes in Spanish populations: a reanalysis of dementia prevalence surveys, 1990–2008. BMC Neurol 9:55. 19
Donkin A, Goldblatt P, Lynch K (2002) Inequalities in life expectancy by social class 1972–1999. Health Stat Q 15:5–15
Dowd JJ (1980) Exchange rates and old people. J Gerontol 35:596–602
Edmonson R (2013) The sociology of ageing. In: Dening T, Thomas A (eds) Oxford textbook of old age psychiatry. Oxford University Press, Oxford
EDUCO (2015) Crisis y efecto dominó: ¿Quedan más piezas por caer? El bienestar infantil, abuelos y abuelas en la brecha. In: informeeduco (ed) C. P. y. Salvetti& Llombart. EDUCO. Member of Childhood Alliance, Barcelona
Estes C (1991) The new political economy of ageing: introduction and critique. In: Minckler M, Estes C (eds) Critical perspectives of aging: the political and moral economy of growing old. Baywood Publishing Company, Amityville
Faulkner M (2001) The onset and alleviation of learned helplessness in older hospitalized people. Aging Ment Health 5:379–386
George LK (2009) Social and economic factors related to psychiatric disorders in late life. In: Blazer DG, Steffens DC (eds) The American Psychiatric Publishing textbook of geriatric psychiatry, 4th edn. American Psychiatric Publishing, Washington, DC
Gilleard C, Higgs P (2000) Cultures of ageing: self, citizen and the body. Prentice-Hall, London

Glaser K, Price D, Di Gessa G, Ribe E, Stutchbury R, Tinker A (2013) Grandparenting in Europe: family policy and grandparent's role in providing childcare. Grandparents plus, London
Harris D (2007) The sociology of aging. Edition: 3. Publisher: New York: Rowman & Littlefield
Havighurst R, Neugarten B, Tobin J (1963) Disengagement patterns of aging. Chicago University Press, Chicago
Hooyman N, Asuman Kiyak H (2013) Aging in other countries and across cultures in the United States. In: Social gerontology, 9th edn. Pearson, Edinburgh
Ishii K, Tado'oka Y (2015) The influence of pathogen threat on ageism in Japan: the role of living with older adults. Shinrigaku Kenkyu 86:240–248
James W, Witte J, Galbraith M (2006) Havighurst's social roles revisited. J Adult Dev 13:52–60
Jaspers K (1997) In: Hoenig J, Hamilton MW (eds) General psychopathology, vol 1. Johns Hopkins University Press, Baltimore
Jiménez S, Vilaplana C, Viola A (2016) Observatorio de dependencia. In: Estudios sobre la economía española. FEDEA, Madrid
Johannesen M, LoGiudice D (2013) Elder abuse: a systematic review of risk factors in community-dwelling elders. Age Ageing 42:292–298
Koster A, Bosma H, Kempen GI, Penninx BW, Beekman AT, Deeg DJ, van Eijk JT (2006) Socioeconomic differences in incident depression in older adults: the role of psychosocial factors, physical health status, and behavioral factors. J Psychosom Res 61(5):619–627
Letenneur L, Launer LJ, Andersen K, Dewey ME, Ott A, Copeland JR, Dartigues JF, Kragh-Sorensen P, Baldereschi M, Brayne C, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A (2000) Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group. Am J Epidemiol 151(11):1064–1071
Levy B (2009) Stereotype embodiment: a psychosocial approach to aging. Curr Dir Psychol Sci 18:332–336
Levy BR, Slade MD, Kunkel SR, Kasl SV (2002) Longevity increased by positive self-perceptions of aging. J Pers Soc Psychol 83:261–270
Lobo A, Saz P, Marcos G, Día JL, De-la-Cámara C (1995) The prevalence of dementia and depression in the elderly community in a southern European population. The Zaragoza study. Arch Gen Psychiatry 52:497–506
Lobo A, Lopez-Anton R, Santabárbara J, de-la-Cámara C, Ventura T, Quintanilla MA, Roy JF, Campayo AJ, Lobo E, Palomo T, Rodriguez-Jimenez R, Saz P, Marcos G (2011) Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population. Acta Psychiatr Scand 124(5):372–383
Lobo-Escolar A, Saz P, Marcos G, Quintanilla MA, Campayo A, Lobo A, the ZARADEMP Workgroup (2008) Somatic and psychiatric comorbidity in the general elderly population: results from the ZARADEMP Project. J Psychosom Res 65(4):347–355
Marcos G, Santabárbara J, Lopez-Anton R, De-la-Cámara C, Gracia-García P, Lobo E, Pírez G, Menchón JM, Palomo T, Stephan BC, Brayne C, Lobo A, Z. Workgroup (2016) Conversion to dementia in mild cognitive impairment diagnosed with DSM-5 criteria and with Petersen's criteria. Acta Psychiatr Scand 133:378–385
Marioni RE, Proust-Lima C, Amieva H, Brayne C, Matthews FE, Dartigues JF, Jacqmin-Gadda H (2015) Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. BMC Public Health 15:1089
McHugh P, Slavney P (1998) The perspectives of psychiatry. John Hopkins University Press, Baltimore
Midanik LT, Soghikian K, Ransom LJ, Tekawa IS (1995) The effect of retirement on mental health and health behaviors: the Kaiser Permanente Retirement Study. J Gerontol B Psychol Sci Soc Sci 50(1):S59–S61
Moody H (1988) Towards a critical gerontology: the contribution of the humanities to theories of ageing. In: Birren JE, Bengtson VL (eds) Emergent theories of aging. Springer, New York, pp 19–40
Murphy E (1982) Social origins of depression in old age. Br J Psychiatry 141:135–142

Polanski F (2014) Caricatures of aging in German newspapers and magazine cartoons. Historical comparison between the 1960s and the present. Z Gerontol Geriatr 47:329–336
Quintanilla López MA (2006) Valoración de la dependencia en una muestra comunitaria de personas mayores de 55 años y su relación con factores sociodemográficos y psicopatológicos. Tesis doctoral, Universidad Zaragoza. https://www.educacion.gob.es/teseo/mostrarDetalle.do
Riley M, Foner A, Riley JW (1999) The ageing and society paradigm. In: Bengston V, Schaie K (eds) Handbook of theories of ageing. Springer, New York, pp 327–343
Rippon I, Kneale D, de Oliveira C, Demakakos P, Steptoe A (2014) Perceived age discrimination in older adults. Age Ageing 43:379–386
Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD Jr, Regier DA (1984) Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 41(10):949–958
Rockwood K, Fox RA, Stolee P, Robertson D, Beattie BL (1994) Frailty in elderly people: an evolving concept. CMAJ 150:489–495
Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, Gonzalez-Colaço Harmand M, Bergman H, Carcaillon L, Nicholson C, Scuteri A, Sinclair A, Pelaez M, Van der Cammen T, Beland F, Bickenbach J, Delamarche P, Ferrucci L, Fried LP, Gutiérrez-Robledo LM, Rockwood K, Rodríguez Artalejo F, Serviddio G, Vega E, FOD-CC group (Appendix 1) (2013) Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 68(1):62–67
Romero-Ortuno R, Kenny RA (2012) The frailty index in Europeans: association with age and mortality. Age Ageing 41(5):684–689
Romero-Ortuno R, O'Shea D (2013) Fitness and frailty: opposite ends of a challenging continuum! Will the end of age discrimination make frailty assessments an imperative? Age Ageing 42:279–280
Schieman S, Van Gundy K, Taylor J (2002) The relationship between age and depressive symptoms: a test of competing explanatory and suppression influences. J Aging Health 14:260–285
Schoevers RA, Beekman AT, Deeg DJ, Geerlings MI, Jonker C, Van Tilburg W (2000) Risk factors for depression in later life; results of a prospective community based study (AMSTEL). J Affect Disord 59:127–137
Semrau M, Burns A, Djukic-Dejanovic S, Eraslan D, Han C, Lecic-Tosevski D, Lobo A, Mihai A, Morris J, Palumbo C, Robert P, Stiens G, Stoppe G, Volpe U, Rikkert MO, Sartorius N (2015) International Dementia Alliance (IDEAL) study group. Development of an international schedule for the assessment and staging of care for dementia. J Alzheimers Dis 44(1):139–151
Settersten RA Jr, Angel JL (eds) (2011) Handbook of sociology of aging. Springer, New York
Stuckelberger A, Abrams D, Chastonay P (2012) Age discrimination as a source of exclusion in Europe: the need for a human rights plan for older persons. In: Keating N, Scharf T (eds) From exclusion to inclusion in old age: a global challenge. Policy, Bristol
Vo K, Forder PM, Tavener M, Rodgers B, Banks E, Bauman A, Byles JE (2015) Retirement, age, gender and mental health: findings from the 45 and up study. Aging Ment Health 19:647–657
WHO (2003) Department of gender, w. a. h. Gender, health and ageing. Gender and Health information sheet. http://www.who.int/gender-equity-rights/knowledge/a85586/en/
WHO (2012) Definition of an older or elderly person. In: Health statistics and information systems. World Health Organization. http://www.who.int/healthinfo/survey/ageingdefnolder/en/
Wu YH, Damnee S, Kerherve H, Ware C, Rigaud AS (2015) Bridging the digital divide in older adults: a study from an initiative to inform older adults about new technologies. Clin Interv Aging 10:193–200
Wurm S, Benyamini Y (2014) Optimism buffers the detrimental effect of negative self-perceptions of ageing on physical and mental health. Psychol Health 29:832–848
Yang K, Victor C (2011) Age and loneliness in 25 European nations. Ageing Soc 31:1368–1388
Zaidi A (2008) Features and challenges of population ageing: the European perspective, Policy Brief March (I). European Centre for Social Welfare Policy and Research, Vienna

Epidemiology of Mental Disorders (Including Cross-Cultural Comparisons)

4

Ee Heok Kua and Rathi Mahendran

Abstract

This review covers a wide swathe of the research worldwide on the epidemiology of mental disorders in late life. Data on the prevalence and incidence of mental disorders are important not only for mental health professionals but also health policy makers who have to plan services for an increasing number of elderly people. Although epidemiological data today are mainly from developed countries, in recent years many developing countries have conducted studies on dementia in community-dwelling elderly.

From the published data of elderly populations 65 years and over, the prevalence of depressive disorders is estimated at 2–21% and dementia between 2% and 8%. Most studies have reported a higher prevalence of Alzheimer's disease than vascular dementia. Research on survival after a diagnosis of dementia indicates a varying period from 5 to 12 years. The reported prevalence of anxiety disorders is 3–14%, and comorbidity of anxiety-depression is high ranging from 40% to 90%. Schizophrenia, bipolar disorder, and other psychotic disorders are less common in old age.

The wide variations in prevalence rates especially for depressive disorders could be due to the differences in sampling methodology, interview instruments, and diagnostic criteria.

Epidemiological studies have identified risk factors which are crucial for early detection and interventions in preventive psychiatry. In the last decade, there are encouraging results from a few interventional programs in the prevention of dementia and depression in late life.

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_5

Keywords
Epidemiology • Depression • Dementia • Anxiety • Schizophrenia • Elderly

Contents

Introduction

Psychiatric epidemiology shows patterns of disorders which are of relevance to the clinicians and health policy makers. The information derived is not just about the number of cases in the population but also factors associated with a particular mental disorder and what factors influence the course of the disorder. Understanding the distribution and determinants of the mental disorder can be the foundation for interventions in preventive psychiatry. With the aging of the populations in developed and developing countries, psychiatric and social services are hard pressed to provide for the increasing number of elderly people with mental disorders. Before planning services, health policy makers need data on the extent of these disorders in the community. Many developing countries do not have epidemiological data, and to borrow information from developed countries may not always be appropriate. A milestone in psychiatric epidemiology is the initiative of the World Health Organization to conduct multisite surveys using similar research protocols (Sartorius 1988). International collaboration has combined teams from developed and developing countries to form consortia like the 10/66 Dementia Research Group (Prince 2010) and Research on East Asia Psychotropic Prescription or REAP (Chong et al. 2010; Xiang et al. 2012) to conduct epidemiological research that can provide better comparison worldwide.

There are three methods to collect data on the prevalence of a mental disorder: hospital outpatient clinic, primary care clinic, and the community. Some hospitals in the UK and Scandinavia have clinics with case registers, which are able to trace service usage by elderly people, and information collected can indicate the extent of

a mental disorder and outcome of treatment. In the primary care clinic, the prevalence of a mental disorder can be difficult to estimate if patients drift from one clinic to another as often observed in many Asian countries. There are cultural differences in the way emotional distress is communicated, and somatic presentation of depression may mislead the primary care doctor. Moreover, because of the specter of stigmatization, patients in many developing countries may prefer to see a traditional healer to avert shame or embarrassment. Therefore, the prevalence of a mental disorder in the primary care clinic will be low due to underreporting.

Community surveys provide more accurate information on the extent of mental disorders in the general population. Because of the large sample size in surveys, many studies would use a short questionnaire to screen potential cases. The lack of standardization of screening questionnaires has been recognized as a major factor in international comparison of epidemiological data. The validity and reliability of case detection thresholds have to be considered. Neuropsychological tests which are mainly from the USA or UK need normative data in developing countries. Performance on many tests used in screening and assessment for dementia is known to be education dependent. The challenges of using brief cognitive screening instruments have been reported in a survey conducted by the International Psychogeriatric Association – the authors highlighted issues such as ethnicity, culture, language, literacy, and elderly with sensory impairments (Shulman et al. 2006).

To ensure uniformity and validity in epidemiological surveys, common assessment questionnaires have been introduced. The London-New York study on the elderly used a structured clinical interview instrument, Geriatric Mental State (GMS), constructed by Copeland and co-workers (1976) to assess the prevalence rates for depression and dementia (Gurland et al. 1983). A computerized program of the GMS called AGECAT (Copeland et al. 1986) was used in the European and Asian surveys on mental disorders in late life. The GMS is also in the assessment package of the 10/66 Dementia Research Group.

In dementia research worldwide, there are differences in the diagnostic criteria applied, and this may account for variations in the results. Many centers prefer the criteria from the *Diagnostic and Statistical Manual (DSM) of Mental Disorders* from the American Psychiatric Association (1987 and 1994), and others use the International Classification of Diseases (ICD-9, ICD-10) from the World Health Organization (1980 and 1992). However, there are a few centers in the USA that prefer the criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984).

Data from most epidemiological research are derived from cross-sectional studies in the elderly population. In recent years, there are more longitudinal aging studies worldwide reflecting the need to understand the natural history of mental disorders in the elderly, including early and late clinical signs. Such studies which require enormous human resources and financial support are important not only in preventive psychiatry but also relevant in training doctors to help them identify the early symptoms and signs of a mental disorder.

Depressive Disorders

Prevalence and Incidence

Table 1 shows the prevalence of depressive disorders in the elderly from research in different countries around the world. Most of the studies used the GMS interview schedule and included rural and urban communities. There is wide variation in rates from a high of 21.3% in Taiwan to a low of 2.3% in Spain. The published reports on low prevalence could be due to methodological factors. Disabilities, which are

Table 1 Prevalence of depressive disorders among community-living elderly

Author	Country	Age (years)	Sample size	Method	Prevalence
Blazer et al. (1987)	USA	≥65	1,304	DIS/ DSM-III	Dysthymia: 2.0%
					Major depression: 0.8%
Copeland et al. (1987)	UK	≥65	1,070	GMS	All depressive disorders: 11.2%
Lobo et al. (1995)	Spain	≥65	1,080	GMS	Dysthymia: 1.3%
				DSM-III-R	Major depression: 1.0%
Kua et al. (1997)	Singapore	≥65	1,062	GMS-AGECAT	All depressive disorders: 6% (men 5.9%, women 6.1%)
Newman et al. (1998)	Canada	≥65	1,119	GMS: DSM-IV	Minor depression: 3.6%
					Major depression: 0.86%
Forsell and Winblad (1999)	Sweden	≥75	875	DSM-IV	Major depression: 4.1%
Chong et al. (2001)	Taiwan	≥65	1,500	GMS-AGECAT	Depressive disorders: 21.3% (men 16.8%, women 35.4%)
Xavier et al. (2002)	Brazil	≥80	77	DSM-IV	Minor depression: 12%
Chen et al. (2005)	China	≥60	1,600	GMS-AGECAT	All depressive disorders: 6% (men 3.4%, women 8.5%)
McDougall et al. (2007)	UK	≥65	2,640	GMS-AGECAT	All depressive disorders: 8.7% (men 6.5%, women 10.4%)
Gureje et al. (2007)	Nigeria	≥65	2,152	DSM-IV	Major depression: 7.1%
Kessler et al. (2012)	USA	≥65	709	DSM-IV	Major depressive disorder 2.3%

DIS Diagnostic Interview Schedule
DSM-III Diagnostic and Statistical Manual of Mental Disorders 3rd Edition
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders 3rd Edition: Revised
DSM-IV Diagnostic and Statistical Manual of Mental Disorders 4th Edition
GMS Geriatric Mental State Schedule
GMS-AGECAT Geriatric Mental State-Automated Geriatric Examination for Computerized Assisted Taxonomy

common in old age, may make it more difficult for elderly people to take part in surveys, and comorbid physical illness may lead to "masking" of depressive features. Another possible explanation is that some older patients with clinically significant depression underreport their symptoms. The studies from China and Brazil were from rural communities with prevalence of 6% and 12%, respectively, which are higher than the rates of 2–4% in the urban surveys in Spain, Canada, and Sweden. The time frame to use in reporting data from community surveys on the prevalence of mental disorders is sometimes not clear. Some authors focus on estimates of recent prevalence to avoid biases associated with selective recall. Other reports include those with met criteria for mental disorders in the past 12 months or even at any time in their life.

The European Collaborative Group on Depression (EURODEP) consortium reported a combined prevalence of 12.3% with men 8.6% and women 14.1% (Copeland et al. 1999). Even within the same country, there was wide difference in rates of depressive disorders, for example, the Liverpool study (Copeland et al. 1987) reported a prevalence of 10.0% (7.6% in men and 10.6% in women), and the London study (Livingston et al. 1990) reported a considerably higher figure of 17.3% (14.3% in men and 19.2% in women). This was also observed in the research from the USA and Canada when studies were conducted at different times with different diagnostic criteria and using different assessment questionnaires. The earlier findings by Blazer et al. (1987) were conducted in North Carolina using the DSM-III diagnostic criteria (American Psychiatric Association 1987), and the more recent report by Kessler et al. (2012) had data from the much larger US National Comorbidity Survey using the DSM-IV diagnostic criteria (American Psychiatric Association 1994). In the Canadian Community Health Survey (Patten et al. 2006), the point prevalence of major depressive disorder in the elderly was estimated at 0.9%, which was quite similar to the earlier study by Newman et al. (1998) – however, the 12-month prevalence of major depressive disorder in the Canadian Community Health Survey was 1.9%.

A number of studies have shown the prevalence of depressive disorders to be higher in the older elderly. Roberts et al. (1997) reported an increase in prevalence of major depressive episode from 6.9% at 60–69 years to 10.4% at 70–79 years and 12.7% at 80 years or more. Palsson and co-workers (2001) found the 1-month prevalence of DSM-III-R depressive disorder was 5.6% at age 70, 5.9% at age 75, 11.2% at age 79, and 13.8% at age 83. Among persons aged 90 years or more in Sweden, the prevalence of depression was 7.9% and dysthymia 1.2%. (Forsell et al. 1995) The prevalence of GMS cases was 24% for the German population of the very old (aged 85 years or more) (Meller et al. 1997).

Doctors in primary care have observed that many elderly people may have depressive symptoms but do not fulfill the DSM criteria for depressive disorder. Judd et al. (1994) defined subsyndromal depression as having two or more symptoms of depression for most or all of the time in a 2-week period, in persons who do not otherwise meet DSM criteria for a current major depressive disorder or dysthymia. Subsyndromal or subclinical depression can affect quality of life and lead to

excessive use of services (Pincus et al. 1999; Preisig et al. 2001). Such patients are often seen at primary care and present as somatic complaints with functional impairment. In an epidemiological study of 1,092 elderly (Soh et al. 2008) from a multiethnic stratified random sample of older adults aged 60 or more who were examined using the GMS schedule, the prevalence of subsyndromal depression in an Asian population was 9.6% (Chinese 10.1%, Malay 8.2%, Indian 12.6%).

The prevalence of depression in nursing homes is reported to be much higher than rates in the community. In the Netherlands, a survey of 333 nursing homes elderly showed a prevalence of 8.1% and subclinical depression at 24% (Jongenelis et al. 2004). The rate for major depression among residents in three US nursing homes varied from 14% at one extreme to 42% at the other (Gerety et al. 1994; Evers et al. 2002). In Australia, the prevalence of depression in elderly residents in nursing homes was also reported at a high rate of 33% (Snowdon et al. 1996).

Most studies have indicated that the incidence of first-onset depression increases with age. In the UK, Copeland et al. (1992) estimated that the incidence of depression in old age was at least 2.37% per year. A study in Sweden of 875 nondepressed elderly with a mean age of 85 reported the incidence of depression at 4.1% (Forsell and Winblad 1999). Another Swedish study showed an incidence of first-onset depression at 1.7% for those aged 70–79 and 4.4% for those in the ages 79–85 (Palsson et al. 2001). Among a community sample aged 65 years or more in Cache County, USA, the incidence rate of any depression per 1,000 person-years was 16.36 (men 13.09, women 19.44), and major depression was 10.5 (8.9 for men, 11.9 for women) (Norton et al. 2006).

Risk Factors

Community studies have yielded significant results on risk factors in late-life depression, including physical disabilities, poor social support, functional limitations, lower income, and impaired cognition (Cole and Dendukuri 2003). Disability may lead to depression because of decreased capability and increased dependence on others especially when the elderly lives alone. Cross-sectional and longitudinal studies have provided evidence of a close relationship between physical ill-health and depression (Mojtabai and Olfson 2004). The prevalence of depression is considerably increased among people with Parkinson's disease, cancer, stroke, and other serious medical problems (Snowdon 1994). The association between depression in late life and chronic diseases like diabetes mellitus and chronic obstructive pulmonary disease is well documented (Ho et al. 2014). Prince and colleagues (1997a) suggested that the association between changes in physical health status and depression ratings related mainly to the degree of consequent functional impairment.

Depression and cardiovascular diseases are common in late life and will be the leading causes of the economic burden of diseases in the next decade. The concept of vascular depression suggests that cerebrovascular diseases, such as stroke, are especially relevant in the etiology of depression in old age (Alexopoulos et al. 1997).

A systematic review found a pooled estimate of 33% for depression after stroke (Hackett et al. 2005).

The extent of depression among people with dementia is also high (12% compared to 4% of non-demented people aged 75 years or more), and depression is associated with increased levels of disability in this population (Forsell and Winblad 1998). It has been noted that the rate of depression may be higher in cases of vascular dementia than in Alzheimer's disease – 21% versus 3% (Newman 1999).

In many Asian countries, the rapid development in industrialization and disintegration of the family structure in recent decades may have undermined the social foundations for filial piety and other traditional virtues (Lim et al. 2011). This decline in intergenerational cohesion and maintenance of filial obligations has in turn contributed to the older person's experience of disappointment, sadness, and grief. Poor social support and loneliness have been consistently found to predict depression in elderly Chinese (Lim and Ng 2010). Studies in some European countries also showed similar results on depression and decreased social network and support (Kivela et al. 1996; Prince et al. 1997b; Arean and Reynolds 2005; Djernes 2006). Hospitalization or bereavement was experienced four to six times more often by depressed elderly people than controls (Brilman and Ormel 2001). There are higher rates of depression among those who are widowed, divorced, or separated (Regier et al. 1993). Osborn et al. (2003) concluded that social isolation and having no confiding relationships are more relevant as factors associated with late-life depression than living alone per se. In Latin American, a Brazilian study (Blay et al. 2007) reported a high rate of depression in old people especially for those with lower income, poorer health, and functional status and who were single or divorced. In China, it was found that lower educational level and monthly income, rural abode, and presence of one or more major medical conditions were associated with increased vulnerability to depression in the elderly (Ma et al. 2008).

Outcome of Depression

There is a paucity of information on the course of depression in the elderly living in the community. A few reported studies have shown that depression in late life seemed to have a poor prognosis. In South Africa, Ben-Arie et al. (1990) followed up a group of 20 depressed elderly people diagnosed in a community survey of 150 elderly subjects using the Present State Examination (Wing et al. 1974) and found that nine (45%) were still depressed after 3 years. In the UK, Copeland et al. (1992) reassessed a group of 107 depressed elderly after 3 years and found 30.8% were still in depression, 4.7% had dementia, and 23.4% had died.

A study of 35 elderly Chinese living in the community who had depression, as diagnosed with the GMS-AGECAT, also showed a bleak outcome. After 5 years, 31 were traced – 10 (32.2%) were still depressed, only 8 (25.8%) recovered, 5 (16.1%) had died, 5 (16.1%) were categorized as subclinical depression, 2 (6.5%) had anxiety disorder, and there was 1 case of dementia (Kua 1993). In another study in Ireland, 127 depressed elderly assessed by the GMS-AGECAT were followed up for 3 years,

and the authors reported that 30.2% had died, 34.9% had persistent depression, 24.5% had other case or subclinical mental disorders, and only 10.4% recovered (Denihan et al. 2000). In the Amsterdam longitudinal study, a cohort of patients was followed up for 6 years; there were remissions in 23%, severe chronic course in 32%, and a middle group with fluctuating course in 44% (Beekman et al. 2002).

Dementia

Prevalence and Incidence

There is a global concern about the rising tide of dementia because it will exact a heavy toll on health services and impact family life and the national economy (Larson and Langa 2008). By 2040, it is estimated that about 71% of the 81.1 million dementia cases in the world will be in developing countries (Ferri et al. 2005). And every year, there are approximately 4.6 million new cases of dementia, with the highest growth projections in China and India. Epidemiological research on dementia provides invaluable data on risk factors which can help healthcare providers and policy makers to plan preventive measures to slow down deterioration of cognitive functions and improve quality of life of the elderly sufferers.

Dementia prevalence estimates vary considerably worldwide as shown in Table 2. An early study of elderly people in New York by Gurland et al. (1983) used a modified version of the GMS, and the prevalence of dementia in a sample of 445 subjects was estimated to be 4.9%. A larger study in Liverpool of 1,070 elderly living in the community (Copeland et al. 1987) used the computerized GMS-AGECAT and reported a prevalence of 5.2%. The first study in China by Li et al. (1989) used the GMS schedule, and the reported prevalence of dementia was 1.8%. A more recent survey in China in four cities of over 34,807 Chinese aged at least 55 years in 79 rural and 58 urban communities reported a crude prevalence estimate of 5.0%, Alzheimer's disease (AD) 4.8%, and vascular dementia (VD) 1.1% (Zhang et al. 2005). In Africa, a study in Nigeria showed a low prevalence of 2.3% compared with an African-American population in Indiana, USA, where a survey reported a higher rate of 8.2% (Hendrie et al. 1995). A high prevalence of 8.0% was also reported by the Canadian Study of Health and Aging Working Group (1994), who surveyed elderly people 65 years and more living in community and institutional settings. A community survey in Singapore showed a higher prevalence of dementia for elderly Malay people than elderly Chinese, and the rate in the elderly Malays was quite similar to the New York and Liverpool results (Kua and Ko 1995).

The EURODEM consortium used data from eight European countries (Lobo et al. 2000) and showed a gradual increase of prevalence from 0.4% for both gender in the age group 60–64 to 11.0% for men and 12.6% for women in the age group 80–84 and 22.1% for men and 30.8% women who were 90 years or more. In Hong Kong, Chiu and her team (1998) showed that the rate in elderly Chinese increased from 1.7% in those 70–74 years to a high of 25.8% in those 90 years or more. In the USA, dementia prevalence increased with age from 5% in the eighth decade to 37.4% over

Table 2 Dementia: prevalence studies

Author	Country	Age (years)	Sample size	Method	Prevalence
Gurland et al. (1983)	USA	≥65	445	GMS	All dementias: 4.9%
Haseagawa et al. (1986)	Japan	≥65	1,498	DSM-III	All dementia: 4.7%
					AD: 1.1%, VD: 2%
Copeland et al. (1987)	UK	≥65	1,070	GMS-AGECAT	All dementias: 5.2%
Lobo et al. (1995)	Spain	≥65	1,080	GMS/DSM-III-R	AD: 4.3%, VD: 0.6%
Liu et al. (1996)	Taiwan	≥65	1,016	DSM-III-R	65–74 years: 2.0%
					75–84 years: 8.3%
					85 and older: 24.4%
Hendrie et al. (1995)	Nigeria	≥65	2,494	DSM-III	All dementia: 2.3%
					AD: 1.4%, VD: 0.72%
Chiu et al. (1998)	Hong Kong	≥70	1,034	DSM-IV	70–74 years: 1.7%
					75–79 years: 4.1%
					80–84 years: 10.7%
					85–89 years: 18.8%
					90 and older: 25.8%
Farrag et al. (1998)	Egypt	≥65	1,366	DSM-IV	All dementia: 5.93%
					AD: 2.86%, VD: 1.25%
Quiroga et al. (1999)	Chile	≥65	2,213	DSM-III-R	All dementia: 4.3%
Guk et al. (2003)	South Korea	≥65	1,037	DSM-IV	All dementia: 7.1%
				NINCDS-ADRDA	AD: 4.2%, VD: 2.4%
De Silva et al. (2003)	Sri Lanka	≥65	703	DSM-IV	All dementia: 4.0%
				NINCDS-ADRDA	AD: 2.8%, VD: 0.6 %

(*continued*)

Table 2 (continued)

Author	Country	Age (years)	Sample size	Method	Prevalence
Ikeda et al. (2004)	Japan	≥65	1,438	DSM-III-R	All dementia: 4.2%
				NINCDS-ADRDA	AD: 1.5%, VD: 1.9%
Shaji et al. (2005)	India	≥65	1,934	DSM-IV	All dementia: 2.9%
				ICD-10	AD: 1.6%, VD: 1.1%
Zhang et al. (2005)	China	≥65	34,807	NINCDS-ADRDA	All dementia: 5.0%
					AD 2.0%, VD 0.9%
Molera et al. (2007)	Venezuela	≥65	2,438	DSM-IV	AD: 4.0% (3.3–4.8)
					VD: 2.1% (1.6–2.7)
Plassman et al. (2007)	USA	>71	856	DSM-III-R	All dementia: 13.9%
				DSM-IV	AD: 9.7%, VD: 2.4%

AD Alzheimer's disease, *VD* vascular dementia
DSM-III Diagnostic and Statistical Manual of Mental Disorders 3rd Edition
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders 3rd Edition: Revised
DSM-IV Diagnostic and Statistical Manual of Mental Disorders 4th Edition
NINCDS-ADRDA National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
ICD-10 International Classification of Diseases 10th revision
GMS Geriatric Mental State
GMS-AGECAT Geriatric Mental State-Automated Geriatric Examination for Computerized Assisted Taxonomy

age 95 years (Plassman et al. 2007). In a meta-analysis of 22 different studies, Jorm et al. (1987) indicated that the prevalence doubles every 5.1 years up to the age of 95.

Comparison of results from different populations can be difficult if diverse methods are used. It has been observed that elderly people with little or no education may not do well in cognitive tests even in the absence of cognitive impairment – the task may be unfamiliar or the information irrelevant. Tasks involving literacy and numeracy can be problematic causing biased results. The 10/66 Dementia Research Group has made an attempt to improve the validity of methods used in cross-cultural research (Prince 2010). The group has conducted numerous studies in Europe, Latin America and the Caribbean, Africa, India, Russia, China, and Southeast Asia (Prince et al. 2003; Ferri et al. 2005; Rodriguez et al. 2008). The estimates of dementia prevalence for those aged 60 years or more were higher for Western Europe (7.29%), South Asia (5.65%), and Latin America (8.50%); those from East Asia were lower (4.98%). This variation might indicate differences in population age structure, genetics, and lifestyle but could

also be due to difficulty in standardizing dementia assessment. Rodriguez et al. (2008) summarized the 10/66 survey of 14,960 residents aged over 65 years in 11 sites (China, India, Cuba, Dominican Republic, Venezuela, Mexico, and Peru) and showed the prevalence of dementia according to the DSM-IV varied widely from less than 1% in India and rural Peru, to 6.4% in Cuba. The mean age-adjusted prevalence estimate for dementia among people aged 65 years or more living in developing countries was calculated to be 5.3% (Kalaria et al. 2008).

Prince et al. (2013) conducted a systemic review of the global literature on the prevalence of dementia and meta-analysis in 21 Global Burden of Diseases regions. The age-standardized prevalence for those >60 years varied, 5–7% in most world regions, with a higher rate in Latin America (8.5%) and lower rate in sub-Saharan African regions (2–4%). The sample size of the populations studied ranged from <500 subjects in a third of European countries to >3,000 subjects in the East Asian countries like China. Although the majority of countries used the DSM-III/DSM-IV diagnostic criteria, a few countries used the ICD-10 and GMS-AGECAT. Most of the surveys were conducted different – some were one phase design and others were two or more phases. The response proportion was generally satisfactory between 60% and 79%, although a few European countries had <60%, while the majority of East and South Asian countries were between 80% and 100%.

Comparing the subtypes of dementia, the prevalence of AD is higher than VD (Table 2). The rate for AD varies from a low of 1.1% in Japan to a high of 4.3% in Spain. Prevalence estimates of VD range from 0.6% in Spain to 2.1% in Venezuela. In contrast to most countries, the prevalence of VD in Japan is higher than AD (Haseagawa et al. 1986; Ikeda et al. 2004). The autopsy reports of elderly people with dementia indicated that AD was more common than VD, even in the Japanese studies (Table 3).

Relatively lower annual incidence estimates of 1.2% are reported in certain countries, such as Brazil, Nigeria, and India (Nitrini et al. 2004; Hendrie et al. 2001; Chandra et al. 2001). In China, Li et al. (2007) in a 2-year follow-up study of 1,593 community-dwelling elderly aged 60 years and more showed a low annual incidence of 0.45%, and the Italian Longitudinal Study of Aging also reported a low incidence rate of 0.76% (Di Carlo et al. 2007). In Australia, Piguet et al. (2003) in a 6-year follow-up study of 337 elderly 75 years and more reported a higher incidence of 2.78% annually. In the Cardiovascular Health Study in North America (Fitzpatrick et al. 2004), the incidence at age 80 was much higher at 19.2% for AD and 14.6% for VD.

The EURODEM study indicated a low incidence of 0.2% for age group 60–64 years in both gender and rising gradually to 4.0% for men and 8.2% for women who were 90 years or more (Lobo et al. 2000). The study with the largest sample of 2,507 elderly people with at least one follow-up assessment was conducted by Liu and co-workers in Taiwan (1996). They found that the incidence increased with age: the rate was 0.77% for age group 65–74, 2.51% for age group 75–84, and 6.19% for those aged 85 or more. Consistent with many reports, the steep rise in incidence of total dementia with age was mainly attributed to AD rather than VD, which decreased markedly in the very old group. All the studies have shown

Table 3 Types of dementia in autopsy reports

	n	Country	Percentage of total autopsy cases				
			AD	VD	MIX	DLB	Others
Mizutani and Shimada (1992)	27	Japan	33.3	18.5	22.0	15.0	12.0
Akatsu et al. (2002)	158	Japan	46	22	2	18	12
Schneider et al. (2009)							
Community cohort	194	USA	49.45	39.2	44.3	24.7	1.5
Clinical cohort	280		66.1	17.9	27.5	21.4	6.1
Brayne et al. (2009)	113	UK	67	35	26	5	?
Jellinger and Attems (2010)	1,110	Austria	42.9/24.6	10.8	5.5	9.7	6.6

AD Alzheimer's disease, *VD* vascular dementia
AD + CVLs (cerebrovascular lesions)
AD + LB (Lewy body)
MIX mixed dementia
DLB dementia Lewy body

that the incidence of dementia increases with age. Jorm and Jolley (1998) concluded that the incidence of dementia rises exponentially up to the age of 90.

In recent years, there is research interest to find out how many of those elderly with mild cognitive impairment will progress eventually to dementia. Investigators at the Cache County study reported 46% of elderly with cognitive impairment converted to dementia compared to 3.3% among those without cognitive impairment (Tschanz et al. 2006).

Risk Factors

Genetic and environmental factors, including socioeconomic conditions, nutrition, and educational status, have been suggested as possible risk factors of dementia. The susceptibility gene, APOE-4 allele, as a general risk factor for AD is well documented (Saunders et al. 1993). However, the association of the APOE-4 allele with Alzheimer's disease has been shown to vary among different ethnic groups – a comparative analysis showed that the APOE-4 allele is a risk factor for AD in African-Americans, but not in Yoruba Nigerians (Murrell et al. 2006; Gureje et al. 2006).

Low educational achievement has been shown to be a risk factor for dementia. Low literacy is often linked to poverty or lower socioeconomic status, which is associated with poorer health, lower access to health care, and increased risk of dementia (Fratiglioni et al. 2004; Borenstein et al. 2006).

Multidisciplinary research has provided moderately strong evidence supporting the role of vascular factors and related disorders like diabetes mellitus, obesity, and smoking as risk factors (Hofman et al. 1997; Luchsinger et al. 2001; Norton et al. 2014). The cardiovascular risk factors for AD and VD are a history of stroke (Di Carlo et al. 2007), hypertension (Skoog et al. 1996; Fitzpatrick et al. 2004; Qiu et al. 2010), and arrhythmias (Ott et al. 1997). Investigators have found that deficiency in

dietary and nutritional factors (e.g., homocysteine, B vitamins, and diet pattern) is associated with memory impairment (Luchsinger and Mayeux 2004).

A study by Devanand et al. (1996) suggested a link between depression and AD. In the MacArthur study on "Successful Aging," depressive symptoms predicted cognitive decline in previously high-functioning elders (Chodosh et al. 2007). Ownby et al. (2006) in a meta-analysis of 22 studies showed that depression increased the risk for development of dementia in late life.

Outcome of Dementia

The interest to know more about the life expectancy of dementia started with research from North America and Western Europe. Reviewing the results from numerous studies from 1962 to 1990, Van Dijk and co-workers (1991) reported that there was a definite increase in mortality for dementia patients as compared to the general population of elderly. They also showed that there was a higher survival rate for AD than VD patients, and a higher survival rate for female than for male patients. More recently, in a 15-year prospective study in Southwestern Pennsylvania of a cohort of 1,670 adults 65 years and older, it was found that AD increased the risk of mortality by 40% in the cohort as a whole (Ganguli et al. 2005).

The duration of survival of dementia varies from 5 to 12 years (Table 3). In the Finnish study by Molsa et al. (1995), 218 AD patients and 115 VD patients were followed up for 14 years, and the authors found the survival rate for AD was 7.3 years and VD 6.4 years. The duration concurred with the Baltimore Longitudinal Study of Aging (Brookmeyer et al. 2002) which reported a median life span between 7 and 10 years for patients whose illness were diagnosed when they were in their 60s and early 70s. An extensive US study (Heyman et al. 1996) showed no statistical difference in survival rates between white Americans and African-American patients with AD.

In Asia, one of the first studies on life expectancy of AD patients was the Japanese Hisayama study reported by Matsui et al. (2009). A total of 828 non-demented elderly 65 years and more were followed up, and the authors found the survival curve of dementia cases aged 65–89 years was significantly lower than that of age- and sex-matched controls. A recent report from Korea on survival analyses of AD patients included a large study of 724 consecutive patients from a memory disorder clinic in a tertiary hospital in Seoul (Go et al. 2013). The overall median survival from the time of diagnosis was 9.3 years. The mean period from the onset of the symptoms to the time of diagnosis was 2.8 years, which means the duration of AD is about 12.1 years.

A Singapore study in a general hospital memory clinic reported on the duration of the three stages of deterioration in dementia – mild, moderate, and severe using the clinical dementia rating (CDR) scale (Hughes et al. 1982; Morris 1993) for assessment of severity. The mean duration of the mild phase (CDR 1) was 5.6 years, moderate phase (CDR 2) 3.5 years, and severe phase (CDR 3) 3.2 years (Kua et al. 2014).

Is the Prevalence and Incidence of Dementia Declining?

Manton et al. (2005) analyzed 17 years of national long-term surveys in the USA (1982–1999) and found a decrease in dementia prevalence from 5.7% to 2.9% during that period. They pointed to higher levels of education, a reduction in stroke rates, and other factors as possible contributors to the decrease. The recent report from the UK (Matthews et al. 2013) compared the Cognitive Function and Ageing Study (CFAS) I and II, two surveys of populations 65 years of age or older – CFAS I, conducted between 1989 and 1994, and CFAS II, conducted between 2008 and 2011, each with a sample size of more than 7,500. The authors showed that dementia prevalence rate was 8.3% in CFAS I, as compared with 6.5% in CFAS II. They concluded that populations born later had a lower risk of dementia than those born earlier, probably because of higher education levels and better prevention of vascular disease. The evidence supports the theory that better education, controlling vascular and other risk factors during midlife and early old age, has unexpected benefits.

A more recent study by Satizabal et al. (2016) discussed the temporal trends in the incidence of dementia over three decades among participants in the Framingham Heart Study. In the analysis, which included 5,205 persons 60 years or older, they found that the incidence of 3.6% in the 1970s declined gradually to 2.8% in the 1980s, 2.2% in the 1990s, and 2.0% in the 2000s and early 2010s. The authors concluded that although most vascular risk factors (except obesity and diabetes) and risk of dementia associated with stroke, atrial fibrillation, or heart failure decreased over time, none of these trends completely explain the decrease in the incidence of dementia.

Anxiety Disorders

The epidemiology of anxiety disorders in the elderly is not as extensively studied as with dementia or depression. However, recent research suggests that anxiety disorders may be as common as depression in late life and is also associated with considerable disease burden (Byrne and Pachana 2010). Table 4 shows the results of community studies which were mainly from Europe and North America. The overall prevalence of anxiety disorders is high in some European countries – 14% in France, 13.7% in the UK, and 10.2% in the Netherlands. Low rates were reported in Singapore, Canada, and Sweden. Comparing gender, the prevalence of anxiety disorders is higher in elderly women than in men (Lindesay et al. 1996). The more recent study by Kessler et al. (2012) reported a rate of 7.6% in the US National Comorbidity Survey.

Specific phobia is often considered the most common among the anxiety disorders. Prevalence estimates vary from 2% to 12% in populations aged 65 years or more (Ritchie et al. 2004; Preville et al. 2008; Beekman et al. 1998; Chou 2009; Sigstrom et al. 2011; Kessler et al. 2012). A Swedish study using DSM-IV criteria

Table 4 Survival studies of dementia

Author	Country	Sample size	Results
Molsa et al. (1995)	Finland	14-year follow-up of 333 dementia patients: 218 (65%)	Mean survival: AD 7.3 years – men 5.0 years, women 7.8 years
		AD, 115 (35%) VD	VD 6.4 years – men 5.1 years, women 6.7 years
Heyman et al. (1996)	USA	1,036 AD patients from 21 centers	Mean survival of AD from time of entry into study: men 5.7 years and women 7.2 years
Brookmeyer et al. (2002)	USA	Baltimore Longitudinal Study of Aging – follow-up of 2,476 elderly (1,556 men, 910 women)	Median life span of AD patients between 7 and 10 years
Ganguli et al. (2005)	USA	15-year prospective study of 1,670 adults 65 years and older	Mean duration of survival of AD patients 5.9 years
Matsui et al. (2009)	Japan	828 Japanese elderly with no dementia were followed up for 17 years	10-year survival rate of dementia was 13.6% compared with 29.3% of matched controls
Go et al. (2013)	South Korea	Survival analysis of 724 AD patients	Median survival from onset of first symptom was 12.6 years
Kua et al. (2014)	Singapore	77 AD patients from a memory clinic	Mean duration in each phase
			Mild: 5.6 years, mod:3.5 years, sev: 3.2 years

reported the prevalence of social phobia as 1.8% for those aged 65 years and older and 1.9% for those aged 70 years or more (Karlsson et al. 2009). Panic disorder is considered very uncommon among the elderly – 1% in the Netherlands (Beekman et al. 1998), 0.3% in Canada (Bland et al. 1988), and 0.7% in the USA (Kessler et al. 2012). For obsessive compulsive disorder, studies on populations aged 65 years or more indicated low prevalence rates ranging from 0.2% to 1.5% (Beekman et al. 1998; Ritchie et al. 2004; Grenier et al. 2009). The studies also showed that obsessive compulsive disorder was more common among elderly women than elderly men. Beekman et al. (1998) reported a rate of 0.6% in the elderly with a peak prevalence of 2.7% in women 65–74 years compared with 0.3% in women 55–64 years or 0.8% in women 75–85 years. The American study by Regier et al. (1988) also showed a similar low rate of 0.8% – men 0.7% and women 0.9% (Table 5).

Comorbidity of depression and anxiety disorders is very high in late life with figures between 40% and 90% (Lenze et al. 2001; Cairney et al. 2008; Kvaal et al. 2008; King-Kallimanis et al. 2009; Byers et al. 2010). In the UK, Lindesay and co-workers (1996) reported that 91% of the elderly with general anxiety in the population also had depression. However, Bland and colleagues in Canada (1988) reported that 95% of those with depression had symptoms of anxiety, while Jeste et al. (2006) found a lower rate of 42% of depressed elderly with comorbid anxiety.

Table 5 Epidemiology of anxiety disorders in community-dwelling elderly

Author	Country	Age (years)	Sample size	Country method	Prevalence
Regier et al. (1988)	USA	≥65	5,071	DIS	Overall prevalence 5.5%
					Phobic disorder 4.8%
Bland et al. (1988)	Canada	≥65	358	DIS	Overall prevalence 3.5%
Lindesay et al. (1989)	UK	≥65	890	GMS DSM- III	Overall prevalence 13.7%
					3.7% GAD, 10.0% phobic disorders
Kua (1992)	Singapore	≥65	612	GMS-AGECAT	Overall prevalence 0.5%
Beekman et al. (1998)	Netherlands	55–85	3,107	HADS	Overall prevalence 10.2%
Forsell and Winblad (1998)	Sweden	≥78	966	CPRS	Overall prevalence 3.2%
Ritchie et al. (2004)	France	≥65	1,873	DSM-IV	Overall prevalence 14%
					Men 8.7%, women 18.1%
Kessler et al. (2012)	USA	>65	709	DSM-IV	Overall prevalence 7.6%

DIS Diagnostic Interview Schedule
HADS Hospital Anxiety and Depression Scale
CPRS Comprehensive Psychopathological Rating Scale
GAD generalized anxiety disorder
DSM-III Diagnostic and Statistical Manual of Mental Disorders 3rd Edition
DSM-III-R Diagnostic and Statistical Manual of Mental Disorders 3rd Edition: Revised
DSM-IV Diagnostic and Statistical Manual of Mental Disorders 4th Edition
GMS Geriatric Mental State
GMS-AGECAT Geriatric Mental State-Automated Geriatric Examination for Computerized Assisted Taxonomy

Schizophrenia, Bipolar Disorder, and Other Psychotic Disorders

The term paraphrenia was previously used to describe psychotic syndromes in the elderly. Currently used terms are late-onset schizophrenia or late-life psychosis encompassing visual and auditory hallucinations and delusions arising in late life. Population studies indicated that the prevalence of self-reported psychotic symptoms in the elderly without dementia ranges from 1.7% to 4.2% (Ritchie et al. 2004; Henderson et al. 1998; Livingston et al. 2001). The incidence of first-onset psychotic symptoms was estimated at 5.3 per 1,000 person-years for people aged 70 and

90 years and only 45% of those who developed first-onset psychotic symptoms developed dementia (Östling and Skoog 2002).

The findings from a community study in the UK of 5,222 persons aged 65 years and over showed a prevalence of DSM-III-R schizophrenia in 0.12 % and delusional disorder 0.04 % (Copeland et al. 1998). In the USA, a study from the Epidemiologic Catchment Area showed a prevalence of only 0.2 % for schizophrenia in the elderly (Keith et al. 1989), while a Danish study (Nielsen and Nielsen 1989) reported a 6-month prevalence rate ranging from 0.4% to 0.6%. In Singapore, Kua (1992) used the GMS-AGECAT instrument to examine a sample of 612 community-based Chinese elderly aged 65 and over and reported that 0.5% had schizophrenia. Research in the USA estimated the 1-year prevalence of bipolar disorder in the elderly population aged 65 years or more to range from 0.1% to 0.7% (Weissman et al. 1988; Lin et al. 2014).

A study in Amsterdam of patients aged 60 years and older, in contact with a mental health organization, reported a 1-year prevalence estimates of 0.55% for schizophrenia, 0.14% for schizoaffective disorder, and 0.03% for delusional disorder; the estimated prevalence of schizophrenia among women (0.68%) was almost twice as high as the estimated prevalence among men (0.35%) (Meesters et al. 2012). The extent of psychotic disorders in elderly people living in the community may be seriously underestimated in service-based studies, as affected individuals generally are not inclined to seek help and their functional capacity is often intact. Many elderly people with serious mental illness are not connected to mental health service either because they fail to seek treatment or because they are disengaged from treatment. Because the Amsterdam study is clinic based, there is a possibility of underreporting.

In the USA, a study on bipolar disorder among the elderly was reported by Goldstein et al. (2006). The data was from the National Epidemiologic Survey on Alcohol and Related Conditions conducted between 2001 and 2002. The target population of the survey was civilian noninstitutionalized population, and the prevalence of bipolar disorder in the 8,121 elderly (65 years and older) was 1.03%. The 12-month psychiatric comorbidity of the elderly with bipolar disorder included alcohol use disorder (38.1%), panic disorder (11.9%), generalized anxiety disorder (9.5%), and dysthymia (7.1%). Elderly men with bipolar disorder reported a higher prevalence of alcoholism, and women reported a higher prevalence of panic disorder.

In pharmacological treatment, a major collaborative study of antipsychotic prescription for schizophrenia in late life was initiated 15 years ago in some Asian countries, including China, Japan, Hong Kong, South Korea, Taiwan, Thailand, Malaysia, and Singapore (Chong et al. 2010; Xiang et al. 2012). The Research on East Asia Psychotropics or REAP consortium is probably the biggest psychopharmaco-epidemiological study in the world. Inpatient and outpatient studies showed a changing trend of prescription from first to second generation antipsychotic medications and the gradual shift in prescriptive habit from polypharmacy to monotherapy.

Prevention

The recent publications on global mental health and the call for action have highlighted inequity of services and human resource around the world (Becker and Kleinman 2013; Lancet Global Mental Health Group 2007). However, in the publications, primary prevention has not been adequately emphasized, and preventive psychiatry in late life is not even mentioned. Sartorius (2002) enumerated four sources of action in preventive psychiatry: first, mental health professionals should advocate that measures for primary prevention be applied; second, promotion of research on causes of mental disorders; third, undergraduate and postgraduate psychiatric education to include primary preventive psychiatry; and fourth, building alliances and supporting activities for primary prevention. Research on epidemiology is not just as an exercise in counting but especially to learn ways to reduce diseases' effects on individuals and populations.

Health education to encourage lifestyle changes including exercise is an effective method to prevent depression (Bridle et al. 2012; Rawtaer et al. 2015). Training to detect early signs of depression should begin in medical school where teaching programs should involve primary care posting with adequate exposure to cases of depression in the early stages. Curriculum should be designed to help medical students identify clinical and subsyndromal cases.

Primary healthcare has an essential role to play in the prevention, detection, and management of mental disorders in late life. For many low-income countries, the most cost-effective approach is community healthcare personnel educating, supporting, and advising family caregivers of the elderly with mental disorders. The high prevalence of depression and the low rates of detection and treatment are challenges that require primary care doctors' participation and collaboration with psychiatrists (Chiu et al. 2009). Efforts to lower the prevalence of depression in the elderly require improvement in the prevention and treatment of chronic physical illnesses like hypertension and diabetes mellitus.

A major step toward primary prevention of depression is to encourage city planners to design public places that will allow elderly people to congregate to prevent social isolation and loneliness. Aging in place means that public housings should be built with environment-friendly design for elderly people and common spaces for young and old to meet. A challenge for policy makers is to plan cities not just for youth but for all ages – accessible buildings, green environment, and communal spaces to encourage social connectedness. A study of Chinese elderly living in crowded accommodations in the Chinatown district of Singapore showed a prevalence of depression of 5.7%. Another study of Chinese elderly in the suburbia indicated a higher rate of 9.5%. The Chinatown elderly tended to congregate daily along the common corridors of their flats or the community centers – they belonged to the same dialect groups and there was daily social interaction; although poorer, the environment provided a supportive ecological system. The suburbian elderly lived in more affluent flats but did not meet as often or mixed as much with their neighbors – they were more isolated. The social ecology of Chinatown bonded by clanship ties provided a robust support network (Goh et al. 2015).

There are now more robust studies to show that health education, lifestyle and control of diabetes mellitus, and hypertension can prevent the onset or delay the progression of dementia. Lifestyle modifications include exercise, long-term adherence to a balanced diet, and cognitive training. Early multi-domain psychosocial interventions for synergistic effects can reduce the incidence of dementia and improve elderly people's quality of life (Gill and Seitz 2015; Gillette-Guyonnet et al. 2009). The FINGER randomized controlled trial by researchers in Finland has shown that a multifaceted intervention that included diet, exercise, cognitive training, and vascular monitoring can improve cognitive health as assessed on a comprehensive neuropsychological test battery in a group of elderly aged 60–77 years who were at risk of developing dementia (Ngandu et al. 2015).

The most cost-effective way to prevent dementia might be through dietary or lifestyle interventions in communities at variable risk of cardiovascular disease. Studies suggest that midlife history of disorders that affect the vascular system, such as hypertension, type 2 diabetes, and obesity, increases the risk for dementia (Skoog et al. 1996; Whitmer et al. 2005; Kivipelto et al. 2006; Luchsinger and Mayeux 2004). Diets rich in fruits, vegetables, and fiber improve well-being and significantly reduce development of the pathological processes. Tea, a beverage originated from China and widely consumed among Chinese, has been suggested to delay cognitive decline in old age (Feng et al. 2010).

The lower risk of dementia among population groups such as Chinese and rural Indians are intriguing and suggest some possibly unique elements of Asian lifestyles, including traditional dietary patterns (Scarmeas et al. 2009; Feng et al. 2009; Feart et al. 2015). Research in dietary and nutritional factors (such as folate, fish and omega-3 fatty acids consumption, turmeric, etc.) have been shown by a growing body of evidence to contribute to the prevention of cognitive decline (Ng et al. 2006; Venketasubramanian et al. 2010). In Korea and China, *ginkgo biloba* has been consumed since ancient times for its medicinal value to improve memory. However, the evidence of predictable and clinically significant benefit of *ginkgo biloba* for people with dementia is still inconclusive (Birks and Grimley Evans 2007).

A nondrug program to promote mental health for the elderly (Wu et al. 2014) includes health education and psychosocial interventions including tai chi exercise, art therapy, mindfulness practice, and music reminiscence. This model is based on brief integrative personal therapy (Feng et al. 2011), and participants showed improvements in scores on the anxiety, depression, and cognitive scales. This inexpensive and culturally acceptable approach could be replicated in other communities (Rawtaer et al. 2015).

Conclusion

Epidemiological research can contribute to a better understanding of the etiology, natural history, and prevention of a mental disorder. The main sources of variation in the prevalence studies on mental disorders in late life lie in methods of identifying cases, sample size, inclusion of elderly from institutional homes, range of ages

covered, proportion of the very old, criteria of diagnosis, rates expressed as point prevalence or period prevalence, and the interview instrument used.

Neuropsychiatric assessment is the best method to screen individuals for dementia and depression in most developing countries. The mini mental state examination (Folstein et al. 1975) has been translated into many languages, but its use as an initial screening tool is limited because in many developing countries, the primary care doctor has no luxury of time to administer a questionnaire which may take 20 min or more. The challenge for researchers now is to construct a brief cognitive screening questionnaire that is not biased by education or language and could be used in a busy clinic in Asia, Africa, or Latin America where the healthcare professionals at the primary care clinic are either a general practitioner or just a nurse.

Many older adults with mental disorders do not receive treatment, and those who do are more likely to see a primary care doctor (Gallo and Coyne 2000). An integrated service should link primary care and community clinics to specialist service in the hospital. The array of services should also include day care centers and respite facilities for family caregivers. In developed countries, long-term institutional care constitutes the main cost, whereas in developing countries, informal care, usually at home, is invariably the only method of care.

Dementia is one of the main causes of disability in late life. People with dementia are heavy consumers of health services, and in developed countries, most direct costs arise from community and residential care. The societal burden due to dementia is set to grow to epidemic proportion worldwide. Results of most studies show that the majority of cases of dementia are in the community and not in institutional care – the burden of care is in the family. Worldwide, family caregivers are the cornerstone of support for people with dementia, and they experience significant psychological, physical, and economic strain. Every effort to reduce the global impact of dementia would be a worthwhile investment. Detection of mild dementia is crucial because the putative medications and psychological interventions are more responsive in the early phase. Interventional strategies in psychosocial therapy, diet, and stability of chronic illnesses like diabetes mellitus and hypertension are critical in lowering the rates of dementia. Such therapeutic measures will also improve the quality of life of the elderly and prevent a rapid decline of cognitive functions. The natural history of dementia may change with time with better medications and lifestyle change to halt its progression. Medications to stabilize diabetes mellitus and hypertension will also prevent cognitive decline. It is suggested that an active lifestyle and balanced diet from early life may be more effective in preventing cognitive decline than starting exercise and taking nutritional supplements in late life. The biggest benefits in reducing the overall burden of dementia can be achieved through policy and public health initiatives promoting primary prevention of cognitive decline rather than efforts directed toward the elderly who have developed dementia (Gill and Seitz 2015).

Epidemiological research is important to plan services for the elderly, but in many countries especially in developing countries, although such services are scarce, there is still a reluctance to visit mental health services because of the stigma of mental illness. Names of terms like “dementia” and “schizophrenia” sound derogatory when translated into the vernacular or local dialects in many Asian countries. Recently,

there are attempts in China, Japan, and Korea to rethink such names and use more appropriate and respectful terms so as to encourage more elderly people to seek help early (Sartorius et al. 2014; Chiu et al. 2014). Low public awareness, underdiagnosis, and undertreatment may reduce the need for mental health service for the elderly. Collaboration with the mass media to increase awareness and investment in training for health professionals is important.

International collaborative studies like the 10/66 Dementia Research Group and Research on East Asia Psychotropics or REAP have improved the quality of psychiatric research methodology in many developing countries. The REAP consortium has leveraged on the collaborative network as a platform for training clinical and leadership skills of mental health professionals in many Asian countries (Chauhan 2009; Chee et al. 2011; Wang et al. 2011; Li et al. 2013). This can be a new paradigm for international epidemiological studies – to provide not just data for service planning and preventive psychiatry, but also opportunities to improve training to ensure better quality of psychiatric practice and care in developing countries.

Cross-References

- ▶ Anxiety in Late Life
- ▶ Cognition and Bipolar Disorder in Older Adults (Including Question of "Neuroprogression")
- ▶ Cognitive and Neuropsychiatric Screening Tests in Older Adults
- ▶ Depression in Late Life: Etiology, Presentation, and Management
- ▶ (Neurobiology of) Dementia: Causes, Presentation, and Management
- ▶ Prevention of Alzheimer's Disease and Alzheimer's Dementia
- ▶ Schizophrenia and Cognition in Late Life

References

Akatsu H, Takahashi M, Matsukawa N, Ishikawa Y, Kondo N, Sato T, Nakazawa H, Yamada T, Okada H, Yamamoto T, Kosaka K (2002) Subtype analysis of neuropathologically diagnosed patients in a Japanese geriatric hospital. J Neurol Sci 196:63–69

Alexopoulos GS, Myers BS, Young RC, Campbell S, Silbersweig D (1997) 'Vascular depression' hypothesis. Arch Gen Psychiatry 54:915–922

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd edn, rev. American Psychiatric Association, Washington, DC

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, DC

Areán PA, Reynolds CFI (2005) The impact of psychosocial factors on late-life depression. Biol Psychiatry 58:277–282

Becker AE, Kleinman A (2013) Mental health and the global agenda. N Engl J Med 369:66–73

Beekman ATF, Bremmer MA, Deeg DJ, van Balkom AJ, Smit JH (1998) Anxiety disorders in later life: a report from the longitudinal aging study Amsterdam. Int J Geriatr Psychiatry 13:717–726

Beekman ATF, Geerlings SW, Deeg DJH, Smit JH, Schoevers RS (2002) The natural history of late-life depression: a 6-year prospective study in the community. Arch Gen Psychiatry 59:605–611

Ben-Arie O, Welman M, Teggin AF (1990) The depressed elderly living in the community. Br J Psychiatry 157:425–427
Birks J, Grimley Evans J (2007) *Ginkgo biloba* for cognitive impairment and dementia. Cochrane Database Syst Rev 2:CD003120
Bland R, Newman S, Orn H (1988) Prevalence of anxiety disorders in the elderly in Edmonton. Acta Psychiatr Scand 338:57–63
Blay SL, Andreoli SB, Fillenbaum GG, Gastal FL (2007) Depression morbidity in later life: prevalence and correlates in a developing country. Am J Geriatr Psychiatry 15:790–799
Blazer DG, Hughes DC, George LK (1987) The epidemiology of depression in an elderly population. Gerontologist 27:281–287
Borenstein AR, Copenhaver CI, Mortimer JA (2006) Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord 2:63–72
Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, Paykel E, Mukaetova-Ladinska EB, Huppert FA, O'Sullivan A, Dening T (2009) The Cambridge City Over-75 s Cohort Cc75c Study Neuropathology Collaboration. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge City over-75 s cohort (CC75C) study. J Alzheimers Dis 18:645–658
Bridle C, Spanjers K, Patel S, Atheron NM, Lamb SE (2012) Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomized controlled trials. Br J Psychiatry 201:180–185
Brilman EI, Ormel J (2001) Life events, difficulties and onset of depressive episodes in later life. Psychol Med 31:859–869
Brookmeyer R, Corrada MM, Curriero FC, Kawas C (2002) Survival following a diagnosis of Alzheimer's disease. Arch Neurol 59:1764–1767
Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML (2010) High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch Gen Psychiatry 67:489–496
Byrne G, Pachana NA (2010) Anxiety and depression in the elderly: do we know any more? Curr Opin Psychiatry 23:504–509
Cairney J, Corna LM, Veldhuizen S, Herrmann N, Streiner DL (2008) Comorbid depression and anxiety in later life: patterns of association, subjective well-being, and impairment. Am J Geriatr Psychiatry 16:201–208
Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia (1994) Canadian Medical Association Journal 150:899–913
Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, DeKosky ST, Ganguli M (2001) Incidence of Alzheimer's disease in a rural community in India: the Indo-US study. Neurology 57:985–989
Chauhan A (2009) Leadership program for young psychiatrists: an experience of a lifetime. Asia Pac Psychiatry 1:46–47
Chee KY, Zakaria H, Rusli AR, Tassniyom K, Kua EH (2011) Short course on leadership and professional development for young psychiatrists and trainees in Kuala Lumpur, Malaysia. Asia Pac Psychiatry 3:157–178
Chen R, Li W, Zhi H, Xia Q, Copeland JR, Hemingway H (2005) Depression in older people in rural China. Arch Intern Med 165:2019–2025
Chiu HFK, Lam LCW, Chi I, Leung T, Li SW, Law WT, Chung DWS, Fung HHL, Kan PS, Lum M, Ng J, Lau J (1998) Prevalence of dementia in Chinese elderly in Hong Kong. Neurology 50:1002–1009
Chiu E, Ames D, Draper B, Snowdon J (2009) Depressive disorders in the elderly. In: Herman H, Maj M, Sartorius N (eds) Depressive disorders, 3rd edn. Wiley-Blackwell, Chichester
Chiu HFK, Sato M, Kua EH, Lee MS, Yu X, Ouyang WC, Yang YK, Sartorius N (2014) Renaming dementia – an East Asian perspective. Int Psychogeriatr 26:885–887
Chodosh J, Kado DM, Seeman TE, Karlamangla AS (2007) Depressive symptoms as a predictor of cognitive decline. MacArthur studies of successful aging. Am J Geriatr Psychiatry 15:406–415

Chong MY, Chen C, Tsang H, Yeh T, Lee Y, Chen C, Lee Y, Tang T, Lo H (2001) Community study of depression in old age in Taiwan: prevalence, life events and socio-demographic correlates. Br J Psychiatry 178:29–35

Chong MY, Tan CH, Shinfuku N, Yang SY, Sim K, Fuji S, Chung EK, Kua EH (2010) Prescribing antipsychotic drugs for inpatients with schizophrenia in Asia: comparison of REAP-2001 and REAP-2004 studies. Asia Pac Psychiatry 2:77–84

Chou KL (2009) Specific phobia in older adults: evidence from the national epidemiologic survey on alcohol and related conditions. Am J Geriatr Psychiatry 17:376–386

Cole MG, Dendukuri N (2003) Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry 160:1147

Copeland JRM, Kelleher MJ, Kellett JM (1976) A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly. The Geriatric Mental State schedule. Development and reliability. Psychol Med 6:439–449

Copeland JR, Dewey ME, Griffiths-Jones HM (1986) Computerised psychiatric diagnosis system and case nomenclature for elderly subjects: GMS and AGECAT. Psychol Med 16:89–99

Copeland J, Dewey M, Wood N, Searle R, Davidson I, Mc William C (1987) Range of mental illness among the elderly in the community: prevalence in Liverpool using the GMS-AGECAT package. Br J Psychiatry 150:815–822

Copeland JR, Davidson IA, Dewey ME, Gilmore C, Lankin BA, McWilliam C, Saunders PA, Scott A, Sharma V, Sullivan C (1992) Alzheimer's disease, other dementias, depression and pseudo-dementia: prevalence, incidence and three-year outcome in Liverpool. Br J Psychiatry 161:230–239

Copeland JRM, Dewey ME, Scott A, Gilmore C, Larkin BA, Cleave N, McCracken CFM, McKibbin PE (1998) Schizophrenia and delusional disorder in older age: community prevalence, incidence, comorbidity, and outcome. Schizophr Bull 24:153–161

Copeland JR, Beckman AT, Dewey ME, Hooijer C, Jordan A, Lawlor BA, Lobo A, Magnusson H, Mann AH, Meller I, Prince MJ, Reischies F, Turrina C, deVries MW, Wilson KC (1999) Depression in Europe geographical distribution among older people. Br J Psychiatry 174:312–321

De Silva HA, Gunatilake SB, Smith AD (2003) Prevalence of dementia in a semi-urban population in Sri Lanka: report from a regional survey. Int J Geriatr Psychiatry 18:711–715

Denihan A, Kirby M, Bruce Z, Coakley D, Lawlor B (2000) Three-year prognosis of depression in the community-dwelling elderly. Br J Psychiatry 176:453–452

Devanand DP, Sano M, Tang MX et al (1996) Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch Gen Psychiatry 53:175–182

Di Carlo A, Lamassa M, Baldereschi M, Inzitari M, Scafato E, Farchi G, Inzitari D (2007) CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology 68:1909–1916

Djernes JK (2006) Prevalence and predictors of depression in populations of elderly: a review. Acta Psychiatr Scand 113:372–387

Evers MM, Samuels SC, Lantz M, Khan K, Brickman AM, Marin DB (2002) The prevalence, diagnosis and treatment of depression in dementia patients in chronic care facilities in the last six months of life. Int J Geriatr Psychiatry 17:464–472

Farrag A, Farwiz HM, Kher EH et al (1998) Prevalence of Alzheimer's disease and other dementing disorders: Assiut-Upper Egypt study. Dement Geriatr Cogn Disord 9:323–328

Feart C, Samieri C, Rondeau V et al (2009) Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 302:638–648

Feart C, Samieri CC, Barberger-Gateau P (2015) Mediterranean diet and cognitive health: an update of available knowledge. Current Opinion in Clinical Nutrition & Metabolic Care 18:51–62

Feng L, Li J, Yap KB, Kua EH, Ng TP (2009) Vitamin B-12, apolipoprotein E genotype, and cognitive performance in community-living older adults: evidence of a gene-micronutrient interaction. Am J Clin Nutr 89:1263–1268

Feng L, Gwee X, Kua EH, Ng TP (2010) Cognitive function and tea consumption in community dwelling older Chinese in Singapore. J Nutr Health Aging 14:433–438

Feng L, Cao Y, Zhang Y, Wee ST, Kua EH (2011) Psychological therapy with Chinese patients. Asia Pac Psychiatry 3:167–172
Ferri CP, Prince M, Brayne C et al (2005) Global prevalence of dementia: a Delphi consensus study. Lancet 366:2112–2117
Fitzpatrick AL, Kuller IH, Ives DG, Lopez OL, Jaqust W, Breitner JC, Jones B, Lyketsos C, Dulberg C (2004) Incidence and prevalence of dementia in the cardiovascular health study. J Am Geriatr Soc 52:195–204
Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method of grading the cognitive state of patients for the clinician. J Psychiatry Res 12:189–198
Forsell Y, Winblad B (1998) Major depression in a population of demented and nondemented older persons: prevalence and correlates. J Am Geriatr Soc 46:27–30
Forsell Y, Winblad B (1999) Incidence of major depression in a very elderly population. Int J Geriatr Psychiatry 14:368–372
Forsell Y, Jorm AF, von Strauss E, Winblad B (1995) Prevalence and correlates of depression in a population of nonagenarians. Br J Psychiatry 167:61–64
Fratiglioni L, Paillard-Borg S, Winblad B (2004) An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 3:343–353
Gallo JJ, Coyne JC (2000) The challenge of depression in late life – bridging science and service in primary care. JAMA 284:1570–1572
Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST (2005) Alzheimer's disease and mortality: a 15-year epidemiological study. Arch Neurol 62:779–784
Gerety MB, Williams JW, Mulrow CD, Cornell JE, Kadri AA, Rosenberg J, Chiodo LK, Long M (1994) Performance of case-finding tools for depression in the nursing home: influence of clinical and functional characteristics and selection of optimal threshold score. J Am Geriatr Soc 42:1103–1109
Gill SS, Seitz DP (2015) Lifestyles and cognitive health: what older individuals can do to optimize cognitive outcomes. JAMA 314:774–775
Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B (2009) Commentary on 'A roadmap for the prevention of dementia II. Leon Thal symposium 2008'. The multi-domain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimers Dement 5:114–121
Go SM, Lee KS, Seo SW, Chin J, Kang SJ, Moon SY, Na DL, Cheong HK (2013) Survival of Alzheimer's disease patients in Korea. Dement Geriatr Cogn Disord 35:219–228
Goh LG, Kua EH, Chiang HD (2015) Ageing in Singapore: the next 50 years. Gerontological Society, Singapore
Goldstein BI, Herrmann N, Shulman KI (2006) Comorbidity in bipolar disorder among the elderly: results from an epidemiological community sample. Am J Psychiatry 163:319–321
Grenier S, Préville M, Boyer R, O'Connork, Scientific Committee of the ESA Study (2009) Prevalence and correlates of obsessive-compulsive disorder among older adults living in the community. J Anxiety Disord 23:858–865
Guk HS, Kim JK, Cho MJ (2003) Community study of dementia in the older Korean rural population. Aust N Z J Psychiatry 37:606–612
Gureje O, Ogunniyi A, Baiyewu O, Price B, Unverzagt FW, Evans RM, Smith-Gamble V, Lane KA, Gao S, Hall K, Hendrie HC, Murrell JR (2006) APOE ε4 is not associated with Alzheimer's disease in elderly Nigerians. Ann Neurol 59:182–185
Gureje O, Kola L, Afolabi E (2007) Epidemiology of major depressive disorder in elderly Nigerians in the Ibadan Study of Ageing: a community-based study. Lancet 370:957–964
Gurland BJ, Copeland JRM, Kelleher MJ, Kuriansky J, Sharpe L et al (1983) The mind and mood of ageing. The mental health problems of the community elderly in New York and London. Haworth Press, London
Hackett ML, Yapa C, Parag V, Anderson CS (2005) Frequency of depression after stroke: a systematic review of observational studies. Stroke 36:1330–1340

Haseagawa K, Homma A, Imai Y (1986) An epidemiological study of age-related dementia in the community. Int J Geriatr Psychiatry 1:45–55

Henderson AS, Korten AE, Levings C, Jorm AF, Christensen H, Jacomb PA, Rodgers B (1998) Psychotic symptoms in the elderly: a prospective study in a population sample. Int J Geriatr Psychiatry 13:484–492

Hendrie HC, Osuntokun BO, Hall KS, Oqunniyi AO, Hui SL, Unverzaqt FW, Gureje O, Rodenberg CA, Baiyewu O, Musick BS (1995) Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. Am J Psychiatry 152:1485–1492

Hendrie HC, Ogunniyi A, Hall KS (2001) Incidence of dementia and Alzheimer's disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. JAMA 285:739–747

Heyman A, Peterson B, Fillenbaum G, Pieper C (1996) The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Demographic and clinical predictors of survival in patients with Alzheimer's disease. Neurology 46:656–660

Ho SHC, Ng TP, Feng L, Johnson F, Mahendran R, Kua EH (2014) Co-existing medical comorbidity and depression: multiplicative effects on health outcomes in older adults. Int Psychogeriatr 26:1221–1229

Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, van Broeckhoven C, Grobbee DE (1997) Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. Lancet 349:151–154

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. Br J Psychiatry 140:566–572

Ikeda M, Fukuhara R, Shigenobu K, Hokoishi K, Maki N, Nebu A et al (2004) Dementia associated mental and behavioural disturbances in elderly people in the community: findings from the first Nakayama study. J Neurol Neurosurg Psychiatry 75:146–148

Jellinger KA, Attems J (2010) Prevalence of dementia in the oldest-old: an autopsy study. Acta Neuropathol 119:421–433

Jeste D, Hays J, Steffens D (2006) Clinical correlates of anxious depression among elderly patients with depression. J Affect Disord 90:37–41

Jongenelis K, Pot AM, Eisses AMH, Beckman AT, Kluiter H, Ribbe MW (2004) Prevalence and risk indication of depression in elderly nursing home patients: the AGED study. J Affect Disord 83:135–142

Jorm AF, Jolley D (1998) The incidence of dementia: a meta-analysis. Neurology 51:728–733

Jorm AF, Korten AE, Henderson AS (1987) The prevalence of dementia: a quantitative integration of the literature. Acta Psychiatr Scand 76:465–479

Judd LL, Rapaport MH, Paulus MP, Brown JL (1994) Subsyndromal symptomatic depression: a new mood disorder? J Clin Psychiatry 55(Suppl):18–28

Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D et al (2008) Alzheimer's disease and vascular dementia in developing countries: prevalence, management and risk factors. Lancet 7:812–826

Karlsson B, Klenfeldt IF, Sigström R, Waern M, Ostlings, Gustafson D, Skoog I (2009) Prevalence of social phobia in non-demented elderly from a Swedish population study. Am J Geriatr Psychiatry 17:127–135

Keith SJ, Regier DA, Rae DS (1989) Schizophrenic disorders. In: Robins LN, Regier DA (eds) Psychiatric disorders in America. The Free Press, New York

Kessler RC, Petukhova M, Sampson NA, Zaslasky AM, Wittchen HU (2012) Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res 21:169–184

King-Kallimanis B, Gu AM, Kohn R (2009) Comorbidity of depressive and anxiety disorders for older Americans in the national comorbidity survey-replication. Am J Geriatr Psychiatry 17:782–792

Kivelᾳ SL, Kongas-Savario P, Laippala P, Pahkala K, Kesti E (1996) Social and psychosocial factors predicting depression in old age: a longitudinal study. Int Psychogeriatr 8:635–644
Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J (2006) Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 5:735–741
Kua EH (1992) A community study of mental disorders in elderly Singaporean Chinese using the GMS-AGECAT package. Aust N Z J Psychiatry 26:502–506
Kua EH (1993) The depressed elderly Chinese living in the community: a five-year follow-up study. Int J Geriatr Psychiatry 8:427–430
Kua EH, Ko SM (1995) Prevalence of dementia among elderly Chinese and Malay residents of Singapore. Int Psychogeriatr 7:439–446
Kua EH, Ko SM, Fones SLC, Tan SL (1997) Epidemiology of depression in elderly Chinese living in Singapore. JAMA (Suppl) 13:29–32
Kua EH, Ho E, Tan HY, Tsoi C, Thng C, Mahendran R (2014) The natural history of dementia. Psychogeriatrics 14:196–201
Kvaal K, McDougall FA, Brayne C, Matthews FE, Dewey ME, MRC CFAS (2008) Co-occurrence of anxiety and depressive disorders in a community sample of older people: results from the MRC CFAS (Medical Research Council Cognitive Function and Ageing Study). Int J Geriatr Psychiatry 23:229–237
Lancet Global Mental Health Group (2007) Scale up services for global mental health: a call for action. Lancet 370:1241–1252
Larson EB, Langa KM (2008) The rising tide of dementia worldwide. Lancet 372:430–432
Lenze E, Rogers J, Martire L, Mulsant B, Rollman B, Dew M, Schulz R, Reynolds C (2001) The association of late-life depression and anxiety with physical disability. A review of the literature and prospectus for future research. Am J Geriatr Psychiatry 9:113–135
Li G, Shen YC, Chen CH, Zhao YW, Li SR, Lu MG (1989) An epidemiological survey of age-related dementia in an urban area of Beijing. Acta Psychiatr Scand 79:557–563
Li S, Yan F, Li G, Chen C, Zhang W, Liu J, Jia X, Shen Y (2007) Is the dementia rate increasing in Beijing? Prevalence and incidence of dementia 10 years later in an urban elderly population. Acta Psychiatr Scand 115:73–79
Li ZB, Zheng LN, Yang JJ, Zhong N, Liu L, Chiu E, Zhao M (2013) Teachers of psychiatry meeting on evaluation to improve quality of research, held in Shanghai, China, organized by the Pacific Rim College of Psychiatrists. Asia Pac Psychiatry 5:214–216
Lim LL, Ng TP (2010) Living alone, lack of a confidant and psychological well-being of elderly women in Singapore: the mediating role of loneliness. Asia Pac Psychiatry 2:33–40
Lim HXL, Chang WC, Yu X, Chiu H, Chong MY, Kua EH (2011) Depression in Chinese elderly populations. Asia Pac Psychiatry 3:46–53
Lin JC, Karno MP, Grella CE, Ray LA, Liao DH, Moore AA (2014) Psychiatric correlates of alcohol and tobacco use disorders in US adults 65 years and older: results from the 2001–2002 National Epidemiologic Survey of Alcohol and Related Conditions. Am J Geriatr Psychiatry 22:1356–1363
Lindesay J, Briggs K, Murphy E (1989) The guy's/age concern survey: prevalence rates of cognitive impairment, depression and anxiety in an urban elderly community. Br J Psychiatry 155:317–329
Lindesay J, Briggs K, Murphy E (1996) The guy's/age concern survey. Prevalence rates of cognitive impairment, depression and anxiety in an urban elderly community. Br J Psychiatry 11:65–70
Liu CK, Lai CL, Tai CT, Lin RT, Yen YY, Howng SL (1996) Incidence and subtypes of dementia in southern Taiwan: impact of socio-demographic factors. Neurology 50:1572–1579
Livingston G, Hawkins A, Graham N, Blizard B, Mann A (1990) The Gospel Oak Study: prevalence rates of dementia, depression and activity limitation among elderly residents in inner London. Psychol Med 20:137–146
Livingston G, Kitchen G, Manela M, Katona C, Copeland J (2001) Persecutory symptoms and perceptual disturbance in a community sample of older people: the Islington study. Int J Geriatr Psychiatry 16:462–478

Lobo A, Saz P, Marcos G, Dia J-L, De-La-Camara C (1995) The prevalence of dementia and depression in the elderly community in a southern European population. The Zaragoza study. Arch Gen Psychiatry 52:497–506

Lobo A, Launer LJ, Fratiglioni L (2000) Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54:S4–S9

Luchsinger JA, Mayeux R (2004) Dietary factors and Alzheimer's disease. Lancet Neurol 3:579–587

Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R (2001) Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. Am J Epidemiol 54:635–641

Ma X, Xiang Y, Li S, Xiang Y, Guo H, Hou Y, Cai Z, Li Z, Li Z, Tao Y, Dang W, Wu X, Deng J, Ungvari GS, Chiu HFK (2008) Prevalence and sociodemographic correlates of depression in an elderly population living with family members in Beijing, China. Psychol Med 38:1723–1730

Manton KC, Gu XL, Ukraintseva SV (2005) Declining prevalence of dementia in the U.S. elderly population. Adv Gerontol 16:30–37

Matsui Y, Tanizaki Y, Arima H, Yomenoto K, Doi Y, Ninomiya T, Sasaki K, Lida M, Iwaki T, Kanba S, Kiyohara Y (2009) Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study. J Neurol Neurosurg Psychiatry 80:366–370

Matthews FE, Arthur A, Barnes LE et al (2013) A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 382:1405–1412. doi:10.1056/NEJMp1311405

McDougall FA, Kvaal K, Matthews FE, Paykel E, Jones PB, Dewey ME, Brayne C (2007) Prevalence of depression in older people in England and Wales: the MRC CFA study. Psychol Med 37:1787–1795

McKhann G, Drachman DA, Folstein M, Katzman R, Price DL, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease – report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34:939–944

Meesters PD, Lieuwe DH, Comijs HC, Stek ML, Smeets-Janssen et al (2012) Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a dutch catchment area. Am J Geriatr Psychiatry 20:18–28

Meller I, Fichter MM, Schröppel H (1997) Risk factors and psychosocial consequences in depression of octo- and nonagenarians: results of an epidemiological study. Eur Arch Psychiatry Clin Neurosci 247:278–287

Mizutani T, Shimada J (1992) Neuropathological background of twenty-seven centenarian brains. J Neurol Sci 108:168–177

Mojtabai R, Olpson M (2004) Major depression in community-dwelling middle-aged and older adults: prevlance 2- and 4-years follow-up symptoms. Psychol Med 34:623–634

Molera AE, Pino-Ramirez G, Maestre GE (2007) High prevalence of dementia in a Caribbean population. Neuroepidemiology 29:107–112

Molsa PK, Martila RJ, Rinne UK (1995) Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand 91:159–164

Morris JC (1993) The Clinical Dementia Rating (CDR): current vision and scoring rules. Neurology 43:2412–2414

Murrell JR, Price B, Lane KA, Baiyewu O, Gurejo O, Oqunniyi A, Unverzaqt FW et al (2006) Association of apolipoprotein E genotype and Alzheimer disease in African Americans. Arch Neurol 63:431–434

Newman SC (1999) Prevalence of depression in vascular dementia and Alzheimer's disease in a population sample. J Affect Disord 52:169–176

Newman SC, Sheldon CT, Bland RC (1998) Prevalence of depression in an elderly community sample: a comparison of GMS-AGECAT and DSM-IV diagnostic criteria. Psychol Med 28:1339–1345

Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH (2006) Curry consumption and cognitive function in the elderly. Am J Epidemiol 164:898–906

Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Antikaninen R et al (2015) A 2-year multidomain intervention of diet, exercise, cognitive training and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): randomized controlled trial. Lancet 385:2255–2263

Nielsen JA, Nielsen J (1989) Prevalence investigation of mental illness in the aged in 1961, 1972, and 1977 in a geographically delimited Danish population group. Acta Psychiatr Scand 79:95–104

Nitrini R, Caramelli P, Jr H, Bahia VS, Caixeta LF, Radanovic M, Anghinah R et al (2004) Incidence of dementia in a community-dwelling Brazilian population. Alzheimer Dis Assoc Disord 18:241–246

Norton MC, Skoog I, Toone L, Corcoran C, Tschanz JT, Lisota RD, Hart AD, Zandi PP, Breitner JCS, Welsh-Bohmer KA, Steffens DC (2006) Three-year incidence of first-onset depressive syndrome in a population sample of older adults: the Cache County Study. Am J Geriatr Psychiatry 14:237–245

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 13:788–794

Osborn DP, Fletcher AE, Smeeth L, Stirling S, Bulpitt CJ, Breeze E, Ng ES, Nunes M, Jones D, Tulloch A (2003) Factors associated with depression in a representative sample of 14217 people aged 75 and over in the United Kingdom: results from the MRC trial of assessment and management of older people in the community. Int J Geriatr Psychiatry 18:623–630

Östling S, Skoog I (2002) Psychotic symptoms and paranoid ideation in a non-demented population-based sample of the very old. Arch Gen Psychiatry 59:53–59

Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A (1997) Atrial fibrillation and dementia in a population-based study. The Rotterdam study. Stroke 28:316–321

Ownby RL, Crocco E, Acevedo A, Vineeth J, Loewenstein D (2006) Depressed mood and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. Arch Gen Psychiatry 63:530–538

Palsson SP, Ostling S, Skoog I (2001) The incidence of first-onset depression in a population followed from the age of 70 to 85. Psychol Med 31:1159–1168

Patten SB, Wang JL, Willians JVA, Currie S, Beck CA et al (2006) Descriptive epidemiology pf major depression in Canada. Can J Psychiatry 51:84–90

Piguet O, Grayson DA, Creasey H, Bennett HP, Brooks WS, Waite LM, Broe GA (2003) Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney older persons study. Neuroepidemiology 22:165–171

Pincus HA, Davis WW, McQueen LE (1999) 'Subthreshold' mental disorders: a review and synthesis of studies on minor depression and other 'brand names'. Br J Psychiatry 174:288–296

Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29:125–132

Preisig M, Merikangsa KR, Angst J (2001) Clinical significance and comorbidity of subthreshold depression and anxiety in the community. Acta Psychiatr Scand 104:96–103

Préville M, Boyer R, Grenier S, Dubé M, Voyer P, Punti R, Baril MC, Streiner DL, Cairney J et al (2008) The epidemiology of psychiatric disorders in Quebec's older adult population. Can J Psychiatry 53:822–832

Prince M (2010) The contribution of cross-cultural research to dementia care and policy: an overview focusing on the work of the 10/66 Dementia Research Group. In: Krishnamoorthy ES, Prince M, Cummings JL (eds) Dementia – a global approach. Cambridge University Press, Cambridge

Prince MJ, Harwood RH, Blizard RA, Thomas A, Mann AH (1997a) Impairment, disability and handicap as risk factors for depression in old age. The Gospel Oak Project V. Psychol Med 27:311–321

Prince MJ, Harwood RH, Blizard RA, Thomas A, Mann AH (1997b) Social support deficits, loneliness and life events as risk factors for depression in old age. The Gospal Oak Project. Psychol Med 27:323–332

Prince M, Acosta D, Chiu H, Scazufca M, Varghese M (2003) Dementia diagnosis in developing countries: a cross-cultural validation study. Lancet 361:909–917

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: a systemic review and meta-analysis. Alzheimers Dement 9:63–75

Qiu C, Xu W, Fratiglioni L (2010) Vascular and psychosocial factors in Alzheimer's disease: epidemiological evidence toward intervention. J Alzheimers Dis 20:689–697

Quiroga P, Calvo C, Albala C, Urquidi J, Santos JL, Pérez H, Klaassen G (1999) Apolipoprotein E polymorphism in elderly Chilean people with Alzheimer's disease. Neuroepidemiology 18:48–52

Rawtaer I, Mahendran R, Yu J, Fam J, Feng L, Kua EH (2015) Psychosocial interventions with art, music, tai chi and mindfulness for subsyndromal depression and anxiety in older adults: a naturalistic study in Singapore. Asia Pac Psychiatry 7:240–250

Regier DA, Boyd JH, Burke JD, Rae DS, Myers JM, Krammer M (1988) One-month prevalence of mental disorders in the United States. Arch Gen Psychiatry 45:977–986

Regier DA, Farmer ME, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Kamo M, Locke BZ (1993) One-month prevalence of mental disorders in the United States and socio-demographhic characteristics: the Epidemiologic Catchment Area study. Acta Psychiatr Scand 88:35–47

Ritchie K, Artero S, Beluche I, Ancelin ML, Mann A, Dupuy AM, Malatosse A, Boulenger JP (2004) Prevalence of DSM-IV psychiatric disorder in the French elderly population. Br J Psychiatry 184:147–152

Roberts RE, Kaplan GA, Shema SJ, Trawbridge WJ (1997) Does growing old increase the risk for depression. Am J Psychiatry 154:1384–1390

Rodriguez JJL, Ferri CP, Ascota D, Guerra M, Huang Y, Jacob KS, Krishnamoorthy ES, Salas A, Acosta I, Dewey ME et al (2008) The prevalence of dementia in Latin America, India and China. A 10/66 Dementia Research Group population-based survey. Lancet 372:464–474

Sartorius N (1988) Cross-cultural and international collaboration in mental health research and action. Experience from the mental health programme of the World Health Organisation. Acta Psychiatr Scand 78(Suppl 344):71–74

Sartorius N (2002) Fighting for mental health. Cambridge University Press, Cambridge

Sartorius N, Chiu HFK, Kua EH, Lee MS, Ouyang WC, Sato M, Yang YK, Yu X (2014) Name change for schizophrenia. Schizophr Bull 40:255–258

Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S (2016) Incidence of dementia over three decades in the Framingham Heart study. N Engl J Med 374:523–532

Saunders AM, Schmader K, Breitner J, Benson MD, Brown WT, Goldfarb L, Goldqaber D, Manwaring MG et al (1993) Apolipoprotein E epsilon 4 allele distributions in late-onset Alzheimer's disease and in other amyloid-forming diseases. Lancet 342:710–711

Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentinos TMX, Stern Y (2009) Physical activity, diet, and risk of Alzheimer disease. JAMA 302:627–637

Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA (2009) The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis 18:691–701

Shaji S, Bose S, Verghese A (2005) Prevalence of dementia in an urban population in Kerala, India. Br J Psychiatry 186:136–140

Shulman K, Herrmann N, Brodaty H, Chiu H, Lawlor B, Ritchie K, Scanlan JM (2006) IPA survey of brief cognitive screening instruments. Int Psychogeriatr 18:281–294

Sigström R, Östling S, Karlsson B, Waern M, Gustafson D, Skoog I (2011) A population-based study on phobic fears and DSM-IV specific phobia in 70-year olds. J Anxiety Disord 25:148–153

Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L (1996) 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145

Snowdon J (1994) The epidemiology of affective disorders in old age. In: Chiu E, Ames D (eds) Functional psychiatric disorders of the elderly. Cambridge University Press, Cambridge

Snowdon J, Burgess E, Vaughan R, Miller R (1996) Use of antidepressants, and the prevalence of depression and cognitive impairment in Sydney nursing homes. Int J Geriatr Psychiatry 11:599–606

Soh KC, Kumar R, Niti M, Kua EH, Ng TP (2008) Subsyndromal depression in old age: clonical significance and impact in a multi-ethnic community sample of elderly Singaporeans. Int Psychogeriatr 1:188–200

Tschanz JT, Welsh-Bohmer KA, Lyketsos CG, Corcoran C, Green RC, Hayden K, Norton MC, Zandi PP, Toone L, West NA et al (2006) Conversion to dementia from mild cognitive disorder: the Cache Country study. Neurology 67:229–234

Van Dijk PTM, Dippel DWS, Habbena JDF (1991) Survival of patients with dementia. J Am Geriatr Soc 39:603–610

Venketasubramanian N, Sahadevan S, Kua EH, Chen CPL, Ng TP (2010) Interethnic differences in dementia epidemiology: global and Asia-pacific. Dement Geriatr Cogn Disord 30:492–498

Wang Y, Chen WJ, Li YY, Wang ZY, Chen J, Xu YF (2011) Teachers of psychiatry meeting in Shanghai: a leadership training course. Asia Pac Psychiatry 4:87–89

Weissman MM, Leaf PJ, Tischler GL, Blazer DG, Karno M, Bruce ML, Florio LP (1988) Affective disorders in five United States communities. Psychol Med 18:141–153

Whitmer RA, Gunderson EP, Barrett-Conner E, Quesenberry CP Jr, Yaffe K (2005) Obesity in middle age and future risk of dementia: a 27-year longitudinal population based study. BMJ 330:1360

Wing JK, Cooper JE, Sartorius N (1974) The measurement and classification of psychiatric symptoms. Cambridge University Press, London

World Health Organization (1980) International classification of diseases, 9th revision (ICD9). World Health Organization, Geneva

World Health Organization (1992) The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization, Geneva

Wu DX, Feng L, Yao SQ, Tian XF, Mahendran R, Kua EH (2014) The early dementia prevention programme in Singapore. Lancet Psychiatry 1:9–11

Xavier FM, Ferraza MP, Argimon I, Trentini CM, Poyares D, Bertollucei PH, Bisol LW, Moriquchi EH (2002) The DSM-IV 'Minor depression' disorder in the oldest old: prevalence rate, sleep patterns, memory function and quality of life in elderly people of Italian descent in Southern Brazil. Int J Geriatr Psychiatry 17:107–116

Xiang YT, Dickerson F, Kreyenbuhl J, Ungvari GS, Wang CY, Si TM et al (2012) Common use of antipsychotic polypharmacy in older Asian patients with schizophrenia between 2001 and 2009. J Clin Psychopharmacol 32:809–813

Zhang ZX, Zahner GE, Roman GC, Liu J, Hong Z, Qu QM, Liu XH, Zhang XJ, Zhou B, Wu CB, Tang MN, Hong X, Li H (2005) Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol 62:447–453

Part II

Diagnosis and Assessment

(Neurobiology of) Dementia: Causes, Presentation, and Management

5

David Bensamoun, Aurélie Mouton, Eric Ettore, Philippe Robert, and Renaud David

Abstract

Alzheimer's disease is the main type of dementia in aging populations and is characterized by a progressive impairment in cognitive abilities associated with behavioral and psychological changes and a progressive loss of autonomy. Other dementia syndromes in aging can, however, be observed but their frequency is lower. The present chapter will describe the clinical course and aetiologies of the main dementia syndromes in elderly populations as well as the main therapeutic options for the management of dementia.

Keywords

Dementia • Alzheimer's disease • Vascular dementia

Contents

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_7

Introduction: Dementia, an Overview

More than 40 million individuals are currently living with dementia worldwide. Alzheimer's disease (AD) is the more frequent type of dementia, accounting for up to 65% of all causes of dementia, depending on studies (Brunnstrom et al. 2009), with a average prevalence around 45% (Goodman et al. 2016). Beside AD, other types of dementia syndromes can be observed and will be described in the chapter.

Most recent studies indicated a plateau in the increased prevalence of dementia, most particularly in high-income countries that could be partly explained by a better control of associated cardiovascular risks (diabetes, obesity, dyslipidemia). In low- and middle-income countries, however, the total number of individuals with dementia will continue to increase.

Time course and lead symptoms usually provide reliable information on the putative underlying dementia subtypes (predominance of memory, behavioral, speech, and vision impairments), but the recent development of in-vivo biomarkers (CSF markers, neuroimaging) tend to increase the accuracy of clinical diagnoses and highlighted the importance of atypical clinical presentations.

Overview of the Main Dementia

Epidemiology and Risk Factors of Dementia

Epidemiology

The prevalence of dementia increases with age but may differ according to the subtypes of dementia.

Alzheimer's Disease

The prevalence of AD after 65 years is currently estimated at around 7% worldwide, but AD remains largely under diagnosed. Prevalence of AD also increases with age. AD accounts for around 45% of all causes of dementia (Goodman et al. 2016). Incidence of dementia is, however, different across countries with a lower incidence in occidental countries partly due to a better control of cardiovascular risk factors. On the other hand, an increased incidence is being observed in newly industrial countries, such as China, where these factors only started to be taken into account in the health policies. Early-onset AD individuals are getting more and more recognized and are often related to genetic mutations.

Other Dementias

The second cause of dementia, after AD, is vascular dementia (~30% of dementia) (Kalaria et al. 2008), followed by dementia with Lewy bodies (DLB) (up to 10% of all dementia cases). DLB represents the second cause of neurodegenerative dementia in older people (McKeith 2004) and affects 0.7% of subjects aged more than 65.

Frontotemporal dementia (FTD) is the second most frequent form of presenile dementia following Alzheimer's disease with a prevalence of 15–22 per 100,000 in the age group between 45 and 65 years (Kurz et al. 2014).

Other types of dementia syndromes are less prevalent. Progressive supranuclear palsy (PSP) and corticobasal syndrome are more rare disease. The age-adjusted prevalence for PSP is 6.4 per 100,000 (Schrag et al. 1999).

Risk Factors

Several risk factors have been identified in AD and related disorders and are presented below.

Alterable Risk Factors

	1. Cardiovascular risk factor	
High blood pressure	Relationship between high blood pressure (HBP) and neuropathological lesions of AD, cerebral atrophy, senile plaques, and neurofibrillary tangles.	(Petrovitch et al. 2000)
	Association between HBP during "middle life" and cognitive decline and dementia, but HBP during "late life" not associated with cognitive decline. Systolic blood pressure > 160 mmHg associated with more senile plaques in neocortex and hippocampal cortex. Diastolic blood pressure > 95 mmHg associated with more important neurofibrillary tangles in hippocampal cortex.	(Tzourio et al. 1999; Qiu et al. 2005)
Diabetes	Association between diabetes and risk of developing AD and vascular dementia. Different mechanisms could be involved: direct effect of diabetic vasculopathy and indirect effect promoting neuropathological lesions.	(Biessels et al. 2006)
	Products of carbohydrates degradation could be involved in the pathogenesis of AD. The role of insulin degradation enzyme in metabolism control of the B amyloid protein in the brain is possible with also an interaction with APOE4.	(Bian et al. 2004)
	Associations between diabetes and hippocampal cortex atrophy; insulin resistance was correlated with amygdala cortex atrophy.	(den Heijer et al. 2003)
Dyslipidemia	High cholesterolemia level during "middle life" has been associated with an increased risk of AD.	(Sambamurti et al. 2004)
Tobacco	Only one large prospective study demonstrated that cumulated smoking exposure accelerated cognitive decline among nondemented individuals with a dose response relationship.	(Ott et al. 2004)
Obesity	The relation between weight and AD has been demonstrated.	(Stewart et al. 2005; Whitmer et al. 2005)

(*continued*)

	First, loss of weight could represent a precocious sign of dementia and can occur long time before diagnosis.	
	2. Nutritional factor	
Antioxidants	Several studies have shown a relation between antioxidants and decreased risk of dementia. Despite discordant results, a possible beneficial effect of vitamin E, vitamin C, carotenoid, and selenium has been discussed	(Engelhart et al. 2002)
Poly unsaturated fatty acid (PUFA)	Higher risk of cognitive decline among individuals with high level of PUFA omega-6 and conversely decrease risk for individuals with high level of FPUA omega-3.	(Heude et al. 2003)
Vitamin B and Folate	Animal studies suggest that folate deficit may be at the origin of the amyloid genesis. Folate consumption and other group B vitamins is a determinant of homocysteine plasma level. Supplementation in vitamin B6, folate, and B12 required in case of documented deficiency. Supplementation in vitamin B6, B12, and folate in case of documented deficiency is still the rule. The research of a vitamin deficiency is necessary in an alimentary deficiency context. Indeed, there exist an inverse relationship between homocysteine rate and food intake or plasma rate of B6, B12, and folate intake.	(Luchsinger et al. 2007; Ravaglia et al. 2005)
	3. Physic activity	
	Association between regular and sustained physical activity and cognitive decline or dementia among individuals aged 65+	(Weuve et al. 2004; Abbott et al. 2004)
	4. Education	
	Low educational level, evaluated by formal years of education, is associated with increased risk of developing AD	(Letenneur et al. 1999)
	5. Cognitive activity and social network	
	Hobbies like reading, playing, dancing, gardening, travelling have been associated with a decreased risk of AD and other dementia.	(Wang et al. 2006)
	Level of social engagement during “middle life” (unlike during “late life” for individuals with low social engagement) was not associated with an increased risk of dementia. In late life, however, individuals with low social engagement had increased risk of developing dementia.	(Saczynski et al. 2006)
	Several studies have showed the protective role of social network on cognitive decline	(Fratiglioni et al. 2004; Bennett et al. 2006)

Iatrogenic Factors

Anticholinergic Effect	The general view is that anticholinergic-induced cognitive impairment is reversible after discontinuation of medications with anticholinergic effect. However, several investigators have reported that anticholinergics may be associated with an increased risk for sustained cognitive deficits, such as mild cognitive impairment or dementia.	
	One biologically plausible mechanism for these findings is that cumulative use of these agents results in pathologic changes in the brain similar to those observed with AD.	
	A prospective population-based cohort among individuals aged 65 + without dementia at study entry has shown, after a 10-year follow-up, that higher cumulative anticholinergic use is associated with an increased risk for dementia. Indeed, for a cumulative daily dose of anticholinergic drugs during 3 years or more, patients had a 50% increased risk of dementia. The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistaminic agents, and bladder anti muscarinic agents. Physicians have to be careful with anticholinergic drugs as shown in a recent large cohort study in Ontario, Canada, of 79,067 community dwelling and long-term care residing older adults. Community dwelling participants consulted an average of eight different physicians in the year after a newly prescribed cholinesterase inhibitor drug. The odd of high anticholinergic drug burden (measured with anticholinergic risk scale > = 2) in this prior year was 24% higher for every five additional physicians providing care (OR = 1,24 (1,21–1,26) IC 95%.	(Gray et al. 2015; Reppas-Rindlisbacher et al. 2016)
Benzodiazepines	Regarding benzodiazepines, the link with cognitive decline is yet debated; a short-term prescription is still the recommended.	

Genetic Factors

Other Factors

	Several pathologies and environmental factors have been discussed as risk factors of dementia, but scientific evidences are currently too contradictory and/or insufficient to conclude.	
	1. Medical factors	
Cardiac diseases	Atrial fibrillation, Heart failure, Coronary heart diseases, with the hypothesis of a chronic brain hypoperfusion	
Chronic obstructive pulmonary disease and sleep apnea syndrome	Associated with cognitive decline and affect short term and verbal memory and attention	(Incalzi et al. 1997)
Traumatic brain injury	Associated with significant impact to develop AD in several cohort studies and one meta analysis. Neuropathological lesions similar to AD have been described in ex-boxers after repeated brain traumatic lesions.	(Fleminger et al. 2003; Plassman et al. 2000)
	2. Environmental factors	
Hydric aluminum	Increased risk of dementia or AD (RR1.5–2.5) for a hydric aluminum concentration higher than 100 or 110 mg/l.	(Rondeau et al. 2000; Rondeau 2002)
Pesticides exposure	Pesticides exposure has shown a moderate effect on cognitive performance	(Baldi et al. 2003)
Occupational risk	Exposure to magnetic fields and work in the following domains: electricity, phone, transport, or solvents were studied. Many study results are, however, negative.	

The Main Dementia Syndromes

Clinical Course of Dementia

Over the years, diagnostic criteria for dementia have evolved and currently include biomarker evidences (whenever they are available as part of daily routine assessments) in addition to usual clinical symptoms, at least for AD, the most frequent type of dementia. In addition, intermediate clinical stages likely at risk of developing dementia, described as *Mild Cognitive Impairment* (Petersen et al. 1999) or, more recently, *Mild Neurocognitive Disorder* (DSM-5), have to be considered. These stages are characterized by a marked cognitive decline without significant consequences on daily personal autonomy. Several features forming the cognitive deficit of dementia are usually described and may vary in their chronology and severity according to the type of dementia and can be summarized as follows:

- Decline in memory abilities. Memory in recent events is usually impaired with spared memory for older events (at least in the beginning of the disease).
- Decline in attentional and executive functions. Executive functions refer to the classical frontal syndrome, involving several cognitive abilities such as initiation, planning, working memory, organization of information, selective and sustained attention, spatial orientation.
- Decline in language abilities such as word finding difficulty.
- Decline in visuospatial abilities.

Cognitive disturbances in dementia can be assessed using dedicated neuropsychological tools such as interviews and questionnaires (Jansen et al. 2016). The use of new type of cognitive assessment methods involving Information and Communication Technologies (ICT) is also currently growing (Robert et al. 2013). In addition to cognitive impairment, behavioral and psychological symptoms in dementia (BPSD), also called neuropsychiatric symptoms, are frequently observed in dementia. They often may precede the onset of the cognitive decline and may occur all along the evolution of the disease. They usually have a negative impact on the disease process and must be sought absolutely during the successive evaluations of the dementia course.

More recent diagnostic criteria for AD have proposed to add biomarkers evidences such as specific genetic mutations or specific functional neuroimaging patterns (Dubois et al. 2010, 2014; Albert et al. 2011; McKhann et al. 2011; Morris et al. 2014). These recent criteria often require having access to specific technical platforms such as brain imaging platforms and/or biological platforms, and therefore, the more recent diagnostic criteria for dementia syndromes cannot be applied in daily routine in all types of medical settings.

Alzheimer's Disease

Cognition

Typical AD is characterized by impairment of recent memory, such as inability to remember important recent events (days or weeks ago), whereas older memories such as childhood events are usually spared. Initial memory disturbances in AD are recognized as deficits in the storage of new information, the episodic memory deficit, associated with specific patterns of responses on words-recall memory tests (deficits in free recall without cueing effect and presence of intrusion errors) (Sarazin et al. 2007). Language is also frequently affected in AD with difficulties in finding correct words during spontaneous speech. Object naming and verbal fluency might be also impaired in moderate stages of AD. Impairments in executive functioning are also described but usually not during the early stages of the disease. During the evolution of AD, the aphasia (impairment of language)-apraxia (difficulties in motor planning to perform movements)-agnosia (difficulties in recognizing and process sensory information) syndrome is usually reported.

Behaviors

Up to 70–90% of individuals living with dementia will experience BPSD, at least once, during the evolution of AD (Lyketsos et al. 2000). Twelve subtypes of BPSD are commonly described using the Neuropsychiatric Inventory (NPI) (Cummings 1997). Among them, apathy is the most frequent symptom, followed by anxiety and depression. Apathy is usually observed from the earliest to the most severe stages of the disease whereas several BPSD are more frequent at the beginning (depression, anxiety) or later in the disease process (delirium, hallucinations, agitation). BPSD contribute to the severity of the dementia syndrome and increase the caregivers' burden.

Several factors can lead to BPSD. Some of them are directly in link with the neurodegenerative process (disruption in neurocircuitry), others are related to the subject's personality or are alterable factors such as acute medical problems, unmet needs (pain, anxiety, fear), environmental factors (over- or understimulation, lack of established routines, lack of activities), caregiver factors (lack of education on dementia, excessive burden, communication issues) (Kales et al. 2015). Alterable factors require specific attention in order to reduce BPSD severity. The main BPSD are delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavior with sleep disturbances, appetite/eating disorder.

Functioning

The inability to maintain the autonomy for the main activities of daily living (make a phone call, prepare the pillbox, cooking, and shopping) is progressive in the course of AD. The loss of autonomy is usually a required criterion for the definition of dementia.

Other Types of Dementia

Vascular Dementia

In 1993, the NINDS-AIREN criteria for the diagnosis of vascular dementia were established and highlighted the heterogeneity of vascular dementia syndromes and aetiologies including ischemic and hemorrhagic strokes, cerebral hypoxic-ischemic events, and senile leukoencephalopathic lesions. The clinical course may be static, remitting, or progressive. Subjects may present specific clinical signs (e.g., gait disorder, incontinence, or mood and personality changes) that support a vascular rather than a degenerative cause. A temporal relationship between stroke and dementia onset increases the probability of the diagnosis. Vascular lesions can be observed on brain imaging. Subjects usually present impairments in multiple cognitive domains. Neuropathological analyses can confirm the diagnosis (Roman et al. 1993).

The term Vascular Cognitive Impairment has been recently proposed (APA 2013) and take into account the different degrees of severity of neurocognitive impairment (minor or major).

The most important cerebrovascular pathology that contributes to cognitive impairment is cerebral infarct. Cerebral infarcts are discrete regions of tissue loss. In clinical-pathological studies, larger volumes and an increased number of macroscopic infarcts are associated with an increased likelihood of dementia. However, there are no currently accepted neuropathological criteria to confirm a clinical diagnosis of VCI (Gorelick et al. 2011). The location of the infarct too plays a role in cognitive impairment (Jellinger 2008). Other common vascular brain lesions can be observed in elderly populations, including white matter degeneration and primary vessel disease (i.e., arteriolosclerosis/lipohyalinosis, atherosclerosis, and cerebral amyloid angiopathy that is characterized by amyloid deposit in arterial walls) and hemorrhages. Hippocampal atrophy, usually attributed to a neurodegenerative aetiology, may also be caused by vascular disease (Gorelick et al. 2011).

As there are no neuropathological criteria, vascular cognitive impairment is a clinico-radiological diagnosis. MRI permits to assess vascular lesions as strokes, leukoencephalopathy, and atrophy. Vascular lesions are frequent and are often associated with neurodegenerative diseases.

Dementia with Lewy Bodies

DLB is a dementia characterized by fluctuating cognitive deficit, visual hallucinations, and Parkinsonism. The cognitive profile is mainly an executive and attention deficit associated with visuospatial troubles. Memory is preserved at the beginning of the disease. Fluctuations can be observed over minutes, hours, or days due to variations in attention. The second clinical feature is the presence of visual hallucinations. These are usually vivid colorful and animate images. Patients may present also with delusion, apathy, and anxiety.

Parkinsonism is present in 25–50% of patients with DLB at the time of the diagnosis, with greater postural instability and facial impassivity and less tremor. Rapid-eye-movement (REM) sleep behavior disorder and autonomic failure with dizziness, syncope, falls, or urinary incontinence can occur. The sensitivity to antipsychotic medications is another characteristic of the disease (Walker et al. 2015). The evolution is progressive and it is not clear yet if survival is worse in DLB or not different, compared to Alzheimer disease (McKeith 2004).

During the third consortium of DLB, a new scheme has been proposed for the pathologic assessment of Lewy bodies (LB) and Lewy neurites (LN) using alpha-synuclein immunohistochemistry and semiquantitative grading of lesion density. The pattern of regional involvement is more important than the total LB count (brainstem, limbic, or neocortical region predominant). These new criteria take into account both Lewy-related and Alzheimer disease (AD)-type pathology to allocate a probability that these are associated with the clinical DLB syndrome (McKeith et al. 2005).

Dementia Related to Parkinson's Disease (PDD)

Clinical features in DLB and PDD are similar. Dementia in Parkinson disease is characterized by the occurrence of cognitive or behavioral troubles with a loss of

autonomy in subjects with a diagnosis of Parkinson disease. Visual hallucination may occur too.

The prevalence of dementia in PD is close to 30% and at least 75% of individuals with PD who survive for more than 10 years will develop dementia (Aarsland and Kurz 2010).

To separate DLB from PDD, an arbitrary limit of 1 year is currently used: if dementia occurs before or in the first year after Parkinsonism, it will be classified as DLB.

Neuropathological lesions are similar in Parkinson disease dementia and in DLB: Lewy lesions are found in the brainstem and are also abundant in the isocortex (Duyckaerts and Hauw 2003).

Frontotemporal Dementia

Frontotemporal Dementia (FTD) results from degeneration of the frontal and temporal lobes and usually begins before the age of 65. Three clinical features are usually described according to the localization of the brain lesions. The behavioral variant is characterized by disinhibition, social inappropriateness, apathy, loss of empathy, jocularity, blunting of affects, repetitive behaviors, and hyperorality. Echolalia, reduced verbal output, and mutism may occur at later stages. Cognitive troubles are mainly executive dysfunction with impairment of activities of daily living. Cerebral imaging may reveal ventromedial frontal and anterior temporal atrophy (Rascovsky et al. 2011).

Another syndrome is the nonfluent variant of Primary Progressive Aphasia. Subjects have difficulties finding words, an effortful and halting speech, paraphasias, grammatical errors, and limited comprehension of complex sentences. Activities of daily living are compromised by impaired verbal communication. Aphasia may be accompanied by defective motor planning and programming of speech (apraxia of speech). This syndrome is linked to atrophy in left inferior frontal and anterior superior temporal regions (Grossman 2012).

The semantic variant of primary progressive aphasia (svPPA) or semantic dementia is characterized by a fluent but circumlocutory speech, impaired word finding, naming and single-word comprehension, as well as loss of word and object meaning leading to an impairment of daily living abilities. Imaging shows asymmetric (left > right) atrophy of the anterior and inferior temporal lobe (Gorno-Tempini et al. 2011).

These three syndromes may be associated with movement abnormalities and with features of Progressive Supranuclear Palsy, corticobasal degeneration, and amyotrophic lateral sclerosis.

Four histolopathologic types can be observed. They usually show neuronal loss and astrocytic gliosis as common features but differ with regard to the abnormal processing and deposition of specific proteins. Nowadays three major proteins have been identified: microtubule-associated protein Tau, transactive response DNA-binding protein (TDP), and tumor-associated protein fused in sarcoma (FUS), one protein remains unknown. A family history of FTD is found in 30–50% of cases, with one third showing an autosomal dominant mode of transmission. Five genes have been identified: microtubule-associated protein Tau (MAPT), chromosome 9

open reading frame72 (C9orf72), progranulin (GRN), charged multivesicular body protein 2B (CHMP2B), and valosin containing protein (VCP) (Kurz et al. 2014).

Primary Progressive Aphasia (PPA)

PPAs are paradigmatic disorders of language network breakdown associated with focal degeneration of the left cerebral hemisphere. They are defined by language troubles that remain isolated for at least 2 years, followed by other cognitive functions that may be impaired such as memory and executive functions.

Three PPA syndromes are described: semantic dementia (SD) and progressive nonfluent aphasia (PNFA) that we described in previous paragraph, and logopenic/phonological aphasia (LPA) (Mesulam 2001).

LPA is characterized as a primary phonological loop deficit resulting in impaired verbal short-term (phonological) memory, impaired sentence repetition, and comprehension with sparse spontaneous speech and frequent prolonged word-finding pauses. Anatomically, brain atrophy may be observed in the left posterior temporal cortex and inferior parietal lobule (Gorno-Tempini et al. 2008).

Recent studies suggest that AD may be the most common pathology underlying the LPA clinical syndrome (Magnin et al. 2015). This variant of PPA represents a specific form of AD.

Progressive Supranuclear Palsy

Individuals with the classic PSP-Richardson syndrome (PSP-RS) represent more than 50% of the cases and usually develop their first symptoms in their mid-60s. The characteristic features are postural instability with unprovoked falls, mostly backwards, axial Parkinsonism, and supranuclear gaze palsy with restriction of the range of vertical gaze.

Executive and inhibition deficits are the most prominent cognitive features (Litvan et al. 1996).

Other less prevalent clinical phenotypes have been described:

- PSP-parkinsonism (PSP-p) represents a third of PSP cases and is characterized by asymmetric limb bradykinesia and rigidity without supranuclear vertical gaze palsy in the early stage (Williams et al. 2005).
- PSP-pure akinesia with gait freezing is characterized by gait ignition failure and start hesitation that remain the isolated clinical features for several years (Williams et al. 2007).
- PSP-corticobasal syndrome (PSP-CBS) with progressive functional difficulties with the use of one limb caused by a combination of limb apraxia, parietal sensory impairment, dystonia, myoclonus, levodopa-unresponsive rigidity and bradykinesia, and occasionally alien limb phenomenon (Ling et al. 2010).
- PSP-behavioral variant of frontotemporal dementia (PSP-bvFTD) with behavioral symptoms of FTD and then emergence of typical feature of PSP.
- PSP-progressive nonfluent aphasia (PSP-PNFA) with a language disorder as predominant or even isolated symptom.

Atrophy of the midbrain and superior cerebellar peduncle as well as dilatation of the third ventricle are the characteristic findings of PSP on conventional MRI.

PSP is a tauopathy characterized by extensive subcortical neurofibrillary degeneration (Ling 2016).

Corticobasal Syndrome

The core clinical features of the corticobasal syndrome (CBS) include progressive asymmetric rigidity and apraxia, with additional cortical symptoms (alien limb phenomena, cortical sensory loss, myoclonus, and mirror movements) and basal ganglionic (e.g., bradykinesia, dystonia, and tremor) dysfunctions. In addition to apraxia, cognitive impairment consists of speech and language disorder with nonfluent aphasia, executive and visuoconstructive dysfunction (Boeve 2011).

Only half of clinical CBS have the characteristic findings at autopsy: tauopathy with asymmetric cortical atrophy in the frontoparietal regions, as well as basal ganglia and nigral degeneration named "corticobasal degeneration." The other histopathologic disorders that may be found are Alzheimer's disease (20–30%), PSP (10–20%), FTD, and DLB (Boeve 2011).

Pathophysiology of Alzheimer's Disease

Physiopathological mechanisms precede for years the clinical functional impairment in AD. Two neuropathological lesions have been described: extracellular amyloid plaques (composed of Aβ protein deposition) and intracellular neurofibrillary tangles (fragments of *tau* protein). Amyloid plaques are issued from beta amyloid peptide accumulation (Aβ) in brain tissues. Neurofibrillary tangles are associated with cytoskelletal changes due to hyperphosphorylation of tau protein inside the neuronal cell (Jack et al. 2013; Selkoe and Hardy 2016). These lesions are associated with a specific atrophy pattern and alterations of the cortico-subcortical circuitry (De-Paula et al. 2012). The evolution of the disease is associated with overall and progressive brain atrophy, initially involving the temporal region (hippocampus).

Management

The management of AD and related disorders has to consider both cognitive disturbances, behavioral changes, and functional abilities.

Dementia-dedicated pharmacological treatments have initially focused on the improvement of cognitive and mnesic abilities. Clinical studies have secondarily investigated the benefit of anti-AD agents on BPSD. Additionally, the effect of classical psychotropic drugs on BPSD is regularly investigated with clinical trials.

Nonpharmacologic approaches are also available for the improvement of cognitive, behavioral, and functional abilities but have been often criticized due to methodological issues in validation studies. Current recommendations for the management of BPSD in AD encourage using nonpharmacologic approaches first, considering that patients with dementia have to receive also anti-dementia agents. Psychotropic drugs are second-line treatments.

Nonpharmacological Approaches

Nonpharmacologic approaches (NPA) are now considered to be first-line treatments for BPSD and are intended to have both preventive and symptomatic actions (de Oliveira et al. 2015). There are many types of NPA, and they could provide benefits for cognitive abilities, dependence, and patient's well being, in addition to BPSD improvements. Despite the heterogeneity of available NPA, it is now recognized that these methods require a patient-tailored approach in order to engage subjects in the management, prevention, and stimulation process. It also includes eliminating physical and emotional stressors and establishing daily routines as well as trying to avoid any changes in the patient's environment (Reese et al. 2016). Family and professional caregivers education is also required explaining that behavioral disturbances associated to dementia are common but unintentional (Reese et al. 2016). Caregivers need to know how to adapt their attitudes and strategies to patients' behaviors: for example, caregivers' communication needs to use calm and reassuring tone, allow patient enough time when responding to a question, avoid any environmental noise or distraction, and simplify any tasks and propose activities adapted to patients' preserved capabilities (Gitlin et al. 2012).

The main available NPA are summarized below (Waldemar and Burns 2016):

- Cognitive stimulation (targeted aspects: cognition, autonomy).
- Sensory stimulation: music therapy, aromatherapy, light therapy, multisensory stimulation (targeted aspects: BPSD (agitation, depression, anxiety, sleep), well-being, quality of life).

Results regarding aromatherapy are conflicting but higher levels of evidence (using Melissa or lavender oils) tend to show benefits especially when the oil is applied close to the olfactory system (Press-Sandler et al. 2016).

- Psychosocial stimulation: psychotherapy, art therapy, animal-assisted therapy, gerontotechnology, reminiscence therapy (targeted aspects: BPSD (agitation, depression, apathy), quality of life)
- Environmental intervention: therapeutic garden, light therapy, orientation therapy (targeted aspects: autonomy, quality of life, BPSD (wandering, anxiety))
- Motor stimulation: walk, motor training, gymnastics (targeted aspects: BPSD (depression, sleep, agitation, wandering), balance, cognition, autonomy)
- Caregiver training: coaching, support group, theoretical training, Information and Communication technologies (targeted aspects: BPSD (apathy, agitation), well-being, quality of life, autonomy, caregiver burden)

More recently, Information and Communication technologies (ICT) also called gerontechnologies have started to provide stimulation opportunities for both cognitive and behavioral aspects of dementia. ICT for nonpharmacologic approaches encompass different types of solutions such as serious games, virtual reality (VR) environments, exergames, and multisensory environments. The literature on ICT remains scarce so far but recent studies have shown that stimulation-oriented ICT

could improve affective states such as apathy using a serious game on tablet (Manera et al. 2015) or increase positive emotions and levels of interest using exergames (Ben-Sadoun et al. 2016). More generally, the use of commercial video games tends to increase patients' motivation and levels of involvement compared to conventional rehabilitation approaches (Bonnechere et al. 2016). The gamification process of any cognitive training is likely able to increase participants' motivation and engagement (Lumsden et al. 2016; Gros et al. 2016). The use of VR approaches has already shown benefits to reduce anxiety and depression levels in elderly individuals (Gros et al. 2016).

Pharmacological Approaches

Readers please refer to ▶ Chap. 19, "Pharmacotherapy of Dementia" in this volume.

Management of Non-AD Dementias

Anti-dementia agents have been initially developed for the management of the cognitive disturbances associated to AD. Many studies have also demonstrated the interest of these agents for the treatment of the cognitive decline in other dementia subtypes (mixed dementia, DLB).

Vascular Dementia

Prevention of chronic vascular diseases may help reduce the population burden of vascular dementia.

Donepezil can be useful for cognitive enhancement in individuals with vascular dementia but the effect on functional and global abilities is less consistent. In subjects with mixed Alzheimer disease/vascular dementia, galantamine has shown cognitive, functional, and behavioral benefit (Gorelick et al. 2011).

Considering their possible side-effects and their mild benefit, guidelines have concluded that cholinesterase inhibitors and memantine should not be used in individuals with vascular dementia (O'Brien and Thomas 2015).

Dementia with Lewy Bodies

Donepezil and rivastigmine are recommended for the treatment of people with Lewy body dementia (Parkinson's disease dementia and dementia with Lewy bodies (DLB)), especially for neuropsychiatric symptoms, as delusion, visual hallucination, apathy, and depression. Cholinesterase inhibitors and memantine can improve cognitive abilities in DLB (O'Brien and Burns 2011; Walker et al. 2015). DLB is, most of the time, characterized by the occurrence of visual hallucinations. The use of antipsychotic medications is recommended in case of psychotic symptoms but have to be prescribed with caution in DLB considering the high risk to increase extrapyramidal symptoms with antipsychotics. Several antipsychotics, such as clozapine, with lower Parkinsonism adverse events, should be preferred. This statement is also applicable to all types of dementia with Parkinsonian symptoms. Considering also the vascular adverse events associated with antipsychotic prescribing and the increased risk of stroke, antipsychotics have to be prescribed with caution in case

of identified vascular risk factors and/or past history of vascular events. Clozapine have shown efficacy to improve visual hallucinations in Parkinson's disease but there's no study in DLB; this treatment can induce agranulocytosis so a regular blood monitoring is necessary. Quietapine is another antipsychotic used by clinicians for psychotic symptoms in DLB but its efficacy was shown only in open trials and not confirmed in the only placebo-controlled study.

The first step to improve visual hallucinations and neuropsychiatric features is to reduce the dose of dopaminergic antiparkinsonian drugs. If symptoms persist, an acetylcholinesterase inhibitor may be started, if it has not been already prescribed. Then clozapine or quietapine may be used, with caution, despite there is no strong evidence in DLB (Walker et al. 2015).

Levodopa has not been extensively studied in DLB, but it has been reported to improve Parkinsonism in uncontrolled studies. In case of clinically significant Parkinsonism, however, levodopa should be considered.

Other symptoms can occur in DLB such as rapid eye movement sleep behavior disorders (RBD), autonomic dysfunction, or depression that should be managed too.

Frontotemporal Dementia

The use of cholinesterase inhibitors or memantine is not recommended for FTD. Selective serotonin reuptake inhibitors may help reducing behavioral (but not cognitive) disturbances (Huey et al. 2006; O'Brien and Burns 2011). Antipsychotics are often used, when agitation, disinhibition, or psychotic symptoms have not been controlled by nonpharmacologic approaches, and when they may threaten the patient or carer. Antipsychotics, however, increase the risk of mortality and cerebrovascular events (Kurz et al. 2014).

Several nonpharmacological interventions can be considered. Skill-based compensation methods, environmental modifications to improve function, integration of carers in the rehabilitation process, and activity groups have shown promising results to improve life functioning and quality of life (Kortte and Rogalski 2013).

Speech therapy can be helpful especially in the language variants, and physical therapy should be prescribed when Parkinsonism and mobility problems are present (Kurz et al. 2014).

Conclusion

Despite a better diagnosis accuracy, the wide range of phenotype in dementia ensure a necessary patient based approach in order to adapt pharmacological and non- pharmacological treatment along the course of the disease. Symptomatic issues along the progressive clinical impairment should be constantly adapted considering ecological condition as well as physiological dysfunction. Toward the aetiological treatment, preserving the functional capacities and improving quality of life of patients and caregivers are still an achievable medical goal in dementia.

References

Aarsland D, Kurz MW (2010) The epidemiology of dementia associated with Parkinson disease. J Neurol Sci 289(1–2):18–22

Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H (2004) Walking and dementia in physically capable elderly men. JAMA 292(12):1447–1453

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3):270–279

APA (2013) DSM-V: Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Association, Arlington

Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P (2003) Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol 157(5):409–414

Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS (2006) The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. Lancet Neurol 5(5):406–412

Ben-Sadoun G, Sacco G, Manera V, Bourgeois J, Konig A, Foulon P, Fosty B, Bremond F, d'Arripe-Longueville F, Robert P (2016) Physical and cognitive stimulation using an exergame in subjects with normal aging, mild and moderate cognitive impairment. J Alzheimers Dis 53(4):1299–1314

Bian L, Yang JD, Guo TW, Sun Y, Duan SW, Chen WY, Pan YX, Feng GY, He L (2004) Insulin-degrading enzyme and Alzheimer disease: a genetic association study in the Han Chinese. Neurology 63(2):241–245

Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 5(1):64–74

Boeve BF (2011) The multiple phenotypes of corticobasal syndrome and corticobasal degeneration: implications for further study. J Mol Neurosci 45(3):350–353

Bonnechere B, Jansen B, Omelina L, Van Sint Jan S (2016) The use of commercial video games in rehabilitation: a systematic review. Int J Rehabil Res 39(4):277–290

Brunnstrom H, Gustafson L, Passant U, Englund E (2009) Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. Arch Gerontol Geriatr 49(1):146–149

Cummings JL (1997) The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 48(5 Suppl 6):S10–S16

de Oliveira AM, Radanovic M, de Mello PC, Buchain PC, Vizzotto AD, Celestino DL, Stella F, Piersol CV, Forlenza OV (2015) Nonpharmacological interventions to reduce behavioral and psychological symptoms of dementia: a systematic review. Biomed Res Int 2015:218980

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM (2003) Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia 46 (12):1604–1610

De-Paula VJ, Radanovic M, Diniz BS, Forlenza OV (2012) Alzheimer's disease. Subcell Biochem 65:329–352

Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, Scheltens P (2010) Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9(11):1118–1127

Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P,

Cummings JL (2014) Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 13(6):614–629

Duyckaerts C, Hauw JJ (2003) Lewy bodies, a misleading marker for Parkinson's disease? Bull Acad Natl Med 187(2):277–292. discussion 292-273

Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM (2002) Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 287(24):3223–3229

Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 74(7):857–862

Fratiglioni L, Paillard-Borg S, Winblad B (2004) An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 3(6):343–353

Gitlin LN, Kales HC, Lyketsos CG (2012) Nonpharmacologic management of behavioral symptoms in dementia. JAMA 308(19):2020–2029

Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM (2016) Prevalence of dementia subtypes in U.S. Medicare fee-for-service beneficiaries, 2011–2013. Alzheimers Dement 13(1):28–37

Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S, C. o. E. American Heart Association Stroke Council, C. o. C. N. C. o. C. R. Prevention, Intervention, S. Council on Cardiovascular 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

Gorno-Tempini ML, Brambati SM, Ginex V, Ogar J, Dronkers NF, Marcone A, Perani D, Garibotto V, Cappa SF, Miller BL (2008) The logopenic/phonological variant of primary progressive aphasia. Neurology 71(16):1227–1234

Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M (2011) Classification of primary progressive aphasia and its variants. Neurology 76(11):1006–1014

Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, Yu O, Crane PK, Larson EB (2015) Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med 175(3):401–407

Gros A, Bensamoun D, Manera V, Fabre R, Zacconi-Cauvin A, Thummler S, Benoit M, Robert P, David R (2016) Recommendations for the use of ICT in elderly populations with affective disorders. Front Aging Neurosci 8(269)

Grossman M (2012) The non-fluent/agrammatic variant of primary progressive aphasia. Lancet Neurol 11(6):545–555

Heude B, Ducimetiere P, Berr C, Study EVA (2003) Cognitive decline and fatty acid composition of erythrocyte membranes–The EVA Study. Am J Clin Nutr 77(4):803–808

Huey ED, Putnam KT, Grafman J (2006) A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 66(1):17–22

Incalzi RA, Gemma A, Marra C, Capparella O, Fuso L, Carbonin P (1997) Verbal memory impairment in COPD: its mechanisms and clinical relevance. Chest 112(6):1506–1513

Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 12(2):207–216

Jansen WJ, Handels RL, Visser PJ, Aalten P, Bouwman F, Claassen J, van Domburg P, Hoff E, Hoogmoed J, Leentjens AF, Rikkert MO, Oleksik AM, Smid M, Scheltens P, Wolfs C, Verhey F, Ramakers IH (2016) The diagnostic and prognostic value of neuropsychological assessment in memory clinic patients. J Alzheimers Dis 55(2):679–689

Jellinger KA (2008) Morphologic diagnosis of "vascular dementia" – a critical update. J Neurol Sci 270(1-2):1–12

Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA, Ogunniyi A, Perry EK, Potocnik F, Prince M, Stewart R, Wimo A, Zhang ZX, Antuono P, G. World Federation of Neurology Dementia Research (2008) Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 7(9):812–826

Kales HC, Gitlin LN, Lyketsos CG (2015) Assessment and management of behavioral and psychological symptoms of dementia. BMJ 350:h369

Kortte KB, Rogalski EJ (2013) Behavioural interventions for enhancing life participation in behavioural variant frontotemporal dementia and primary progressive aphasia. Int Rev Psychiatry 25(2):237–245

Kurz A, Kurz C, Ellis K, Lautenschlager NT (2014) What is frontotemporal dementia? Maturitas 79 (2):216–219

Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF (1999) Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. J Neurol Neurosurg Psychiatry 66(2):177–183

Ling H (2016) Clinical approach to progressive supranuclear palsy. J Mov Disord 9(1):3–13

Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, Paviour DC, Lees AJ (2010) Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain 133 (Pt 7):2045–2057

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47(1):1–9

Luchsinger JA, Tang MX, Miller J, Green R, Mayeux R (2007) Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol 64(1):86–92

Lumsden J, Edwards EA, Lawrence NS, Coyle D, Munafo MR (2016) Gamification of cognitive assessment and cognitive training: a systematic review of applications and efficacy. JMIR Serious Games 4(2):e11

Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC (2000) Mental and behavioral disturbances in dementia: findings from the cache county study on memory in aging. Am J Psychiatry 157(5):708–714

Magnin E, Teichmann M, Martinaud O, Moreaud O, Ryff I, Belliard S, Pariente J, Moulin T, Vandel P, Demonet JF (2015) Specificities of the logopenic variant of primary progressive aphasia. Rev Neurol (Paris) 171(1):16–30

Manera V, Petit PD, Derreumaux A, Orvieto I, Romagnoli M, Lyttle G, David R, Robert PH (2015) 'Kitchen and cooking,' a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study. Front Aging Neurosci 7:24

McKeith I (2004) Dementia with Lewy bodies. Dialogues Clin Neurosci 6(3):333–341

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65(12):1863–1872

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (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. Alzheimers Dement 7(3):263–269

Mesulam MM (2001) Primary progressive aphasia. Ann Neurol 49(4):425–432
Morris JC, Blennow K, Froelich L, Nordberg A, Soininen H, Waldemar G, Wahlund LO, Dubois B (2014) Harmonized diagnostic criteria for Alzheimer's disease: recommendations. J Intern Med 275(3):204–213
O'Brien JT, Burns A (2011) Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol 25(8):997–1019
O'Brien JT, Thomas A (2015) Vascular dementia. Lancet 386(10004):1698–1706
Ott A, Andersen K, Dewey ME, Letenneur L, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A, Launer LJ, E. I. R. Group (2004) Effect of smoking on global cognitive function in nondemented elderly. Neurology 62(6):920–924
Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neuro 56:303–308
Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ (2000) Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study. Neurobiol Aging 21(1):57–62
Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, Phillips C, Gau BA, Welsh-Bohmer KA, Burke JR, Guralnik JM, Breitner JC (2000) Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 55(8):1158–1166
Press-Sandler O, Freud T, Volkov I, Peleg R, Press Y (2016) Aromatherapy for the treatment of patients with behavioral and psychological symptoms of dementia: a descriptive analysis of RCTs. J Altern Complement Med 22(6):422–428
Qiu C, Winblad B, Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 4(8):487–499
Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134(Pt 9):2456–2477
Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, Porcellini E, Licastro F (2005) Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr 82(3):636–643
Reese TR, Thiel DJ, Cocker KE (2016) Behavioral disorders in dementia: appropriate nondrug interventions and antipsychotic use. Am Fam Physician 94(4):276–282
Reppas-Rindlisbacher CE, Fischer HD, Fung K, Gill SS, Seitz D, Tannenbaum C, Austin PC, Rochon PA (2016) Anticholinergic drug burden in persons with dementia taking a cholinesterase inhibitor: the effect of multiple physicians. J Am Geriatr Soc 64(3):492–500
Robert PH, Konig A, Andrieu S, Bremond F, Chemin I, Chung PC, Dartigues JF, Dubois B, Feutren G, Guillemaud R, Kenisberg PA, Nave S, Vellas B, Verhey F, Yesavage J, Mallea P (2013) Recommendations for ICT use in Alzheimer's disease assessment: Monaco CTAD expert meeting. J Nutr Health Aging 17(8):653–660
Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A et al (1993) Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43(2):250–260
Rondeau V (2002) A review of epidemiologic studies on aluminum and silica in relation to Alzheimer's disease and associated disorders. Rev Environ Health 17(2):107–121

Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF (2000) Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study. Am J Epidemiol 152(1):59–66

Saczynski JS, Pfeifer LA, Masaki K, Korf ES, Laurin D, White L, Launer LJ (2006) The effect of social engagement on incident dementia: the Honolulu-Asia aging study. Am J Epidemiol 163(5):433–440

Sambamurti K, Granholm AC, Kindy MS, Bhat NR, Greig NH, Lahiri DK, Mintzer JE (2004) Cholesterol and Alzheimer's disease: clinical and experimental models suggest interactions of different genetic, dietary and environmental risk factors. Curr Drug Targets 5(6):517–528

Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, Michel B, Puel M, Volteau M, Touchon J, Verny M, Dubois B (2007) Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. Neurology 69(19):1859–1867

Schrag A, Ben-Shlomo Y, Quinn NP (1999) Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 354(9192):1771–1775

Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8(6):595–608

Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ (2005) A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 62(1):55–60

Tzourio C, Dufouil C, Ducimetiere P, Alperovitch A (1999) Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. Neurology 53(9):1948–1952

Waldemar G, Burns A (2016) Managing behavioral and psychological symptoms in ALzheimer's disease. O. U. Press, Oxford, pp 71–84

Walker Z, Possin KL, Boeve BF, Aarsland D (2015) Lewy body dementias. Lancet 386 (10004):1683–1697

Wang L, Larson EB, Bowen JD, van Belle G (2006) Performance-based physical function and future dementia in older people. Arch Intern Med 166(10):1115–1120

Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F (2004) Physical activity, including walking, and cognitive function in older women. JAMA 292(12):1454–1461

Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K (2005) Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 330 (7504):1360

Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, Holton JL, Revesz T, Lees AJ (2005) Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 128(Pt 6):1247–1258

Williams DR, Holton JL, Strand K, Revesz T, Lees AJ (2007) Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Mov Disord 22(15):2235–2241

Biomarkers of Alzheimer's Disease

6

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder and a major driver of dementia syndromes around the globe. Despite great advances in neurodegenerative research over the past decade, AD remains a significant diagnostic and treatment challenge, and imposes momentous socioeconomic burden. Much of this overall burden is reflected in low- and middle-income countries, which is projected to increase enormously in the future. In order to meet these challenges locally, nationally and internationally, making an accurate and early clinical diagnosis of AD is crucial. A valid diagnosis at early disease stages will not only help accommodate differential prognostic and disease management approaches, but also allow for the assessment of the efficacy of novel therapeutic drugs in clinical trials. As demonstrated by autopsy-proven population-based studies, the quest for early AD diagnosis is hindered by substantial clinical heterogeneity observed in terms of disease presentation and progression. Imaging and fluid-based biomarkers congruent with AD pathophysiology can raise the certainty of clinical diagnosis, and aid in making early and more informed diagnostic decisions. In this chapter, a concise overview of the well-established and promising biomarkers for imaging and fluid-based

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_8

modalities will be explored. Imaging biomarkers of AD derived from the following modalities are discussed: structural magnetic resonance imaging, diffusion tensor imaging, positron emission tomography, single photon emission computed tomography, proton magnetic resonance spectroscopy, as well as functional magnetic resonance imaging. Classical fluid-based biomarkers of AD derived from cerebrospinal fluid and blood are surveyed. The utility of these imaging and fluid-based biomarkers for the differential diagnosis and their potential as primary or secondary endpoints in clinical trails are currently intense topics of investigation. A combination of different imaging biomarkers using the "multimodal approach," or simultaneous quantification of multiple fluid-based biomarkers to identify "biosignatures" are promising applications in AD. Future efforts are needed to standardize research protocols, refine measurement techniques, as well as to replicate controversial findings in autopsyconfirmed samples. Taking advantage of the international multi-centered collaborative efforts and technological refinements that are currently underway, the upcoming decades are sure to bring an exciting era for further advancements in an effort to conquer the "rising tide" of dementia, globally.

Keywords
Alzheimer's disease • Biomarkers • Imaging • Cerebrospinal fluid • Blood • MRI • PET • SPECT • Diffusion tensor imaging • Proton magnetic resonance spectroscopy

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Introduction

Dementia and Alzheimer's Disease (AD)

Globally, an estimated 46.8 million people were living with dementia in 2015 – a figure expected to nearly double every 20 years, approaching 131.5 million by 2050 (Alzheimer's Disease International – Dementia statistics 2016). The worldwide economic cost of dementia in 2015 was estimated at US $818 billion, which included the informal costs of care provided by relatives, as well as the formal costs of care delivered by community and healthcare professionals (Alzheimer's Disease International – Dementia statistics 2016). Much of this overall socioeconomic burden of dementia is reflected in low- and middle-income countries, which is projected to increase enormously in the future (Alzheimer's Disease International – Dementia statistics 2016). Although comorbid diseases together (vascular lesions, Alzheimer's disease [AD], and Lewy body pathology) are the commonest substrate for dementia in population-based studies (Schneider et al. 2007), AD pathology is the most common form of neurodegeneration that remains incurable and is a major driver of the dementia syndrome. In light of this enormous and rising socioeconomic burden, there is an urgent need to understand AD in order to treat or delay its progression, and to curb the "rising tide" at earlier stages.

Neuropathology of AD

AD pathology is characterized by the presence of two hallmark lesions in the brain: (1) extracellular amyloid-beta (Aβ) plaques and (2) intracellular neurofibrillary tangles (NFTs). Aβ plaques may form due to enhanced cleavage of the amyloid precursor protein (APP) into $A\beta_{40}$ and $A\beta_{42}$ peptides, via activity of the β-secretase enzyme. This pathway, by which APP is differentially cleaved, is often referred to as the amyloidogenic pathway. Soluble aggregates of two-to-12 Aβ peptides (or oligomers) may form, which can then further clump together leading to the formation of insoluble fibrils (Ballard et al. 2011). Thus, according to the amyloid cascade hypothesis, the toxicity induced by these Aβ oligomers and fibrils may lead to neurodegeneration (Ballard et al. 2011; Bird 2008). In addition, NFTs are aggregates of tau – a protein which plays an important role in microtubule stabilization and cytoskeletal maintenance. Tau undergoes abnormal hyperphosphorylation forming insoluble fibrils intraneuronally, which predominantly exist as paired helical filaments (PHF) in AD (Friedhoff et al. 2000). These intracellular aggregates and the resulting cytoskeletal dysfunction are thought to contribute to cell death and neurodegeneration. Furthermore, concomitant neuropathologies are commonly observed in AD upon autopsy, including cerebrovascular diseases (e.g., cerebral amyloid angiopathy [CAA], atherosclerosis, arteriolosclerosis, venous collagenosis, lacunes, and microinfarcts), Lewy body pathology, hippocampal sclerosis, and TDP-43 proteinopathy (Hyman et al. 2012; Braak and Braak 1991). These coexisting pathologies, sometimes incidentally discovered upon autopsy, contribute to considerable heterogeneity in disease presentation and progression (Lam et al. 2013).

Immunohistochemistry for Aβ and tau/phosphorylated tau can be applied to postmortem tissues to grade Aβ plaques and NFTs, respectively. Neuritic plaques, characterized by dystrophic neurites, may be stained using thioflavin-S or modified Bielschowsky stains, as per CERAD (Consortium to Establish a Registry for Alzheimer's Disease) guidelines (Hyman et al. 2012). Under the revised scheme for classifying AD neuropathologic change by the international consensus panel, an "ABC" ranking was recommended for evaluating three parameters: "A" amyloid to obtain Aβ plaque score, "B" Braak and Braak stage to quantify NFT pathology, and "C" CERAD to measure neuritic plaque score (Hyman et al. 2012). Neurodegenerative changes in AD have been found to align more closely to the Braak and Braak NFT stages (Braak and Braak 1991) (Table 1) rather than Aβ scores (Jack and Holtzman 2013). NFT stages were also found to correlate more strongly to cognitive function (Jack and Holtzman 2013).

Neuropathological lesions in AD cause widespread disruptions in neurotransmission, especially in the cholinergic neurotransmitter system important for memory and attentional functions (Mufson et al. 2009). Altogether the degeneration of cholinergic neurons in the basal forebrain, neurotransmitter abnormalities, and neuronal loss in vulnerable regions of the brain (e.g., the medial temporal lobe [MTL]) contribute to the clinical symptoms of AD. Significant memory loss is often the classical early symptomatology in the majority of patients, although, visuospatial, language, and other cognitive domains may also be affected early in atypical presentations of AD (Saeed et al. 2016a).

Table 1 Braak and Braak stages for NFT pathology and key regions affected in AD (Braak and Braak 1991)

NFT stages	Major brain regions affected
I and II (transentorhinal stage)	Preferential involvement of transentorhinal region, with mild entorhinal and hippocampal involvement; virtual absence of isocortical involvement
III and IV (limbic stage)	Greater involvement of transentorhinal and entorhinal regions, with mild to moderate hippocampal involvement; low isocortical involvement
V and VI (isocortical stage)	Severe involvement of entorhinal, transentorhinal and other limbic regions, with severe involvement of isocortex

NFT neurofibrillary tangle, *AD* Alzheimer's disease

Clinical Diagnosis of AD

The clinical diagnosis of AD is made by an expert clinician, in accordance with the recent National Institute on Aging and the Alzheimer's Association (NIA-AA) guidelines (McKhann et al. 2011). A concise summary of the NIA-AA criteria is provided below (Table 2). The NIA-AA criteria was updated from the previous criteria of 1984, known as the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria (McKhann et al. 1984). According to the NIA-AA criteria, all AD patients must meet the core clinical features of "all-cause" dementia, defined as an increase in cognitive impairment from a previous level of functioning, which is significant enough to interfere with activities of daily living. Using an additional set of core criteria, the diagnosis of "probable" AD is established. The certainty of "probable" AD diagnosis increases in the presence of AD-causing mutations (e.g., amyloid precursor protein [*APP*], presenilin 1 [*PSEN1*], or presenilin 2 [*PSEN2*]), or progressive cognitive decline on subsequent clinical evaluations compared to previous clinical assessments. The latter signifies the underlying pathology as an active, progressive, and evolving process. In some cases, a patient may meet the core clinical criteria with respect to the nature of cognitive impairment for AD dementia but may present with an atypical disease course or evidence of concomitant pathology. In such instances, "possible" AD dementia may be diagnosed. Finally, although not advocated for routine diagnostic purposes and more suitable for research studies, biomarker evidence consistent with AD pathophysiology may increase the certainty that the clinical syndrome is likely due to AD pathophysiology (McKhann et al. 2011).

Definition and Importance of Biomarkers in AD

A biomarker is defined as any characteristic that can be "objectively measured and evaluated as an indicator of normal biology, pathological process or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group 2001). Biomarkers of AD may be detected non-invasively using a variety of structural

Table 2 Summary of AD diagnostic criteria, as outlined by NIA-AA workgroup (McKhann et al. 2011)

Types of clinical AD dementia	Criteria
All-cause dementia	Core clinical criteria (must be met by all probable or possible AD)
1. Probable AD	Core clinical criteria for probable AD dementia
2. Probable AD, with increased level of certainty	Core clinical criteria for probable AD dementia
	1. Documented decline, OR
	2. Carrier of a causative genetic mutation
3. Possible AD	Meets partial core clinical criteria for probable AD dementia
	1. Atypical course, OR
	2. Etiologically mixed presentation
4. Probable AD, with evidence of AD pathophysiology	Biomarker evidence of AD pathophysiological process
5. Possible AD, with evidence of AD pathophysiology	Meeting clinical criteria for non-AD dementia
	Biomarker evidence of AD pathophysiological process

AD Alzheimer's disease, *NIA-AA* National Institute on Aging and the Alzheimer's Association

magnetic resonance imaging (MRI) techniques (e.g., MRI for the quantification of hippocampal volume) – or through the use of minimally invasive procedures, including intravenous administration of radiotracers (e.g., positron emission tomography [PET] to assess cerebral glucose metabolism or amyloid deposition) and lumbar puncture (e.g., amyloid and phosphorylated tau concentrations in cerebrospinal fluid [CSF]). Selective biomarkers congruent with AD pathology may raise the certainty of the clinical diagnosis (McKhann et al. 2011) and may aid in making early and more confident diagnostic decisions. Biomarker profiles can also be used for the recruitment of study participants, and increasingly only those with reliable biomarker evidence are included in clinical trials of potential disease-modifying agents (Hampel et al. 2010). Finally, biomarkers may show responsiveness to therapeutic interventions in clinical trials and assist in tracking treatment progress by offering measurable clinical outcomes (Hampel et al. 2010; Frank and Hargreaves 2003). An overview of neuroimaging and fluid-based biomarkers of AD is provided below.

Structural Magnetic Resonance Imaging (MRI)-Based Biomarkers in AD

Types of Structural MRI and Applications

In neurodegenerative diseases, many different types of MRI sequences are employed to image the brain noninvasively for the identification of structural biomarkers (Table 3). After quality-control procedures, the images can be processed to obtain cortical thickness, cortical or deep gray matter (GM), or white matter (WM)

Table 3 Different types of structural magnetic resonance images and their main use for biomarker identification in AD

Images	Image types	Main usage
T1	T1 weighted	Patterns or rates of cortical/subcortical atrophy
T2	T2 weighted	Characterization of overt white matter lesions
GRE (T2*)	Gradient-recalled echo	Covert hemorrhagic strokes (or microbleeds)
PD	Proton density weighted	Characterization of overt white matter lesions
DWI/ DTI	Diffusion-weighted/diffusion tensor imaging	White matter tract microstructural integrity
FLAIR	Fluid-attenuated inversion recovery	Characterization of overt white matter hyperintense lesions
SWI	Susceptibility-weighted imaging	Covert hemorrhagic strokes (or microbleeds), venous system, iron deposition

volumes, as well as other structural measures (e.g., displacement of water molecules as an indicator of WM tract integrity). These MRI measures may be analyzed for *a priori* regions of interest (ROI) or across the entire cerebral mantle without an *a priori* ROI specification. The latter analysis may be performed in a voxel-wise manner, using voxel-based morphometry (VBM) techniques.

The three main types of brain tissue – GM, WM, and CSF – appear different with respect to their voxel intensities on T1-weighted (T1), T2-weighted (T2), and PD-weighted (PD) images (Fig. 1). Differences in signal intensities can be exploited to quantify the total intracranial volume, as well as to segment WM, GM, and CSF globally or regionally (Kovacevic et al. 2002) (Fig. 2). In AD, a significant shrinkage in the global brain volume is observed compared to healthy controls, with a relative increase in the total volume of the CSF compartment. Conventional T1-based segmentations often underestimate this increase in CSF voxels, especially near the brain periphery (Ramirez et al. 2011). Hence, improved methods using all three (T1, T2, and PD) sequences have been developed for a more accurate tissue quantification (Kovacevic et al. 2002; Ramirez et al. 2011). Semiautomated methods that combine automated procedures with manual corrections may be more accurate and reliable, than exclusively manual or automated procedures, providing a customized approach especially given the variability in visible cerebrovascular disease which increases with age.

Cerebral microbleeds are frequent in AD due to underlying CAA. As red blood cells contain iron, microbleeds are best visualized using susceptibility-weighted imaging (SWI), or gradient-recalled echo (GRE) T2*-weighted sequences, in which the iron contained in hemosiderin deposits appear black. Specifically, in these images, microbleeds appear as round, dot-like, and hypointense lesions, not readily identifiable on conventional T1, T2, or PD scans (Tang et al. 2014). Fluid-attenuated inversion recovery (FLAIR) imaging, on the other hand, is used to highlight hyperintense (or white), dot-like, or patchy confluent periventricular lesions called cerebral white matter hyperintensities (WMHs) – an indicator of ischemic cerebrovascular disease in AD – by nullifying or "attenuating" the signal

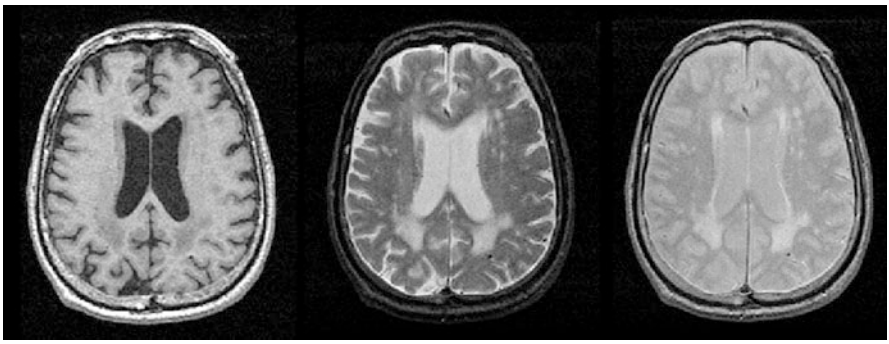

Fig. 1 Axial views of the same brain slice, as seen on T1-weighted (*left*), T2-weighted (*middle*), and proton density-weighted (*right*) images

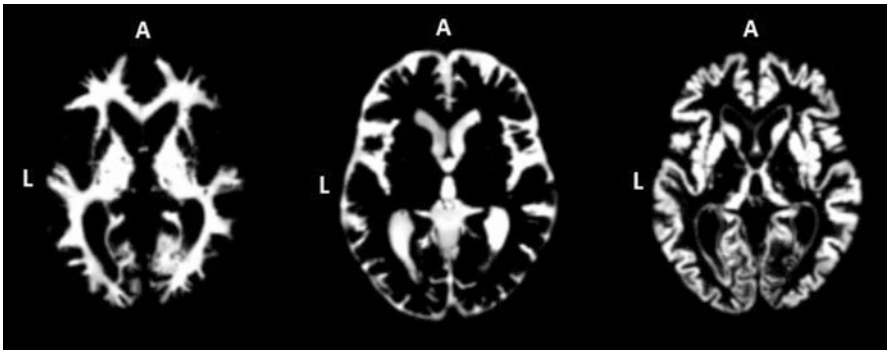

Fig. 2 Axial views of the white matter (*left*), cerebrospinal fluid (*middle*), and gray matter (*right*) automatically segmented using statistical parametric mapping (SPM) software (*A* anterior, *L* left)

due to fluids. Finally, diffusion-weighted imaging (DWI) helps visualize the diffusion of water molecules as may be seen in an acute cerebral infarct. Diffusion tensor imaging (DTI) acquires DWI in multiple directions (typically 30–60) capturing the restricted diffusion of water molecules along the myelinated WM fiber tracks, which can be visualized and quantified as a measure of WM tract integrity.

In the following sections, patterns and rates of atrophy in the brain, cerebral WMHs, and DTI measures are discussed from a biomarker viewpoint.

Cross-Sectional Profile of Cerebral Atrophy in AD

On MRI, AD is characterized by a significant loss of global brain volume along with more focal atrophy of the MTL region, compared to healthy controls and those with Lewy body dementias (includes both dementia with Lewy bodies [DLB] and Parkinson's disease dementia [PDD]) (Braak and Braak 1991; Burton

et al. 2004, 2009). The MTL region encompasses several structures, including the hippocampus, parahippocampal gyrus, entorhinal cortex, and amygdala, which play important roles in short- and long-term episodic memory functions. Using VBM, greater atrophy of the temporal lobe, including the hippocampus and parahippocampal gyrus, was identified, compared to PDD and controls (Burton et al. 2004). Likewise, Whitwell et al. observed a widespread pattern of GM atrophy involving the temporoparietal association cortex as well as MTL region, relative to controls (Whitwell et al. 2007a). When AD patients were compared to DLB, a significantly greater degeneration of the medial and inferior temporal regions was identified among those with AD (Whitwell et al. 2007a). Another study investigated cortical changes in prodromal AD participants and reported greater thinning in the bilateral parietal lobes and left parahippocampal gyrus relative to prodromal DLB and healthy controls, whereas, the entorhinal cortices, parahippocampal gyri, and parietal lobes were preferentially affected among demented AD patients (Blanc et al. 2015).

The majority of studies examining MRI-derived biomarkers were performed on clinically diagnosed participants. However, disproportionate atrophy in the MTL has been confirmed in pathologically proven AD samples as well (Braak and Braak 1991; Burton et al. 2009). In one such autopsy-confirmed study, the visually rated antemortem atrophy in the MTL (using the Scheltens scale on MRI) was identified to be a highly accurate diagnostic marker of AD, compared to patients with DLB and vascular cognitive impairment (sensitivity 91%, specificity 94%) (Burton et al. 2009). The antemortem MTL atrophy was more strongly correlated with postmortem NFT pathology than Aβ plaques, whereas associations with Lewy body pathology were nonsignificant (Burton et al. 2009).

Among AD participants, the greatest MTL atrophy was identified in the pathologically-defined 'limbic-predominant' subtype of AD (relative to 'hippocampal-sparing' or 'typical-AD' subtypes). These pathological subtypes were based on NFT distribution, suggesting that atrophy within the MTL region is strongly influenced by the underlying tau proteinopathy. Conversely, relatively greater cortical atrophy was observed in the 'hippocampal-sparing' AD subtype. The three AD subtypes (typical-AD, limbic-predominant, and hippocampal-sparing) were discriminable using the ratio of hippocampal to cortical volumes, highlighting the utility of MRI derived volumetric measures in predicting neuropathological patterns in AD postmortem (Whitwell et al. 2012).

Global and Subregional Atrophy in the Hippocampus

Compared to controls, smaller hippocampal volumes have been consistently reported in AD, both using ROI and VBM approaches (Laakso et al. 1995) (Fig. 3). Furthermore, a characteristic pattern of hippocampal volume loss was identified in relation to Lewy body spectrum disorders. The largest hippocampal volumes were found in controls, followed sequentially by progressively smaller volumes in PD (effect size vs. controls, 0.66), PDD (1.22), and AD (1.81) (Camicioli et al. 2003). Similarly, entorhinal cortex volumes were smallest in AD compared to controls, followed by DLB and PDD in a characteristic pattern:

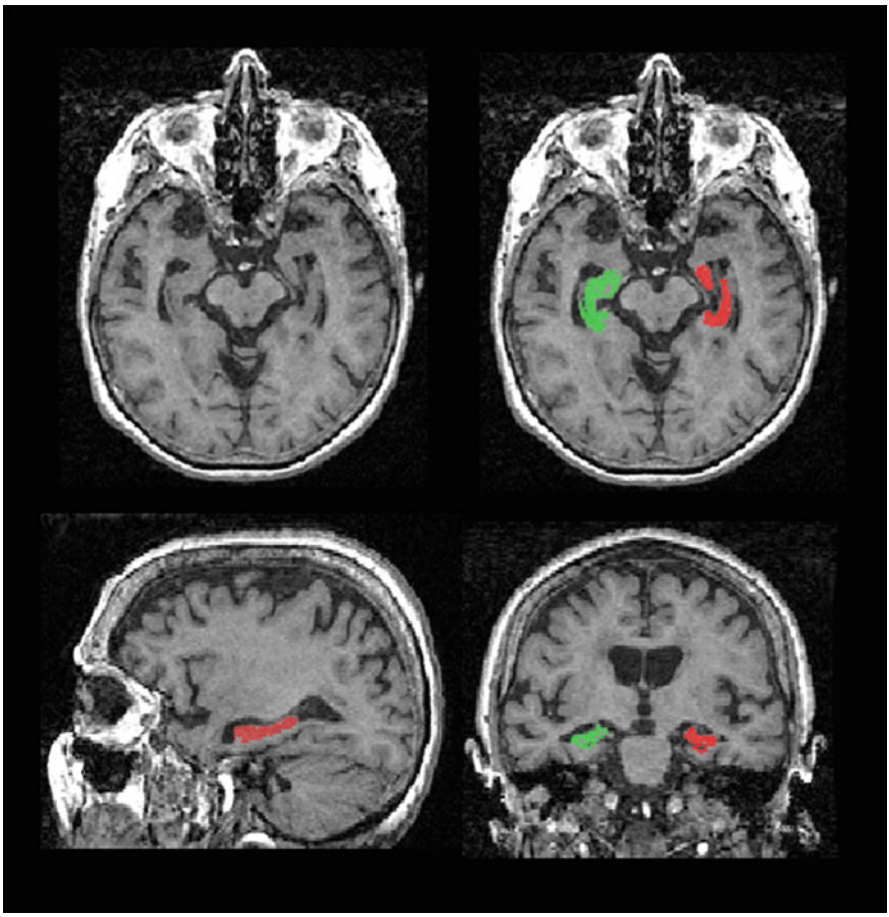

Fig. 3 A binary mask, representing the hippocampi as a specific region of interest, is displayed as an overlay on its T1-weighted image and viewed in axial (*top right*), sagittal (*bottom left*), and coronal sections (*bottom right*)

PDD (percent decrease vs. controls, 14.7), DLB (19.9%), and AD (21.9%) (Kenny et al. 2008).

Global atrophy of the hippocampus may reflect a more selective vulnerability of the hippocampal subregions or subfields. Notably, Firbank et al. reported thinner subiculum, whereas, Mak et al. observed volumetric loss in all hippocampal subfields (except the fissure) in AD versus both DLB and controls (Firbank et al. 2010; Mak et al. 2016). The cornu ammonis 1 (CA1) hippocampal subfield was found to be atrophied in AD (vs. controls) but was relatively preserved in DLB (vs. AD) (Mak et al. 2016). Using ultrahigh-field 7 Tesla MRI, Kerchner et al. further identified greater thinning in the apical neuropil layer of the CA1 subfield in AD versus controls, while no thickness differences in the CA1 cell body or other CA1 subfields were apparent (Kerchner et al. 2010). In a comparison between AD and DLB groups,

while a greater hippocampal volume loss was observed in both groups (percent vs. controls: –29.5 AD, −10.3 DLB), the DLB group was characterized by larger hippocampal volumes compared to AD, with relative preservation of CA1 (percent vs. controls: −18.6 AD, −6.3 DLB) (Mak et al. 2016; Barber et al. 2001).

Several investigations have reported an association between carrying an apolipoprotein E ε4 allele (*APOE* ε4) and smaller hippocampal volumes (Hashimoto et al. 2001; Pievani et al. 2011), suggesting a stronger influence of *APOE* ε4 on regions typically affected by AD pathology. This association in AD, however, is not universally reported with several conflicting findings (Saeed et al. 2016b; Jack et al. 1998). Likewise, greater amygdala atrophy was also observed in AD versus controls, with progressively smaller volumes associated with increasing *APOE* ε4 dose (Hashimoto et al. 2001; Basso et al. 2006). Such data explains why it is important to take *APOE* ε4 status into consideration when designing clinical trials (Saeed et al. 2016a).

Longitudinal Rates of Cerebral Atrophy in AD

The degree of neurodegenerative change over time or rate of atrophy can be a powerful way of monitoring disease progression in clinical trials. Imaging techniques, such as MRI, can be used to measure the trajectory of structural changes in the brain at two or several time points noninvasively. The rate of whole-brain atrophy in AD was measured to be higher (~1.11% per year) compared to healthy controls (~0.47% per year) (Fox et al. 2000). The feasibility and power to detect measurable differences in atrophy rates with a reasonable sample size and time frame were found to be promising (Fox et al. 2000). The rates of ventricular expansion and hippocampal atrophy were also reported to be elevated in AD versus controls (Barnes et al. 2009; Whitwell et al. 2007b). However, in an autopsy-confirmed sample, whole-brain atrophy rates were statistically not different between the AD and mixed AD/DLB dementia subgroups (Whitwell et al. 2007b), possibly indicating that AD pathology was the driver of whole-brain shrinkage and not coexisting Lewy body pathology. Finally, in a meta-analysis including nine studies, the annualized rate of hippocampal atrophy was estimated to be 4.66% in AD versus 1.41% in controls (Barnes et al. 2009). Hippocampal atrophy rates were also useful in distinguishing MCI patients from controls, whereas, whole-brain atrophy rates best discriminated MCI from AD patients (Henneman et al. 2009). Whole-brain and hippocampal rates of atrophy may serve as robust biomarkers of longitudinal changes in AD. Their utility, however, is limited by mixed pathologies. Future studies using autopsy-confirmed samples will be needed to address this limitation and to provide more precise guidance.

White Matter Hyperintensities (WMH) as Biomarkers in AD

WMHs are radiological lesions commonly observed in as many as 90–96% of elderly individuals aged 60 and above (Longstreth et al. 1996). On T2, PD, and

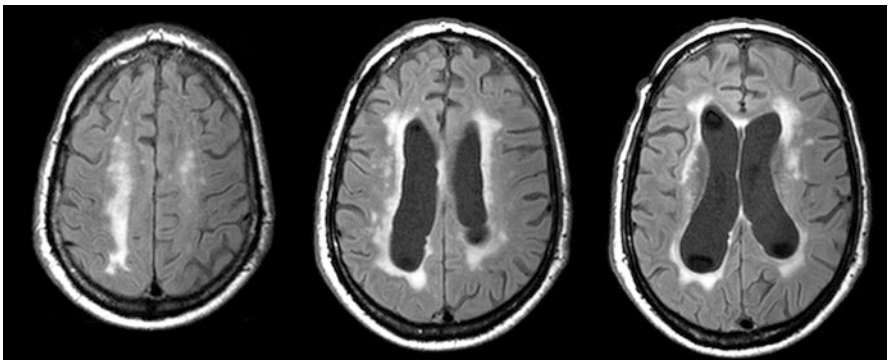

Fig. 4 Fluid-attenuated inversion recovery (FLAIR) MRI of an elderly patient showing periventricular white matter hyperintensities due to cerebral small vessel disease

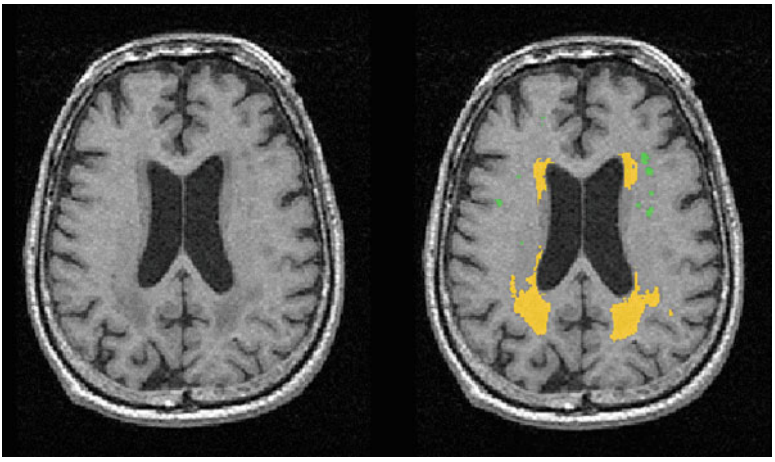

Fig. 5 T1-weighted MRI (left) with lesion mask displayed as an overlay (*right*). White matter hyperintensities appear with a slight hypointensity on T1-weighted MRI (*left image*) and as bright hyperintense regions on T2- and proton density-weighted images (as they appear in Fig. 4, *middle* and *right* images). Lesion mask with *orange* color represents periventricular white matter hyperintensities, and lesion mask with *green* color represents deep white matter hyperintensities

FLAIR images, WMHs appear as focal or confluent hyperintense regions, with slight hypointensity on T1 (Figs. 4 and 5). These WM changes may further be subcategorized as involving the periventricular or deep WM (Fig. 6), which may in turn be differentially influenced by etiological or pathophysiological factors due to their location (Kim et al. 2008). Present literature has associated WMHs with impairments in executive functioning, information processing speed, as well as gait impairments (Garde et al. 2005; Black et al. 2009; Debette and Markus 2010). In a large cardiovascular heart study of community-dwelling volunteers (aged 65 years or older), WMHs were found to be associated with age, silent strokes,

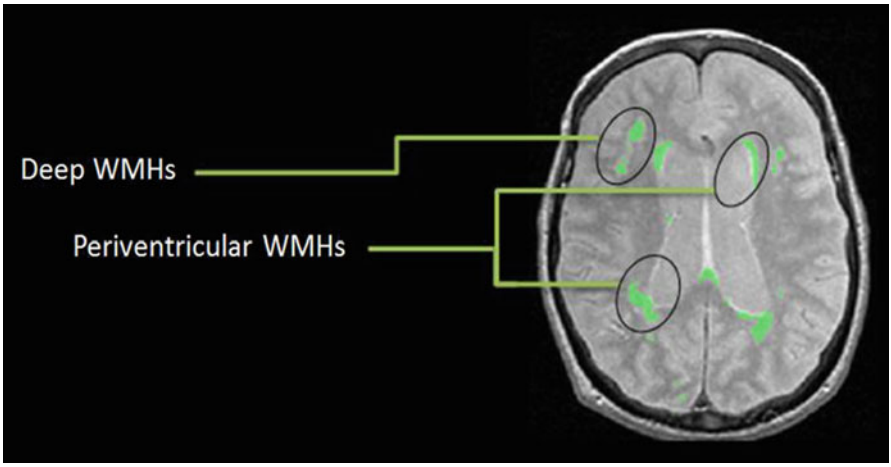

Fig. 6 An example of periventricular and deep white matter hyperintensities (WMHs) displayed with a lesion mask overlay on a PD-weighted image

hypertension, respiratory measures, and income (Longstreth et al. 1996), reinforcing their complex etiology. In a meta-analysis including 46 longitudinal studies, WMHs were confirmed to be associated with an elevated risk of stroke, dementia, and death, as well as faster decline in measures of global cognition, executive function, and processing speed (Debette and Markus 2010). Finally, in the population-based Rotterdam Study (among individuals aged 60–90), the proportion of participants with WM lesions increased with age (de Leeuw et al. 2001). Subcortical and periventricular WM lesions were more common in women than men (de Leeuw et al. 2001). This sex-specific difference is consistent with a greater incidence of Alzheimer's dementia among women, especially at older ages.

Compared to controls, a greater volume of global, periventricular, and deep WMHs were identified in AD (Ramirez et al. 2014). Periventricular WMHs correlated with processing speed, while left temporal WMHs load associated with memory performance (Ramirez et al. 2014). Notably, periventricular WMHs were elevated not only in AD but also among DLB and patients with vascular cognitive impairment (Barber et al. 1999), possibly suggesting common underlying mechanisms. Barber et al. reported periventricular WMHs to be uniquely associated with ventricular dilation, hypothesizing a stronger relationship of periventricular changes with mechanisms of subcortical atrophy. The pathological substrate of confluent periventricular WM disease may in fact be related to vasogenic edema, arising from collagenosis of the deep medullary venular system, which may cause venous insufficiency and perivenular breakdown of the blood-brain barrier (de Leeuw et al. 2001; Moody et al. 1995). Conversely, deep WMHs were found to be associated more strongly with a history of hypertension, implicating ischemic risk factors as predominant mechanisms underlying the deep WMHs (Barber et al. 2000).

On MRI, WMHs are quantifiable reliably and noninvasively. The value of WMHs as a continuous trait variable makes its quantification a potential intermediate biomarker of therapeutic responses in clinical trials. Future studies to investigate the dynamic changes in WMHs may further highlight its unique place as a secondary end point in dementia and stroke research.

Diffusion Tensor Imaging (DTI)-Based Biomarkers in AD

Diffusion tensor imaging (DTI) is an advanced and evolving *in vivo* imaging technique that assesses the microstructural integrity of the cerebral WM tracts (Le Bihan 2003). Such architectural information is derived by measuring the overall diffusivity of water molecules (or mean diffusivity [*D*]), as well as the degree and three-dimensional direction of diffusivity in space (or fractional anisotropy [FA]). Water molecules tend to preferentially move along the fine microstructural WM tracts, and this physical property can be used to image and quantify *D* or FA, which are indirect indicators of the health of WM pathways. Injury to the WM tracts in a specific ROI may inhibit the direction-dependent movement of water, resulting in increased *D* and decreased FA values (Fig. 7).

Several studies have used DTI to investigate WM microstructural changes in AD. Compared to controls, higher *D* and lower FA were observed in AD in the corpus callosum, left centrum semiovale, and WM regions of the frontal, parietal, and temporal lobes (including hippocampus) (Bozzali et al. 2002; Fellgiebel et al. 2004). Choo et al. reported decreased FA in the posterior cingulate cingulum and parahippocampal cingulum in AD relative to controls (Choo et al. 2010). Similarly, Firbank et al. found increased *D* in the left temporal lobe of AD patients, compared to controls (Firbank et al. 2007a). Head et al. explored diffusivity change in normal aging and AD and found the effects of age to be more pronounced in the anterior regions of the brain, including the corpus callosum and frontal WM, rather than the posterior regions (Head et al. 2004). Conversely, although the age-related changes were also observed in early-stage AD, a relatively greater deterioration of posterior WM integrity was apparent, suggesting that the anterior-to-posterior pattern of age-associated changes likely results from mechanisms distinct from AD (Head et al. 2004).

On the other hand, elevated *D* was also identified in MCI patients in regions typically involved in mild or early AD, particularly the hippocampus (Fellgiebel et al. 2004). A decrease in FA in the parahippocampal cingulum was observed in the MCI group (vs. controls), which was also affected in AD along with the posterior cingulate cingulum (vs. controls) (Choo et al. 2010). Finally, Firbank et al. found that the progression of dementia in AD and DLB (measured by global atrophy) associated with disruptions in WM connecting the posterior cingulate and lateral parietal regions (Firbank et al. 2007b). It was, however, unclear whether the WM injury preceded or was a consequence of atrophic insults.

DTI is a promising technique for biomarker identification, as it can be employed to assess WM tract injury and integrity and to evaluate clinical outcomes.

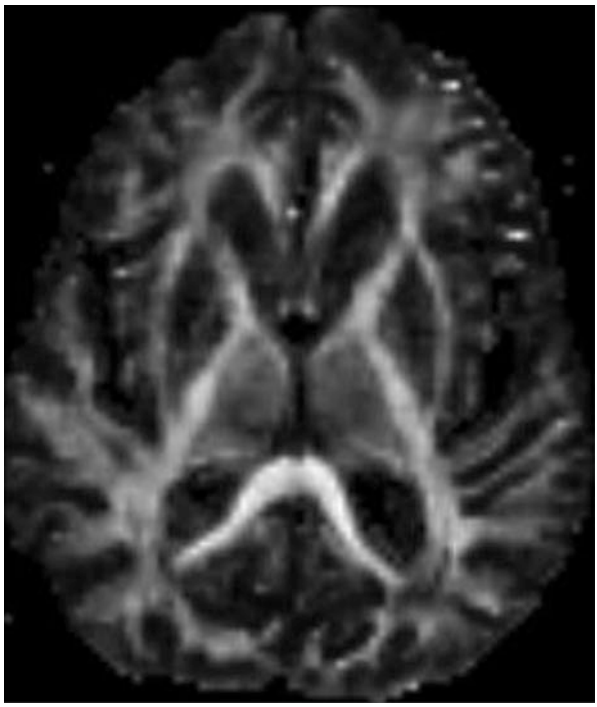

Fig. 7 An example of a diffusion tensor image, graphically displaying tensor estimates of fractional anisotropy (FA) in this figure. As water tends to preferentially move along the white matter tracts, these main microstructural tracts are visible as thick white "lines" within the WM regions of the brain. Damage to these WM tracts will result in a decrease in FA measure

Advancements in techniques and applications will provide new insights into the early WM changes in AD and MCI (Stebbins and Murphy 2009). Future studies with standardized protocols are needed to further establish its validity, as well as to replicate and identify early disease-specific signatures in AD, MCI, and at-risk individuals.

Positron Emission Tomography (PET)-Based Biomarkers in AD

Positron emission tomography (PET) is a functional *in vivo* neuroimaging technique that employs a multitude of different radiotracers to visualize cerebral functions and pathological protein accumulation in AD. Cerebral glucose metabolism can be measured using ^{18}F-labelled fluorodeoxyglucose radiotracer (^{18}F-FDG), where a drop in local uptake is indicative of lower regional glucose metabolism. The brain's Aβ burden was assessed for the first time using Pittsburgh compound B, which is an ^{11}C-labelled thioflavin analogue (^{11}C-PIB). More recently ^{18}F–labelled radioisotopes targeting amyloid deposition have been developed. These have a longer half-life than PIB (110 vs. 20 min) and can therefore be more widely transported to PET scanners available for cancer imaging, without the need for a local cyclotron. The current ligands include florbetapir (Avid Radiopharmaceuticals), flutemetamol (GE Healthcare), and florbetaben (Piramal). Recent developments also allow PET scan detection of PHF, which are aggregates of tau, seen as tangles on pathological

examination. This is providing new premortem insights into the topographical distribution patterns of tau at different disease stages, previously only available at autopsy. Hence, tau PET will also be briefly discussed, along with the potential role of PET for measuring the activity of acetylcholinesterase. Space does not permit fulsome discussion of the burgeoning literature in this rapidly emerging field of brain molecular imaging.

Role of FDG PET in AD

Imaging using ^{18}F-FDG PET is often used to obtain a visual representation of resting-state glucose metabolism in the brain. The resulting PET scan can be quantitatively analyzed, giving a sensitive *in vivo* measure of cerebral metabolism with low variability across multiple centers (Herholz et al. 1993).

In healthy participants, a typical ^{18}F-FDG PET scan reveals intense uptake subcortically in the putamen, caudate nucleus, and thalamus, followed by elevated uptake in cortical GM (Brown et al. 2014). In AD, the classical pattern of abnormal uptake is identified by hypometabolism in the bilateral temporoparietal regions, specifically involving the posterior cingulate gyri, precuneus, and posterior temporal and parietal lobes (Brown et al. 2014). Compared to controls and using VBM analysis, Mosconi et al. found the typical pattern of hypometabolism in temporoparietal and posterior cingulate cortices in a majority of AD patients, with variable involvement of the frontal and hippocampal regions (Mosconi et al. 2008). Additionally, this AD pattern of hypometabolism was also observed in ~80% of MCI patients likely indicating those most likely to progress to AD, as well as in a subset of DLB and in some frontotemporal dementia (FTD) patients (Mosconi et al. 2008). In some cases of DLB, this may reflect concomitant AD-type pathology, although parietal hypometabolism has also been observed in pure DLB cases. In clinically diagnosed FTD cases, parietal hypometabolism may indicate a frontal variant of AD misdiagnosed as FTD, or corticobasal degeneration, a pathological subtype of FTD that demonstrates prominent parietal hypometabolism most often asymmetrically. Compared to AD, occipital hypometabolism was identified as a prominent feature of DLB, while marked hypometabolism in the frontal and temporal cortices was indicative of FTD (Mosconi et al. 2008). Likewise, in a comparison between AD and DLB using ^{18}F-FDG PET, Gilman et al. found similar patterns of cerebral hypometabolism between the two groups, except in the visual cortex where the DLB group showed lower glucose metabolism relative to AD (Gilman et al. 2005).

In a longitudinal study with 1-year of follow-up, a markedly lower baseline metabolism in the parietal, temporal, occipital, frontal, as well as posterior cingulate cortices was detected in AD versus controls (Alexander et al. 2002). At follow-up, further metabolic decline was noted in all regions except in the occipital cortex (Alexander et al. 2002). Studies have also employed FDG PET for the identification of treatment responses to cholinergic enhancers, including donepezil (a centrally selective acetylcholinesterase inhibitor) (Teipel et al. 2006), as well as piracetam (Heiss et al. 1988).

Owing to the high sensitivity, studies using FDG PET have shown reproducible disease-specific patterns. There are some practical limitations, such as the need for qualified and knowledgeable personal to process the scans. Furthermore, reduction in brain volume may also simulate hypometabolism and may lead to artifactual results due to partial volume errors (Brown et al. 2014). Nevertheless, standardization of protocols across multiple centers can yield comparable findings and facilitate diagnosis, despite differences in imaging equipment (Herholz et al. 1993). The feasibility of using FDG PET as an outcome measure in clinical trials is also supported, although pathologically proven studies are needed to further clarify its role in mixed pathologies.

Role of Amyloid PET in AD

Using ^{11}C-PIB PET, the cortical amyloid burden was found to be markedly elevated in AD, independent of the disease severity. Patients with MCI presented with either a similar AD-like pattern suggesting the presence of AD pathology as the underlying etiology, or normal uptake indicating those less likely to progress or develop full-blown AD (Rowe et al. 2007). The regions of greatest ^{11}C-PIB retention in AD included the precuneus or posterior cingulate, frontal cortex, and caudate nuclei, followed by the lateral temporal and parietal cortex (Rowe et al. 2007). Notably, patients with DLB may also present with an elevated cortical ^{11}C-PIB uptake comparable to AD (likely due to concomitant AD-type pathology) (Gomperts et al. 2008). However, retention in the occipital cortex was reported to be lower in AD relative to DLB, which may be helpful in the differential diagnosis (Gomperts et al. 2008). In a 2-year longitudinal study, Engler et al. found ^{11}C-PIB retention to be stable between the baseline and follow-up in AD, although with a significant (~20%) decline in glucose metabolic rate in cortical regions (Engler et al. 2006). This suggests that amyloid deposition in the brain reaches a plateau early in the course of AD dementia, possibly due to brain volume loss (Rowe et al. 2007).

Other investigations have compared ^{11}C-PIB retention in *APOE* ε4 carriers and noncarriers (Rowe et al. 2007; Drzezga et al. 2009). While the uptake was found to be elevated in AD patients compared to controls, the *APOE* ε4 carriers showed stronger and more extensive uptake, particularly in the bilateral temporoparietal and frontal cortex, relative to *APOE* ε4 noncarriers (matched on age and level of cognitive impairment) (Drzezga et al. 2009). Recently, the prevalence of *APOE* ε4 was also found to be elevated across the Lewy body spectrum disorders, highlighting more diverse amyloidogenic as well as non-amyloidogenic mechanisms of this allele (Tsuang et al. 2013). As mixed pathologies are common in AD (Rahimi and Kovacs 2014), some studies have postulated an interaction among amyloid, tau, and alpha-synuclein proteinopathies (Clinton et al. 2010). Further studies are needed to clarify and validate these concepts. Using another amyloid radiotracer ^{18}F-florbetaben, higher uptake ratios were demonstrated in AD in neocortical areas, and results comparable to ^{11}C-PIB PET were found (Villemagne et al. 2011). Examples of amyloid PET scans in AD/MCI patients using ^{18}F-florbetapir are presented (Fig. 8).

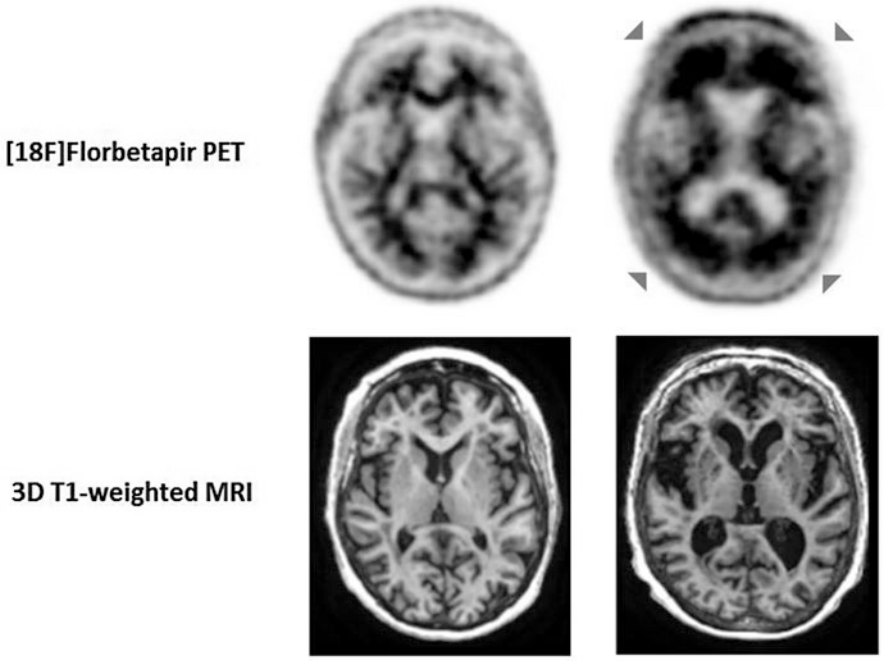

Fig. 8 Examples of amyloid PET scans using the radiotracer ^{18}F-florbetapir (*top row*), along with the corresponding 3D T1-weighted MRIs (*bottom row*). The column of images on the right belongs to an 86-year-old female from an AD study cohort, showing a positive amyloid PET scan (cortical regions are *black* representing high uptake in the frontal and temporal regions bilaterally). The column of images on the left belongs to a 77-year-old female from AD/MCI study cohort, with a negative amyloid PET scan (i.e., a nonspecific retention in the white matter, but no uptake in the cortical mantle)

Amyloid deposition is an early event in AD pathology, and interventions targeted at disrupting this cascade of amyloid aggregation at early stages are desirable. By quantifying and monitoring this retention using ^{11}C-PIB PET, responses to therapeutic interventions in clinical trials can be assessed. A potential limitation of this technique is its nonspecificity for neuritic plaques, as binding to diffuse plaques and even CAA is also observed. Future research is needed to address this limitation and refine the technique.

Role of Tau PET in AD

Following the success of PET ligands for the identification of cerebral amyloid in vivo, efforts are under way to develop selective radiotracers to image tau in the brain. Some novel ligands labelled with fluorine-18 are in development (see overview by Villemagne et al. 2015). Although, tau imaging has several technique-specific as

well as tracer-specific challenges, preliminary forays are showing promise for biomarker identification in AD.

As mentioned above, hyperphosphorylated tau is the other hallmark misfolded protein in AD, which appears pathologically as PHF, constituting the NFTs. It is first evident in humans in the fourth decade of life in the entorhinal cortex, as documented in detail in the Braak and Braak staging system for AD (Braak and Braak 1991). Based on inference from autopsies in different decades of age, these authors described the gradual spread of NFTs from limbic to isocortical to neocortical regions over a 30–40 year period (Braak and Braak 1991), which correlates strongly with functional and cognitive decline in AD (Jack and Holtzman 2013). While amyloid uptake tends to be higher in the frontal regions, PHF-tau concentrations are higher in the parietal and temporal regions according to the early tau PET data (Villemagne et al. 2015).

The ^{18}F-labelled radioligand ^{18}F-AV-1451 (formerly ^{18}F-T807) is a novel PET tracer with high affinity and selectivity for PHF-tau (Chien et al. 2013; Xia et al. 2013). ^{18}F-AV-1451 correlates with disease severity and may also show age-related deposition (Johnson et al. 2016). Recently named flortaucipir, ^{18}F-AV-1451 has already been used in the second wave of the Alzheimer's Disease Neuroimaging Initiative (ADNI-2), a landmark North American biomarker study of more than 1300 participants (normal controls, MCI, and mild AD) that started in 2004 with funding from the National Institutes of Health (NIH) and industry partners (Weiner et al. 2015). The data collected is publically available as soon as it is acquired and has resulted in excess of 1,000 peer-reviewed publications. Flortaucipir will also be used in the ADNI-3 continuation study, which is under way as of September 2016 (www.adni-info.org). Flortaucipir PET is also an optional procedure in the first randomized, double-blind, placebo-controlled clinical trial in the presymptomatic stages of AD. This study randomizes normal elderly individuals (aged 65–85 years), who show flortaucipir uptake on a PET scan, to passive immunotherapy with monthly infusions of solanezumab or placebo for 3 years. The primary goal is to prevent cognitive decline and symptom development (see Anti-Amyloid Treatment in Asymptomatic Alzheimer's study: www.a4study.org).

Another tau PET ligand, ^{18}F-THK5105, detected greater tracer retention in regions harboring a high density of NFT pathology, including the temporal cortex in an AD study (Okamura et al. 2014). Similarly, ^{18}F-THK523 tracer retention followed the known tau distribution in AD patients (Fodero-Tavoletti et al. 2011; Villemagne et al. 2014) and correlated with cognitive measures (but not with ^{11}C-PIB Aβ load) (Villemagne et al. 2014). Yet another radiotracer ^{18}F-FDDNP, which also detects amyloid plaques, showed retention in the temporal, parietal, posterior cingulate, and frontal regions in a characteristic order: lower in controls, higher in MCI, and highest in AD patients, suggesting that it may be useful in monitoring disease progression (Small et al. 2006). Other arylquinoline derivatives have also been tested in mouse models including THK-5105 and THK-5117, showing higher binding affinity than THK-523, as well as richer uptake and faster clearance (Okamura et al. 2013). These early investigations have provided support for molecular tau imaging to be useful in estimating and tracking tau pathology. Molecular tau

imaging will also provide new insights into the relationships between vasculopathy and misfolded proteinopathies of AD (and possibly in Lewy body dementia) in ways never before imagined in the living human (Villemagne et al. 2015). This technique, however, is still in early development, and more research is under way to validate its clinicopathological correlations.

Role of Acetylcholine Esterase Activity on PET in AD

Deficits in acetylcholine are characteristics of both AD and DLB, caused by the degeneration of cholinergic projections (originating from the nucleus basalis of Meynert and septal nuclei), as well as due to dysfunction in muscarinic and nicotinic receptors. Various acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, offer symptomatic improvement by inhibiting the breakdown of available acetylcholine into its metabolites. Radioligands, such as *N*-^{11}C-methyl-piperidin-4-yl propionate (^{11}C-PMP), can measure acetylcholinesterase and cholinergic receptor activity in AD, although the utility of these ligands from a biomarker perspective has not yet been fully established.

Bohnen et al. applied ^{11}C-PMP PET in a small sample of AD patients before and after treatment with donepezil and observed 19% mean inhibition of acetylcholinesterase activity in the temporal, parietal, and frontal cortices and 24% inhibition in the anterior cingulate cortex (Bohnen et al. 2005). Likewise, Kaasinen et al. used another acetylcholinesterase tracer, methyl-^{11}C-*N*-methyl-piperidyl-4-acetate (MP4A), reporting donepezil-induced inhibition in the frontal (roughly 39%), temporal (29%), and parietal (28%) cortices in AD (Kaasinen et al. 2002). Using rivastigmine, the corresponding inhibition was 37% in the frontal, 28% in the temporal, and 28% in the parietal cortex (Kaasinen et al. 2002). Altogether, it was concluded that the attenuation of donepezil- and rivastigmine-induced acetylcholinesterase activity was greater in the frontal than in temporal cortex. This finding may also relate to an overall reduction in the acetylcholinesterase enzyme in the temporoparietal regions in AD (Kaasinen et al. 2002). It was further hypothesized that the clinical improvements in symptomatology using acetylcholinesterase inhibitors may be more associated with enzymatic inhibition in the frontal cortex and less so in the temporal lobe (Kaasinen et al. 2002). These studies show potentially useful applications, but more work is needed in this area to validate these biomarkers.

Single Photon Emission Computed Tomography (SPECT)-Based Biomarkers in AD

Single photon emission computed tomography (SPECT) is an in vivo neuroimaging technique that uses gamma-emitting radiotracers to assess cerebral blood flow. Examples of these tracers include technetium-99m-labelled compounds, such as ^{99m}Tc-hexamethyl propylene amine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD), or iodine-123-labelled compounds, such as

N-isopropyl-*p*-iodoamphetamine (^{123}I-IMP) (Saha et al. 1994). These tracers are lipophilic and freely cross the blood-brain barrier in a manner proportional to the cerebral blood flow, allowing for both visual as well as semiquantitative examination of regional tracer uptake.

In general, perfusion studies using SPECT confirm ^{18}F-FDG PET findings in AD. Using tracers ^{99m}Tc-HMPAO and ^{99}mTc-ECD, marked deficits in perfusion were observed in temporoparietal regions in AD as compared to controls (Colloby et al. 2002; Ceravolo et al. 2003; Lobotesis and Fenwick 2001). As Lewy body pathology frequently coexists with AD, it can be difficult sometimes to differentiate AD from DLB or to even establish a diagnosis of mixed AD/DLB. While a significant hypoperfusion in temporal and parietal regions was characteristic of AD, deficits in parietooccipital regions were found to be more indicative of Lewy body dementia (Colloby et al. 2002; Ceravolo et al. 2003; Lobotesis and Fenwick 2001). Notably, cerebral blood flow abnormalities in parietal and frontal regions may be present in both AD and DLB cases, whereas marked hypoperfusion in the temporal region is a characteristic of AD (Colloby et al. 2002). Furthermore, some DLB patients may also show hypoperfusion in temporoparietal regions. However, concurrent occipital hypoperfusion should raise the possibility of underlying Lewy body pathology, indicating the need to carefully follow up such patients for DLB-associated clinical features (Lobotesis and Fenwick 2001). In an autopsy-confirmed study, a positive SPECT scan was found to raise the likelihood of pathologic AD at postmortem, although it was more useful as adjunctive evidence for "possible" than "probable" AD (Jagust et al. 2001). An example of a SPECT scan in AD relative to healthy control is shown (Fig. 9).

In summary, the characteristic perfusion profile of AD using SPECT can be a useful biomarker and may help differentiate AD cases from other disorders, including DLB and particularly FTD. Future studies investigating the perfusion profiles in

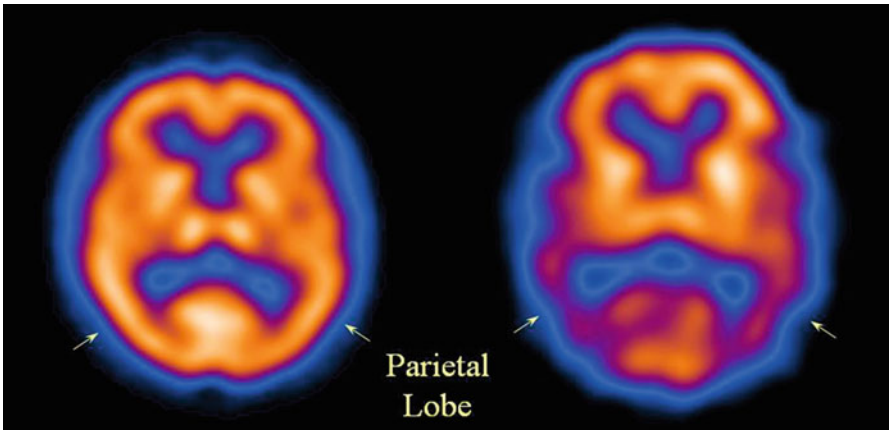

Fig. 9 Single photon emission computed tomography (SPECT) image of a healthy control subject (*left*) and patient with AD (*right*). The arrows point to the parietal lobe, showing decreased perfusion in the parietal lobe (normalized to the cerebellar perfusion) in AD, compared to the healthy control subject

mixed AD/DLB cases as compared to "pure" AD and "pure" DLB could be clinically useful, especially for recruitment of participants to clinical trials of new therapeutics in the development pipeline (e.g., intepirdine, a 5-HT6 receptor antagonist currently in trials for both AD and DLB (www.axovant.com).

Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) as a Biomarker in AD

Proton magnetic resonance spectroscopy (^{1}H–MRS) is a noninvasive imaging technique that uses resonance frequencies of protons to provide biochemical information about compounds in the brain (Soares and Law 2009). In general, MRS signals are less robust than structural MRI due to lower concentrations of metabolites in the brain, relative to water. However, the compound *N*-acetyl aspartate (NAA), an indicator of neuronal health, number, and integrity, is found in high concentrations and can be reliably measured using MRS (Moffett et al. 2007). The levels of NAA drop upon neuronal loss or dysfunction and are often represented as a ratio of creatine (Cr). The concentration of Cr remains relatively stable in the healthy brain (Moffett et al. 2007).

Compared to controls, NAA/Cr levels were found to be reduced in AD, whereas the levels of choline-containing compounds (markers of membrane integrity and inflammation) and myoinositol levels (marker of demyelination and gliosis) were elevated (Griffith et al. 2008). Likewise, Chao et al. identified lower NAA concentrations in cognitively impaired, but non-demented, individuals in the MTL region, compared to controls (Chao et al. 2005). Interestingly, those cognitively impaired patients who progressed to dementia showed lower baseline NAA levels, while nonprogressors had levels comparable to the control group (Chao et al. 2005). Additionally, a significant correlation between reduced MTL NAA levels and impaired memory scores was also identified (Chao et al. 2005). In another study, an increase in NAA and NAA/Cr levels was reported in the parietal lobe of AD patients after 3 months of treatment with donepezil (Jessen et al. 2006). In this study, a favorable response to treatment, as assessed by an increase in NAA metabolite, was predicted by lower baseline levels of NAA/Cr in the parietal lobe (Jessen et al. 2006).

Limitations of most MRS studies are small sample sizes and differing voxels of interest. Studies using NAA or other metabolites can enhance our understanding of the underlying pathophysiology of AD, especially with wider availability of 3 Tesla MRI, which provides better spectral resolution.

Functional Magnetic Resonance Imaging (*f*MRI)-Based Biomarkers in AD

Functional magnetic resonance imaging (*f*MRI) is a blood oxygen level-dependent (BOLD) technique that measures neuronal activity and relies upon the transient changes in blood flow, volume, and oxyhemoglobin/deoxyhemoglobin ratios

(Logothetis et al. 2001). It can be performed under a variety of experimental paradigms (e.g., task-based vs. control conditions) or under resting-state conditions. Some studies measure functional connectivity patterns within key brain circuits involved in AD. One such network of regions that shows preferential activation at resting state has been identified as the "default mode network" (DMN), which includes the medial prefrontal cortex, posterior cingulate cortex (PCC), precuneus, and lateral parietal and medial temporal cortices (Buckner et al. 2008). Early detection of disturbances in the functional connectivity of these networks at preclinical stages may have potential roles as biomarkers of AD.

During a memory-encoding task, reduced activation in the left hippocampus and bilateral parahippocampal gyri was observed in AD (vs. controls) (Rombouts et al. 2000). In studies analyzing the resting-state activity in AD, a consistent decrease in functional connectivity in the DMN was identified, suggesting dysfunctional resting-state interactions among key regions of the brain (Wang et al. 2006; Wu and Li 2011). Wu et al. identified a decline in resting-state connectivity in regions belonging to the DMN that included the PCC, medial prefrontal cortex, inferior parietal cortex, inferior temporal cortex, as well as hippocampus (Wu and Li 2011). These disruptions in DMN circuitry were found to intensify with greater severity of AD (Zhang et al. 2010).

On the other hand, individuals with MCI showed greater activation in the parahippocampal gyrus during an encoding paradigm (Dickerson et al. 2004). Similarly, Celone et al. observed a paradoxical hyperactivation in the hippocampus among the less-impaired MCI subjects (vs. controls), whereas more impaired MCI subjects presented with AD-type decreases in activation (Celone et al. 2006). It is hypothesized that this hyperactivation represents the brain's compensatory response to early neurodegenerative changes. According to this "compensatory recruitment" hypothesis, functional connectivity or BOLD activity may initially increase or expand in the early stages of the disease, as new brain areas are recruited to compensate for the loss of others, followed by an eventual decline later in the course of the disease (Kenny et al. 2012; Hafkemeijer et al. 2012). Consistent with this hypothesis, decreased as well as increased PCC functional connectivity with other DMN regions has been reported (Zhang et al. 2009, 2010). Increased activation in the MTL regions has also been described, which may reflect a compensatory response to accumulating AD pathology and may serve as a biomarker for future clinical decline (Dickerson et al. 2004). Recently, however, a transgenic AD mouse model suggested that limbic hyperactivity may in fact reflect microdischarging in the entorhinal circuits due to toxic amyloid oligomers (Sanchez et al. 2012). This was treatable with small doses of levetiracetam, an anticonvulsant that acts at the synapse by binding to synaptic vesicle protein SV2A. A small intervention trial in MCI subjects confirmed this finding in humans with reduction in the hyperexcitability and some evidence for improved memory (Bakker et al. 2012), leading to a proposed large clinical trial in MCI of a small-dose, slow-release formulation of levetiracetam, HOPE4MCI cosponsored by NIH and AGENEBIO (www.hope4mci.org).

Changes in DMN activity upon switching from resting-state conditions to cognitively demanding tasks have also been studied (Schwindt et al. 2013). In one such

study, AD patients were compared to normal controls during the resting state and a simple visual task. While the controls exhibited a greater DMN connectivity during resting state than task, AD patients failed to show modulation of DMN activity between the two conditions. In addition, the degree of condition-dependent modulation in the PCC and precuneus was predictive of mini-mental status examination scores (Schwindt et al. 2013).

Functional MRI has also been used to investigate changes in brain activation upon treatment with drugs. For example, during face encoding and working memory tasks, increased activation in the fusiform gyrus and prefrontal cortex was observed, respectively (Rombouts et al. 2002). Consistent with PET studies (Kaasinen et al. 2002), these findings highlight regional effects of rivastigmine in AD associated with brain activation in the frontal cortex (Rombouts et al. 2002). Similarly, administration of donepezil was also associated with increased frontal activity in MCI, compared to unmedicated controls (Saykin et al. 2004).

Neuroimaging using BOLD *f*MRI is a promising tool to evaluate functional changes in the brain circuitry, using a variety of conditions and paradigms. It can be used not only to evaluate responses to cognition-enhancing drugs but also to detect resting-state abnormalities at early disease stages. In light of its wider availability, noninvasiveness, and relatively higher resolution, *f*MRI holds great potential to be beneficial in biomarker identification.

Classical Fluid-Based Biomarkers in AD

A dynamic clinicopathological model using biomarkers suggests a temporal progression of the disease from preclinical phases to MCI and finally to dementia. In this model, the accumulation of amyloid is an early preclinical event leading to a cascade of successive neurodegenerative changes, such as accumulation of hyperphosphorylated tau, synaptic depletion, and eventually neuronal loss, ultimately resulting in the clinical manifestations of dementia (Jack et al. 2010; Rosa-Neto et al. 2013). CSF measures have been shown to be useful indicators of AD pathology since CSF in the subarachnoid space as well as in the ventricles intermingle with the interstitium throughout the cerebral tissue quite freely. Several CSF biomarkers have been studied, with the most common being: $A\beta_{40}$, $A\beta_{42}$, total tau, and phosphorylated tau (Hampel et al. 2010).

As discussed earlier, APP undergoes differential cleavage through either amyloidogenic or non-amyloidogenic pathways. The former results in the development of insoluble, hydrophobic $A\beta_{40}$ and $A\beta_{42}$ peptides, which can aggregate into an amyloid plaque (Rosa-Neto et al. 2013; Seeman and Seeman 2011). Other molecules can also form such as soluble $A\beta_{42}$ neurotoxic aggregates (called oligomers) (Gao et al. 2010). In AD, CSF levels of $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio progressively decline, while there is an increase in brain amyloid as detected by amyloid PET (Tolboom et al. 2009; Weigand et al. 2011). This inverse association between CSF $A\beta_{42}$ concentrations and

brain amyloid is thought to occur due to greater retention of Aβ-peptide moieties in the brain as they fibrillate and deposit in the form of amyloid plaques.

In contrast to CSF amyloid, total tau (t-tau) and phosphorylated tau (p-tau) in the CSF represent important biomarkers of neurodegeneration. The tau protein is essential for the proper assembly and stabilization of microtubules within neurons (Kolarova et al. 2012). The tau protein can be modified by abnormal hyperphosphorylation of serine and threonine residues leading to altered expression patterns and ultimately the formation of NFTs – one of the hallmarks of AD (Rosa-Neto et al. 2013). When neurons die, tau leaks into the extracellular space making its way eventually into the CSF. In AD and those with MCI destined to develop AD, t-tau and p-tau levels in CSF are elevated compared to normal controls (Olsson et al. 2016; Blennow and Hampel 2003).

The signature CSF profile of AD, i.e., low $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio and high t-tau and p-tau, is a very useful biomarker to distinguish AD from normal controls and other non-AD forms of dementia (Blennow and Hampel 2003; Andreasen et al. 2001). It is also useful in predicting the conversion of MCI to AD with good diagnostic accuracy (greater than 80%) (Hansson et al. 2006). Compared to CSF, peripheral blood biomarkers would be desirable due to the ease of accessibility; however, $A\beta_{42}$ and $A\beta_{40}$ concentrations in blood show poor predictive accuracy, and concentrations of t-tau show wider variability between patients and controls in blood than in CSF (Olsson et al. 2016). It is notable, however, that the $A\beta_{42}/A\beta_{40}$ ratio in blood may be more predictive than either species alone (Koyama et al. 2012). Measurement of all these fluid biomarkers may be hindered by greater susceptibility to degradation, low concentrations in the periphery, as well as sensitivity to conditions around collection, storage, transportation, and methods of analysis, which has stimulated the much-needed working group efforts for standardization (Kuhlmann et al. 2016; Mattsson et al. 2016).

Regarding peripheral blood tests, several studies have suggested that measuring multiple biomarkers simultaneously beyond amyloid and tau may be useful to obtain "bio-signatures" with good prognostic or diagnostic accuracy. For instance, a panel of molecules, including hormones, proteins, and metals, when measured together in blood attained good diagnostic accuracy (greater than 80%) for AD compared to cognitively normal individuals (Doecke et al. 2012). Similarly, a signature of ten plasma phospholipids was able to predict conversion to MCI or AD over 2–3 years among cognitively normal older adults (Mapstone et al. 2014). Currently, the difficulty in measuring multiple metabolites simultaneously, and the complexity of their interpretation, limits the clinical application of these findings. An alternative approach involves the simultaneous detection of multiple miRNA species, which might be detected relatively simply and cost-effectively via polymerase chain reaction-based techniques. Although excellent diagnostic accuracies have been achieved in individual studies (Leidinger et al. 2013; Kumar et al. 2013), miRNA signatures remain to be validated extensively in multiple large samples. Hence, the search for the holy grail of a blood test for AD and other neurodegenerative disorders continues.

Conclusions

In summary, a combination of noninvasive *in vivo* biomarkers, e.g., structural and functional MRI, DTI, and ^{1}H-MRS, and minimally invasive *in vivo* biomarkers, e.g., PET, SPECT, and CSF concentrations of tau and Aβ, can aid in making early and confident diagnostic decisions. Blood-based biomarkers are also actively being explored. Biomarkers derived from multiple modalities, when consistent with AD pathophysiology, may raise the certainty of the clinical diagnosis. Longitudinal assessments of these biomarkers can offer powerful ways of quantifying therapeutic responses to interventions in clinical trials, by providing measurable primary and secondary end points. It is important to emphasize that the diagnostic and prognostic value of biomarkers are influenced not only by the type but also their methods of measurement. Hence, future efforts are needed to standardize research protocols and refine measurement techniques, as well as to replicate controversial findings in autopsy-proven samples. Although some biomarkers may be more sensitive and specific than others, a combination of selective biomarkers from different modalities may prove more valuable during the diagnostic process. It is hoped that this "multimodal approach" will facilitate personalized or precision medicine strategies for the management of AD.

Acknowledgments The authors would like to thank the Brainlab.ca team in the LC Campbell Cognitive Neurology Research Unit (http://brainlab.ca/) for the provision of MRI and PET images for this chapter. MM is supported by the Department of Medicine at Sunnybrook Health Sciences Centre, University of Toronto, and the Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute (SRI). SEB is supported by the Brill Chair in Neurology (Sunnybrook Research Institute, Department of Medicine, University of Toronto) and the Toronto Dementia Research Alliance. US is supported by the Ontario Graduate Scholarship, Margaret and Howard Gamble Research Grant, Scace Graduate Fellowship in Alzheimer's Research, and Institute of Medical Science Fellowship, University of Toronto.

Cross-References

► Cognitive and Neuropsychiatric Screening Tests in Older Adults
► (Neurobiology of) Dementia: Causes, Presentation, and Management
► Pharmacotherapy of Dementia

Glossary

^{11}C-PIB ^{11}C-labelled Pittsburgh compound B
^{11}C-PMP ^{11}C-labelled *N*-methyl-piperidin-4-yl propionate
^{123}I-IMP ^{123}I-labelled *N*-isopropyl-*p*-iodoamphetamine
^{18}F-FDG ^{18}F-labelled fluorodeoxyglucose
^{1}H-MRS Proton magnetic resonance spectroscopy

^{99m}Tc-ECD ^{99m}Tc-ethyl cysteinate dimer
^{99m}Tc-HMPAO ^{99m}Tc-hexamethyl propylene amine oxime
AD Alzheimer's disease
***APOE* ε4** Apolipoprotein E ε4 allele
APP Amyloid precursor protein
Aβ Amyloid-beta
$Aβ_{40}$ Amyloid-beta – 40 residue peptide
$Aβ_{42}$ Amyloid-beta – 42 residue peptide
BOLD Blood oxygen level dependent
CA1 Cornu ammonis 1
CAA Cerebral amyloid angiopathy
CERAD Consortium to Establish a Registry for Alzheimer's disease
CSF Cerebrospinal fluid
D Mean diffusivity
DLB Dementia with Lewy bodies
DMN Default mode network
DTI Diffusion tensor imaging
DWI Diffusion weighted imaging
FA Fractional anisotropy
FLAIR Fluid-attenuated inversion recovery
FTD Frontotemporal dementia
***f*MRI** Functional magnetic resonance imaging
GM Gray matter
GRE Gradient recalled echo
MCI Mild cognitive impairment
MP4A Methyl-*N*-methyl-piperidyl-4-acetate
MRI Magnetic resonance imaging
MTL Medial temporal lobe
NAA *N*-acetyl aspartate
NFTs Neurofibrillary tangles
NIA-AA National Institute on Aging and the Alzheimer's Association
NIH National Institutes of Health
PCC Posterior cingulate cortex
PD Proton density-weighted
PDD Parkinson's disease dementia
PET Positron emission tomography
PHF Paired helical filaments
p-tau Phosphorylated-tau
ROI Region of interest
SWI Susceptibility-weighted imaging
T1 T1 weighted
T2 T2 weighted
TDP-43 Transactive response DNA-binding protein of 43 kDa

t-tau Total-tau
VBM Voxel based morphometry
WM White matter
WMHs White matter hyperintensities

References

Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM (2002) Longitudinal PET evaluation of cerebral metabolic decline in dementia: a potential outcome measure in Alzheimer's disease treatment studies. Am J Psychiatry 159:738–745. doi:10.1176/appi.ajp.159.5.738

Alzheimer's Disease International – Dementia statistics. n.d.. Available at: https://www.alz.co.uk/research/statistics. Accessed 30 Dec 2016

Andreasen N, Minthon L, Davidsson P, Vanmechelen E, Vanderstichele H, Winblad B et al (2001) Evaluation of CSF-tau and CSF-A{beta}42 as diagnostic markers for alzheimer disease in clinical practice. Arch Neurol 58:373–379. doi:10.1001/archneur.58.3.373

Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE et al (2012) Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron 74:467–474. doi:10.1016/j.neuron.2012.03.023

Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. Lancet 377:1019–1031. doi:10.1016/S0140-6736(10)61349-9

Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT (2000) MRI volumetric correlates of white matter lesions in dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 15:911–916. doi:10.1002/1099-1166(200010)15:10<911::AID-GPS217>3.0.CO;2-T

Barber R, Mckeith IG, Ballard C, Gholkar A, O'brien JT (2001) A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study. Dement Geriatr Cogn Disord 12:198–205. doi:10.1159/000051258

Barber R, Scheltens P, Gholkar A, Ballard C, McKeith I, Ince P et al (1999) White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry 67:66–72. doi:10.1136/jnnp.67.1.66

Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C et al (2009) A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. Neurobiol Aging 30:1711–1723. doi:10.1016/j.neurobiolaging.2008.01.010

Basso M, Gelernter J, Yang J, MacAvoy MG, Varma P, Bronen RA et al (2006) Apolipoprotein E epsilon4 is associated with atrophy of the amygdala in Alzheimer's disease. Neurobiol Aging 27:1416–1424. doi:10.1016/j.neurobiolaging.2005.08.002

Biomarkers Definitions Working Group (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69:89–95. doi:10.1067/mcp.2001.113989

Bird TD (2008) Genetic aspects of Alzheimer disease. Genet Med 10:231–239. doi:10.1097/GIM.0b013e31816b64dc

Black S, Gao F, Bilbao J (2009) Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke 40. doi:10.1161/STROKEAHA.108.537704

Blanc F, Colloby SJ, Philippi N, De Pétigny X, Jung B, Demuynck C et al (2015) Cortical thickness in dementia with Lewy bodies and Alzheimer's disease: a comparison of prodromal and dementia stages. PLoS One 10. doi:10.1371/journal.pone.0127396

Blennow K, Hampel H (2003) CSF markers for incipient Alzheimer's disease. Lancet Neurol 2:605–613. doi:10.1016/S1474-4422(03)00530-1

Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti BJ, Koeppe RA et al (2005) Degree of inhibition of cortical acetylcholinesterase activity and cognitive effects by donepezil treatment in Alzheimer's disease. J Neurol Neurosurg Psychiatry 76:315–319. doi:10.1136/jnnp.2004.038729

Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G et al (2002) White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry 72:742–746. doi:10.1136/jnnp.72.6.742

Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259

Brown RKJ, Bohnen NI, Wong KK, Minoshima S, Frey K a. Brain PET in suspected dementia: patterns of altered FDG metabolism. Radiographics 2014;34:684–701. doi:10.1148/rg.343135065.

Buckner RL, Jessica A-H, Daneil S, Andrews-Hanna JR, Schacter DL (2008) The brain's default network anatomy, function, and consequence. Ann N Y Acad Sci 1124:1–38. doi:10.1196/annals.1440.011

Burton EJ, Barber R, Mukaetova-Ladinska EB, Robson J, Perry RH, Jaros E et al (2009) Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain 132:195–203. doi:10.1093/brain/awn298

Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT (2004) Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 127:791–800. doi:10.1093/brain/awh088

Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA (2003) Parkinson's disease is associated with hippocampal atrophy. Mov Disord 18:784–790. doi:10.1002/mds.10444

Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL et al (2006) Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J Neurosci 26:10222–10231. doi:10.1523/JNEUROSCI.2250-06.2006

Ceravolo R, Volterrani D, Gambaccini G, Rossi C, Logi C, Manca G et al (2003) Dopaminergic degeneration and perfusional impairment in Lewy body dementia and Alzheimer's disease. Neurol Sci 24:162–163. doi:10.1007/s10072-003-0110-6

Chao LL, Schuff N, Kramer JH, Du AT, Capizzano AA, O'Neill J et al (2005) Reduced medial temporal lobe *N*-acetylaspartate in cognitively impaired but nondemented patients. Neurology 64:282–289. doi:10.1212/01.WNL.0000149638.45635.FF

Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY et al (2013) Early clinical PET imaging results with the novel PHF-Tau radioligand [F-18]-T807. J Alzheimer's Dis 34:457–468. doi:10.3233/JAD-122059

Choo IH, Lee DY, Oh JS, Lee JS, Lee DS, Song IC et al (2010) Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 31:772–779. doi:10.1016/j.neurobiolaging.2008.06.015

Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM (2010) Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. J Neurosci 30:7281–7289. doi:10.1523/JNEUROSCI.0490-10.2010

Colloby SJ, Fenwick JD, Williams ED, Paling SM, Lobotesis K, Ballard C et al (2002) A comparison of (99m)Tc-HMPAO SPET changes in dementia with Lewy bodies and Alzheimer's disease using statistical parametric mapping. Eur J Nucl Med Mol Imaging 29:615–622. doi:10.1007/s00259-002-0778-5

de Leeuw F-EE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R et al (2001) Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 70:9–14. doi:10.1136/jnnp.70.1.9

Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 341:1–9. doi:10.1136/bmj.c3666

Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN et al (2004) Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol 56:27–35. doi:10.1002/ana.20163

Doecke JD, Laws SM, Faux NG, Wilson W, Burnham SC, Lam C-PP et al (2012) Blood-based protein biomarkers for diagnosis of Alzheimer disease. Arch Neurol 69:1–8. doi:10.1001/archneurol.2012.1282

Drzezga A, Grimmer T, Henriksen G, Mühlau M, Perneczky R, Miederer I et al (2009) Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology 72:1487–1494. doi:10.1212/WNL.0b013e3181a2e8d0

Engler H, Forsberg A, Almkvist O, Blomquist G, Larsson E, Savitcheva I et al (2006) Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 129:2856–2866. doi:10.1093/brain/awl178

Fellgiebel A, Wille P, Müller MJ, Winterer G, Scheurich A, Vucurevic G et al (2004) Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord 18:101–108. doi:10.1159/000077817

Firbank MJ, Blamire AM, Krishnan MS, Teodorczuk A, English P, Gholkar A et al (2007a) Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease. Psychiatry Res 155:135–145. doi:10.1016/j.pscychresns.2007.01.001

Firbank MJ, Blamire AM, Krishnan MS, Teodorczuk A, English P, Gholkar A et al (2007b) Atrophy is associated with posterior cingulate white matter disruption in dementia with Lewy bodies and Alzheimer's disease. Neuroimage 36:1–7. doi:10.1016/j.neuroimage.2007.02.027

Firbank MJ, Blamire AM, Teodorczuk A, Teper E, Burton EJ, Mitra D et al (2010) High resolution imaging of the medial temporal lobe in Alzheimer's disease and dementia with Lewy bodies. J Alzheimer's Dis 21:1129–1140. doi:10.3233/JAD-2010-100138

Fodero-Tavoletti MT, Okamura N, Furumoto S, Mulligan RS, Connor AR, McLean CA et al (2011) 18F-THK523: a novel in vivo tau imaging ligand for Alzheimer's disease. Brain 134:1089–1100. doi:10.1093/brain/awr038

Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN (2000) Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease – power calculations and estimates of sample size to detect treatment effects. Arch Neurol 57:339–344. doi:10.1001/archneur.57.3.339

Frank R, Hargreaves R (2003) Clinical biomarkers in drug discovery and development. Nat Rev Drug Discov 2:566–580. doi:10.1038/nrd1130

Friedhoff P, von Bergen M, Mandelkow E-M, Mandelkow E (2000) Structure of tau protein and assembly into paired helical filaments. Biochim Biophys Acta – Mol Basis Dis 1502:122–132. doi:10.1016/S0925-4439(00)00038-7

Gao CM, Yam AY, Wang X, Magdangal E, Salisbury C, Peretz D et al (2010) Aβ40 oligomers identified as a potential biomarker for the diagnosis of Alzheimer's disease. PLoS One 5. doi:10.1371/journal.pone.0015725

Garde E, Lykke Mortensen E, Rostrup E, Paulson OB (2005) Decline in intelligence is associated with progression in white matter hyperintensity volume. J Neurol Neurosurg Psychiatry 76:1289–1291. doi:10.1136/jnnp.2004.055905

Gilman S, Koeppe RA, Little R, An H, Junck L, Giordani B et al (2005) Differentiation of Alzheimer's disease from dementia with Lewy bodies utilizing positron emission tomography with [18F]fluorodeoxyglucose and neuropsychological testing. Exp Neurol 191. doi:10.1016/j.expneurol.2004.06.017

Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE et al (2008) Imaging amyloid deposition in Lewy body diseases. Neurology 71:903–910. doi:10.1212/01.wnl.0000326146.60732.d6

Griffith HR, den Hollander JA, Okonkwo OC, O'Brien T, Watts RL, Marson DC (2008) Brain metabolism differs in Alzheimer's disease and Parkinson's disease dementia. Alzheimers Dement 4:421–427. doi:10.1016/j.jalz.2008.04.008

Hafkemeijer A, van der Grond J, Rombouts SA (2012) Imaging the default mode network in aging and dementia. Biochim Biophys Acta – Mol Basis Dis 1822:431–441. doi:10.1016/j.bbadis.2011.07.008

Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J et al (2010) Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov 9:560–574. doi:10.1038/nrd3115

Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L (2006) Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 5:228–234. doi:10.1016/S1474-4422(06)70355-6

Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, Kazui H et al (2001) Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. Neurology 57:1461–1466. doi:ERN-Converted #117; Used to be #1421 and #2126

Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE et al (2004) Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb Cortex 14:410–423

Heiss WD, Hebold I, Klinkhammer P, Ziffling P, Szelies B, Pawlik G et al (1988) Effect of piracetam on cerebral glucose metabolism in Alzheimer's disease as measured by positron emission tomography. J Cereb Blood Flow Metab 8:613–617. doi:10.1038/jcbfm.1988.104

Henneman WJP, Sluimer JD, Barnes J, Van Der Flier WM, Sluimer IC, Fox NC et al (2009) Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. Neurology 72:999–1007. doi:10.1212/01.wnl.0000344568.09360.31

Herholz K, Perani D, Salmon E, Franck G, Fazio F, Heiss WD et al (1993) Comparability of FDG PET studies in probable Alzheimer's disease. J Nucl Med 34:1460–1466

Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC et al (2012) National Institute on Aging – Alzheimer ' s Association guidelines for the neuropathologic assessment of Alzheimer ' s disease. Alzheimer's Dement 8:1–13. doi:10.1016/j.jalz.2011.10.007

Jack CR, Holtzman DM (2013) Biomarker modeling of Alzheimer's disease. Neuron 80:1347–1358. doi:10.1016/j.neuron.2013.12.003

Jack CRJ, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW et al (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9:119–128. doi:10.1016/S1474-4422(09)70299-6

Jack CR, Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG et al (1998) Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. Ann Neurol 43:303–310. doi:10.1002/ana.410430307

Jagust WJ, Thisted R, Devous M (2001) SPECT perfusion imaging in the diagnosis of Alzheimer's disease: a clinical-pathologic study. Neurology 56:950–956

Jessen F, Traeber F, Freymann K, Maier W, Schild HH, Block W (2006) Treatment monitoring and response prediction with proton MR spectroscopy in AD. Neurology 67:528–530. doi:10.1212/01.wnl.0000228218.68451.31

Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D et al (2016) Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann Neurol 79:110–119. doi:10.1002/ana.24546

Kaasinen V, Jarvenpaa T, Roivainen A, Yu M, Oikonen V, Kurki T, Rinne JONK (2002) Regional effects of donepezil and rivastigmine on cortical acetylcholinesterase activity in Alzheimer's disease. J Clin Psychopharmacol 22:615. doi:10.1097/00004714-200212000-00012

Kenny ER, Blamire AM, Firbank MJ, O'Brien JT (2012) Functional connectivity in cortical regions in dementia with Lewy bodies and Alzheimer's disease. Brain 135:569–581. doi:10.1093/brain/awr327

Kenny ER, Burton EJ, O'Brien JT (2008) A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with Lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia. Dement Geriatr Cogn Disord 26:218–225. doi:10.1159/000153432

Kerchner GA, Hess CP, Hammond-Rosenbluth KE, Xu D, Rabinovici GD, Kelley DAC et al (2010) Hippocampal CA1 apical neuropil atrophy in mild Alzheimer disease visualized with 7-T MRI. Neurology 75:1381–1387. doi:10.1212/WNL.0b013e3181f736a1

Kim KW, MacFall JR, Payne ME (2008) Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biol Psychiatry 64:273–280. doi:10.1016/j.biopsych.2008.03.024

Kolarova M, García-Sierra F, Bartos A, Ricny J, Ripova D (2012) Structure and pathology of tau protein in Alzheimer disease. Int J Alzheimers Dis. doi:10.1155/2012/731526

Kovacevic N, Lobaugh NJ, Bronskill MJ, Levine B, Feinstein A, Black SE (2002) A robust method for extraction and automatic segmentation of brain images. Neuroimage 17:1087–1100. doi:10.1006/nimg.2002.1221

Koyama A, Okereke OI, Yang T, Blacker D, Selkoe DJ, Grodstein F (2012) Plasma amyloid-beta as a predictor of dementia and cognitive decline: a systematic review and meta-analysis. Arch Neurol 69:824–831. doi:10.1001/archneurol.2011.1841

Kuhlmann J, Andreasson U, Pannee J, Bjerke M, Portelius E, Leinenbach A et al (2016) CSF Abeta1-42 – an excellent but complicated Alzheimer's biomarker – a route to standardisation. Clin Chim Acta. doi:10.1016/j.cca.2016.05.014

Kumar P, Dezso Z, MacKenzie C, Oestreicher J, Agoulnik S, Byrne M et al (2013) Circulating miRNA biomarkers for Alzheimer's disease. PLoS One 8. doi:10.1371/journal.pone.0069807

Laakso MP, Soininen H, Partanen K, Helkala EL, Hartikainen P, Vainio P et al (1995) Volumes of hippocampus, amygdala and frontal lobes in the MRI- based diagnosis of early Alzheimer's disease: correlation with memory functions. J Neural Transm – Park Dis Dement Sect 9:73–86

Lam B, Masellis M, Freedman M, Stuss DT, Black SE (2013) Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimers Res Ther 5:1. doi:10.1186/alzrt155

Le Bihan D (2003) Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 4:469–480

Leidinger P, Backes C, Deutscher S, Schmitt K, Mueller SC, Frese K et al (2013) A blood based 12-miRNA signature of Alzheimer disease patients. Genome Biol 14:R78. doi:10.1186/gb-2013-14-7-r78

Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C et al (2001) Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 56:643–649. doi:10.1212/WNL.56.5.643

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157. doi:10.1038/35084005

Longstreth WT, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA et al (1996) Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people the cardiovascular health study. Stroke 27:1274–1282. doi:10.1161/01.STR.27.8.1274

Mak E, Su L, Williams GB, Watson R, Firbank M, Blamire A et al (2016) Differential atrophy of hippocampal subfields: a comparative study of dementia with Lewy bodies and Alzheimer disease. Am J Geriatr Psychiatry 24:136–143. doi:10.1016/j.jagp.2015.06.006

Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, MacArthur LH et al (2014). advance on: 415–418 Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med. doi:10.1038/nm.3466

Mattsson N, Zetterberg H, Janelidze S, Insel PS, Andreasson U, Stomrud E et al (2016) Plasma tau in Alzheimer disease. Neurology 87:1827–1835. doi:10.1212/WNL.0000000000003246

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–939. doi:10.1186/alzrt38

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH et al (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 Dement 7:263–269. doi:10.1016/j.jalz.2011.03.005

Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AMA (2007) *N*-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol 81:89–131. doi:10.1016/j.pneurobio.2006.12.003

Moody DM, Brown WR, Challa VR, Anderson RL (1995) Periventricular venous collagenosis: association with leukoaraiosis. Radiology 194:469–476. (Abstract only). doi:10.1148/radiology.194.2.7824728

Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G et al (2008) Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. J Nucl Med 49:390–398. doi:10.2967/jnumed.107.045385

Mufson EJ, Counts SE, Perez SE, Ginsberg SD (2009) Cholinergic system during the progression of Alzheimer's disease: therapeutic implications. Expert Rev Neurother 8:1703–1718. doi:10.1586/14737175.8.11.1703.Cholinergic

Okamura N, Furumoto S, Fodero-Tavoletti MT, Mulligan RS, Harada R, Yates P et al (2014) Non-invasive assessment of Alzheimer's disease neurofibrillary pathology using 18F-THK5105 PET. Brain 137:1762–1771. doi:10.1093/brain/awu064

Okamura N, Furumoto S, Harada R, Tago T, Yoshikawa T, Fodero-Tavoletti M et al (2013) Novel 18F-labeled arylquinoline derivatives for noninvasive imaging of tau pathology in Alzheimer disease. J Nucl Med 54:1420–1427. doi:10.2967/jnumed.112.117341

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M et al (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. doi:10.1016/S1474-4422(16)00070-3

Pievani M, Galluzzi S, Thompson PM, Rasser PE, Bonetti M, Frisoni GB (2011) APOE4 is associated with greater atrophy of the hippocampal formation in Alzheimer's disease. Neuroimage 55:909–919. doi:10.1016/j.neuroimage.2010.12.081

Rahimi J, Kovacs GG (2014) Prevalence of mixed pathologies in the aging brain. Alzheimers Res Ther 6:82. doi:10.1186/s13195-014-0082-1

Ramirez J, Gibson E, Quddus A, Lobaugh NJ, Feinstein A, Levine B et al (2011) Lesion Explorer: a comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. Neuroimage 54:963–973. doi:10.1016/j.neuroimage.2010.09.013

Ramirez J, McNeely AA, Scott CJ, Stuss DT, Black SE (2014) Subcortical hyperintensity volumetrics in Alzheimer's disease and normal elderly in the Sunnybrook Dementia Study: correlations with atrophy, executive function, mental processing speed, and verbal memory. Alzheimers Res Ther 6:49. doi:10.1186/alzrt279

Rombouts SARB, Barkhof F, Van Meel CS, Scheltens P (2002) Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. J Neurol Neurosurg Psychiatry 73:665–671. doi:10.1136/jnnp.73.6.665

Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA et al (2000) Functional MR imaging in Alzheimer's disease during memory encoding. AJNR Am J Neuroradiol 21:1869–1875. doi:10.3174/ajnr.A1493

Rosa-Neto P, Hsiung G-Y, Masellis M (2013) Fluid biomarkers for diagnosing dementia: rationale and the Canadian Consensus on Diagnosis and Treatment of Dementia recommendations for Canadian physicians. Alzheimers Res Ther 5:S8. doi:10.1186/alzrt223

Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G et al (2007) Imaging beta-amyloid burden in aging and dementia. Neurology 68:1718–1725. doi:10.1212/01.wnl.0000261919.22630.ea

Saeed U, Black SE, Masellis M (2016a) Imaging and cerebrospinal fluid biomarkers in Alzheimer's disease and Lewy body dementias. In: Gliebus G (ed) Progress. cogn. impair. its neuropathol. correl. Nova Science Publishers, New York, pp 17–50

Saeed U, Compagnone J, Black SE, Masellis M (2016b) Apolipoprotein E E4 allele and hippocampal volumetrics in Alzheimer's disease: a systematic review of cross-sectional and longitudinal studies. Alzheimer's Dement J Alzheimer's Assoc 12:P713–P714. doi:10.1016/j.jalz.2016.06.1403

Saha GB, MacIntyre WJ, Go RT (1994) Radiopharmaceuticals for brain imaging. Semin Nucl Med 24:324–349. doi:10.1016/S0001-2998(05)80022-4

Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR et al (2012) Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. PNAS 109:2895–2903. doi:10.1073/pnas.1121081109

Saykin AJ, Wishart HA, Rabin LA, Flashman LA, McHugh TL, Mamourian AC et al (2004) Cholinergic enhancement of frontal lobe activity in mild cognitive impairment. Brain 127:1574–1583. doi:10.1093/brain/awh177

Schneider JA, Arvanitakis Z, Bang W, Bennett DA (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 69:2197–2204. doi:10.1212/01.wnl.0000271090.28148.24

Schwindt GC, Chaudhary S, Crane D, Ganda A, Masellis M, Grady CL et al (2013) Modulation of the default-mode network between rest and task in Alzheimer's disease. Cereb Cortex 23:1685–1694. doi:10.1093/cercor/bhs160

Seeman P, Seeman N (2011) Alzheimer's disease: β-amyloid plaque formation in human brain. Synapse 65:1289–1297. doi:10.1002/syn.20957

Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ et al (2006) PET of brain amyloid and tau in mild cognitive impairment. N Engl J Med 355:2652–2663. doi:10.1056/NEJMoa054625

Soares DP, Law M (2009) Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. Clin Radiol 64:12–21. doi:10.1016/j.crad.2008.07.002

Stebbins GT, Murphy CM (2009) Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. Behav Neurol 21:39–49. doi:10.3233/BEN-2009-0234

Tang MY, Chen TW, Zhang XM, Huang XH (2014) GRE T2∗-weighted MRI: principles and clinical applications. Biomed Res Int 2014:312142. doi:10.1155/2014/312142

Teipel SJ, Drzezga A, Bartenstein P, Möller HJ, Schwaiger M, Hampel H (2006) Effects of donepezil on cortical metabolic response to activation during 18FDG-PET in Alzheimer's disease: a double-blind cross-over trial. Psychopharmacology (Berl) 187:86–94. doi:10.1007/s00213-006-0408-1

Tolboom N, van der Flier WM, Yaqub M, Boellaard R, Verwey NA, Blankenstein MA et al (2009) Relationship of cerebrospinal fluid markers to 11C-PiB and 18F-FDDNP binding. J Nucl Med 50:1464–1470. doi:10.2967/jnumed.109.064360

Tsuang D, Leverenz JB, Lopez OL, Hamilton RL, Bennett DA, Schneider JA et al (2013) APOE ε4 increases risk for dementia in pure synucleinopathies. JAMA Neurol 70:223–228. doi:10.1001/jamaneurol.2013.600

Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC (2015) Tau imaging: early progress and future directions. Lancet Neurol 14:114–124. doi:10.1016/S1474-4422(14)70252-2

Villemagne VL, Furumoto S, Fodero-Tavoletti MT, Mulligan RS, Hodges J, Harada R et al (2014) In vivo evaluation of a novel tau imaging tracer for Alzheimer's disease. Eur J Nucl Med Mol Imaging 41:816–826. doi:10.1007/s00259-013-2681-7

Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G et al (2011) Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. J Nucl Med 52:1210–1217. doi:10.2967/jnumed.111.089730

Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L et al (2006) Changes in hippocampal connectivity in the early stages of Alzheimer ' s disease: evidence from resting state fMRI. Neuroimage 31:496–504. doi:10.1016/j.neuroimage.2005.12.033

Weigand SD, Vemuri P, Wiste HJ, Senjem ML, Pankratz VS, Aisen PS et al (2011) Transforming cerebrospinal fluid Aβ42 measures into calculated Pittsburgh compound B units of brain Aβ amyloid. Alzheimer's Dement 7:133–141. doi:10.1016/j.jalz.2010.08.230

Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Cedarbaum J et al (2015) 2014 update of the Alzheimer's disease neuroimaging initiative: a review of papers published since its inception. Alzheimer's Dement 11:e1–120. doi:10.1016/j.jalz.2014.11.001

Whitwell JL, Weigand SD, Shiung MM, Boeve BF, Ferman TJ, Smith GE et al (2007a) Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease. Brain 130:708–719. doi:10.1093/brain/awl388

Whitwell JL, Jack CR, Parisi JE, Knopman DS, Boeve BF, Petersen RC et al (2007b) Rates of cerebral atrophy differ in different degenerative pathologies. Brain 130:1148–1158. doi:10.1093/brain/awm021

Whitwell JL, Dickson DW, Murray ME, Weigand SD, Tosakulwong N, Senjem ML et al (2012) Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. Lancet Neurol 11:868–877. doi:10.1016/S1474-4422(12)70200-4

Wu X, Li R, Fleisher AS, Reiman EM, Guan X, Zhang Y et al (2011) Altered default mode network connectivity in Alzheimer's disease. A resting functional MRI and bayesian network study. Hum Brain Mapp 32:1868–1881. doi:10.1002/hbm.21153

Xia C-F, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D et al (2013) [18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. Alzheimer's Dement 9:666–676. doi:10.1016/j.jalz.2012.11.008

Zhang H-Y, Wang S-J, Liu B, Ma Z-L, Yang M, Zhang Z-J et al (2010) Resting brain connectivity: changes during the progress of Alzheimer disease. Radiology 256:598–606. doi:10.1148/radiol.10091701

Zhang HY, Wang SJ, Xing J, Liu B, Ma ZL, Yang M et al (2009) Detection of PCC functional connectivity characteristics in resting-state fMRI in mild Alzheimer's disease. Behav Brain Res 197:103–108. doi:10.1016/j.bbr.2008.08.012

Dementia and Bioethics

7

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Abstract

As the life expectancy increases dramatically, the burden of Alzheimer's disease (AD), the leading cause of dementia, becomes prominent worldwide. With the rapid progress in biomarkers for the pathology of AD, the early diagnosis of AD is possible, and the ethical issue of pre-dementia AD diagnosis has emerged. This chapter discusses the advantages and disadvantages of early diagnosis of pre-dementia AD. The advantages include: provide with appropriate treatment for concomitant diseases, enhance protective factors and control risk factors, alleviate the anxiety of uncertainty by making an accurate diagnosis, plan for the future, and participate in clinical research, contribute to knowledge, and help future generations. The disadvantages include: risks of false-positive or false-negative diagnosis, possible negative emotional effects on the individuals and their families, social stigma of the disease, costs of diagnostic work-up, and additional workload for memory clinics and cognitive research centers. It is the

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_6

duty of the physicians to recommend whether AD biomarkers are needed as part of the clinical evaluation due to the complexity of the dementia syndrome, and the patient has to decide whether or not to proceed with these tests. Once people decide to be diagnosed early, special communication skills for disclosure are needed followed by education and support.

Keywords
Alzheimer's disease • Ethics • Early diagnosis • Benefits • Risks

Contents

Introduction

Medical advances over the decades have enabled physicians to diagnose and treat diseases earlier and more effectively. This has led to a longer life expectancy. Within two centuries from 1,800 to 2,000, life expectancy at birth rose from about 30 years to a global average of 67 years and to more than 75 years in some countries (Riley 2001). In the last 30 years, approximately 2.5 years of longevity have been gained every decade, both in Europe and in the United States (Garibaldi et al. 2010). Unfortunately, because age is the main risk factor for dementia, there is a near exponential increase of dementia prevalence with age, with numbers almost double every 20 years to 115.4 million in 2050 (Prince et al. 2013). Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60–80% of all cases (International AsD 2013). Although there are many people who still believe that dementia is part of normal aging, this misconception is gradually being changed through international efforts to raise awareness of this disease (http://www.alz.org/advocacy/global-efforts.asp [Internet]). With the announcement by former President of the United States of America Ronald Reagan in 1994 that he was suffering from AD, more attention is paid to this disease by the governments, medical professionals, researchers, and the society. This is especially important as the increasing prevalence of dementia has led to a significant financial burden estimated at US$604 billion worldwide in 2010 (Wimo et al. 2013). In 2014, more than 15 million family members and other unpaid caregivers provided an estimated 17.9 billion hours of care to people with AD and other dementias, equivalent to more than $217 billion in

the United States (2015). Dementia is also the most feared condition by people over the age of 55 years (Brunet et al. 2012). Fortunately, with the combined efforts of medical researchers and scientists worldwide, there is now a better understanding of this disease.

AD is a progressive neurodegenerative disease. Its pathological hallmarks are neuritic plaques from extracellular deposition of β-amyloid (Aβ) fibrils and intraneuronal neurofibrillary tangles from aggregated hyperphosphorylated tau protein, leading to neurodegeneration and brain atrophy. At present, various biomarkers can be used to diagnose these pathological processes in vivo. Cerebrospinal fluid (CSF) Aβ42 levels (Blennow and Hampel 2003) and amyloid positron emission tomography (PET) imaging (Forsberg et al. 2008) can be used to diagnose amyloid pathology, while CSF total tau, phosphorylated tau protein levels (Olsson et al. 2016), and tau PET agent (Mormino et al. 2014) F-AV-1451 (Scholl et al. 2016) can be used to diagnose tau pathology. As these pathophysiological processes occur at least 20 years before AD patients present with clinical symptoms (Villemagne et al. 2013; Bateman et al. 2012; Dubois et al. 2016), it is now possible to diagnose AD at the pre-dementia stage, including asymptomatic preclinical stage of AD and mild cognitive impairment (MCI). Preclinical AD is defined as presence of abnormal β-amyloid and tau biomarkers with or without subtle cognitive impairment (Sperling et al. 2011). Genetic studies in AD have led to the discovery of β-amyloid precursor protein (APP), presenilin1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes and the apolipoprotein E ε4 (*APOEε4*) allele, and one may present at the stage of asymptomatic at risk (Villemagne et al. 2013; Bateman et al. 2012; Knopman et al. 2012; Mormino et al. 2014; Reiman et al. 2012; Vos et al. 2013), called preclinical AD with genetic risk factors. This was supported by studies from the presymptomatic autosomal dominant mutation carriers in the Dominantly Inherited Alzheimer Network (DIAN) group and in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Subjects with *APP*, *PSEN1*, or *PSEN2* genetic mutations have a 100% risk of developing autosomal dominant AD (ADAD) (Bateman et al. 2011). *APOEε4* allele carriers are also at higher risk of developing symptomatic AD when compared to noncarriers. ADAD subjects present clinically at an earlier age (<65) with a relatively rapid progress, while *APOEε4* carriers present with AD at a later age (>65) with gradual progression. Longitudinal studies have also shown that preclinical stage of AD is common in cognitively normal elderly people and is associated with future cognitive decline and mortality (Vos et al. 2013). MCI is defined as the presence of abnormal AD pathophysiological biomarkers and episodic memory impairment (Sperling et al. 2011; Dubois et al. 2007; Albert et al. 2011). The risk of MCI patients progressing to sporadic AD is high, and hence diagnosis at this early stage is of great importance (Marcos et al. 2016; Levey et al. 2006).

The possibility of diagnosing these groups of people in the pre-dementia stage will certainly result in new ethical issues on top of those classical ones faced in AD, such as mental capacity to consent (Coast et al. 2015; Fields and Calvert 2015), maintaining autonomy, and end-of-life care (Fields and Calvert 2015; Dunn et al. 2015; Gauthier et al. 2013; Jongsma and van de Vathorst 2015; van der Steen et al. 2016).

Do people really want to know if they are at the asymptomatic preclinical, genetic at risk or MCI stage 20–25 years before onset of clinical AD? It is a hard question for people to answer, even for physicians specialized in the cognitive field. In this review, we will focus on the ethical issues, from the aspects of advantages and disadvantages of early diagnosis in the pre-dementia stage of AD, and we hope that readers can use the following information to weigh the benefits and risks and decide if they would like to be diagnosed at this early stage of AD.

The Advantages of Knowing the Diagnosis of AD in Pre-dementia Stage

At present, the diagnosis of preclinical AD using biomarkers is only applicable for research studies and not for clinical practice. Guidelines are being made for the appropriate usage for these biomarkers in clinical practice only for certain symptomatic patients (Johnson et al. 2013). However with further validation and standardization of these biomarkers, these tests may eventually be used in clinical practice in the future (Winblad et al. 2016). This will allow earlier diagnosis and hopefully earlier treatment to prevent progression of this disease and access to social support for patients and caregivers.

Provide Appropriate Treatment for Concomitant Diseases

This is extremely important for physicians who see patients in the clinic when they present with subtle or mild cognitive impairment, to diagnose the underlying cause early, especially for conditions which are treatable and reversible. Some are systemic conditions such as hypothyroidism, vitamin B12 deficiency, and obstructive sleep apnea, while others are more localized to the brain, such as cerebral vascular disease, brain tumor, cerebral autoimmune disease, trauma, and normal pressure hydrocephalus. These underlying conditions may be sole or additive. If we advocate early diagnosis and increase this awareness to both the society and physicians, people with early cognitive symptoms or concerns will be encouraged to seek consult earlier. However, it is noted that in the primary care setting, between half and three quarters of people with cognitive impairment have no formal diagnosis (Lopponen et al. 2003; Boustani et al. 2003; Valcour et al. 2000). If these patients have treatable concomitant conditions, their cognitive impairment may be reversible after prompt and appropriate therapy. Many diseases have therapeutic time windows, and delayed treatment may lead to irreversible cognitive impairment. From this point of view, early diagnosis is of great importance to both physicians and patients.

Enhance Protective Factors and Control Risk Factors

The onset of cognitive decline in AD is dependent on genetic factors (Mormino et al. 2014; Lim et al. 2015), cognitive reserve (Rentz et al. 2010; Roe et al. 2011), medical comorbidities that contribute to cognitive function (mood, sleep, endocrine and primary cardiopulmonary, renal and hepatic disorders), and lifestyle factors

(such as exercise and diet) (Head et al. 2012; Liang et al. 2010; Wirth et al. 2014). Some of these factors are modifiable and are either detrimental or beneficial to the pathophysiology of AD. Addressing these risk factors early in subjects at the pre-dementia stage is definitely crucial. The Alzheimer's Association reported in 2015 that from the population-based perspective, regular physical activity and management of cardiovascular risk factors reduce the risk of cognitive decline and may reduce the risk of dementia (Baumgart et al. 2015). Findings from a 2-year randomized controlled trial also suggest that a multi-domain intervention involving diet, exercise, cognitive training, and vascular risk monitoring could improve or maintain cognitive functioning in at-risk elderly people from the general population (Ngandu et al. 2015). The early knowledge of unmodifiable risk factors may also lead to a change in modifiable risk factors as shown in studies where ApoE4 carriers made health-related behavioral changes compared to ApoE4 noncarriers to reduce their dementia risk (Chao et al. 2008; Vernarelli et al. 2010). The total number of Americans above 65 years old with AD will decrease from 5.6 million in 2010 to 4 million in 2020 by delaying the onset of AD by 5 years (OECD 2014). These findings support the notion of early diagnosis and early risk modification, especially when no disease-modifying drugs for AD are available at present.

Alleviate the Anxiety of Uncertainty by Making an Accurate Diagnosis

Genetic risk factors play variable roles in AD presentations. As we mentioned in the introduction, subjects with APP or PSEN genetic mutations have almost 100% risk of developing early-onset symptomatic AD (Bateman et al. 2011), while *APOEε4* allele carriers have a higher risk of developing late-onset symptomatic AD when compared to noncarriers (Hauser and Ryan 2013). People with a positive genetic family history may want to know early if they also have the same gene mutations or *APOEε4* allele. This is especially relevant when one witnesses his family member suffer from AD with gradual decline of his mental capacity; he may want to know if he has the same genetic disorder and eventually develop the same disease.

In a separate scenario, when one is experiencing progressive memory decline, slower thinking, and other types of cognitive changes, the thought of a possible diagnosis of AD and the uncertainty of one's future can be stressful.

An early diagnosis in these two situations can help to alleviate anxiety and uncertainty and allow one to plan the future better.

Plan for the Future

Knowing that one is in the pre-dementia stage of AD and understanding the prognosis of this disease can undoubtedly make one anxious and possibly depressed. This point is quite common and important in persons with a family history of ADAD which one has a 50% risk of inheriting the same genetic mutation (*APP*, *PSEN1*, or *PSEN2* gene). If indeed one has the same genetic mutation, then the risk of developing clinical AD is 100% (Hooper et al. 2013). ADAD has a much earlier age of onset compared to sporadic AD and is labeled as early-onset AD

(Bateman et al. 2012). A recent study of persons with genetic at risk for early-onset AD found that baseline interest in being tested for the genetic mutation was 44% (Hooper et al. 2013), and few people actually chose to be tested. A 2001 clinic-based study of persons at risk for ADAD or frontotemporal dementia found that only 8.7% chose to be tested (Steinbart et al. 2001). This scenario has been portrayed in the film "*Still Alice*", in which the main character Alice suffered from ADAD and her three adult children had to make the decision of whether to go for genetic testing. Two chose to test for the genetic mutation, while one decided not to. Although the news that one daughter tested positive for the genetic mutation threw the whole family into deep sorrow, this was transient, and the family managed to support each other, arrange their lives, and plan for the future. Therefore, if the attending physician and genetic counselor can disclose the bad news through good communication and subsequently offer good social support, we hope that people with such genetic mutations will have an opportunity to plan for their future. Early diagnosis can empower patients and their carers to make important decisions about future treatment, care, and life in general (Derksen et al. 2006; Joosten-Weyn Banningh et al. 2008) and have an opportunity to plan how to spend the rest of their lives, how to organize their finances, and when to stop working (Dempsey 2013).

Participate in Clinical Research, Contribute to Knowledge, and Help Future Generations

Although treatment of AD is still symptomatic at present with cognitive enhancers, significant knowledge has been obtained through basic science and clinical research. In the past two decades, many drug trials have failed, including those targeted at Aβ (Giacobini and Gold 2013; Vellas et al. 2013) and those at the mild to moderate stage of AD (Joosten-Weyn Banningh et al. 2008). This may be due to selection of subjects at the later stage of the disease. Even if the Aβ aggregation has been eradicated, the substantial neuronal network dysfunction and loss may become irreversible, leading to permanent and progressive cognitive decline. If intervention is introduced at an earlier stage of the disease, the results of clinical trials may potentially be promising. Hence, if people with pre-dementia AD (either genetic or sporadic) come forward to get diagnosed early and take part in clinical research, this can definitely lead to better understanding of this disease and further progress in the research of this disease which can benefit both themselves and future generations including their family members.

Regarding mental capacity to make an informed consent, participants at the pre-dementia stage of AD will have full mental capacity compared to participants in the later stages of the disease. They would be in a better position to protect their autonomy, understand and weigh the pros and cons of an early diagnosis, and express their opinion about what risk is acceptable in the informed consent. Other than medical examination, investigations, and medical counseling which are covered by research grants, participation in such clinical trials may also enhance their self-confidence, self-worth, and the perceived society value (Albert et al. 1997).

The Disadvantages of Knowing the Diagnosis of AD in Pre-dementia Stage

After going through the advantages of making an early diagnosis of pre-dementia AD, it is also important to know that there are various disadvantages as well. So what are the disadvantages of knowing diagnosis of pre-dementia AD early?

Risks of False-Positive or False-Negative Diagnosis

This is always a challenge to all physicians when making a diagnosis, and pre-dementia stage of AD is no exception. As patients in the pre-dementia stage of AD have mild or no symptoms, the confirmation of diagnosis is largely dependent on biomarkers. In the recent decade, there are great advancements in the field of dementia biomarkers for amyloid and tau pathology. From early CSF $A\beta_{1-42}$ (Roher et al. 1993) to recent tau-PET imaging (Scholl et al. 2016), more biomarkers for Alzheimer's pathology are now available. However, there are some uncertainties regarding the interpretation of some of these biomarkers (Olsson et al. 2016; Wu et al. 2011; Lingler and Klunk 2013). Both sensitivity and specificity of these biomarkers need to be improved to minimize making false-positive or false-negative diagnoses. People with AD pathology diagnosed solely using biomarkers (preclinical AD) may not necessarily progress into clinical AD, while people who do not have the typical AD pathologies in biomarker testings may later develop into AD (Olsson et al. 2016). The correlation between biomarkers and the degree of cognitive impairment is not straightforward – some people function well despite having the typical plaques and tangles in their brains.

There is still uncertainty about a diagnosis based on biomarkers without full validation (Frisoni and Hansson 2016). Therefore, strict quality control for the use of these biomarkers is extremely critical, and public understanding of the probabilistic versus deterministic nature of biomarkers needs further improvement.

Possible Negative Emotional Effects on the Individuals and Their Families

This is especially relevant to asymptomatic people with positive family history of genetic mutations for ADAD. As previously discussed, the risk of developing symptomatic AD in subjects with autosomal dominant genetic mutations is almost 100% (Bateman et al. 2011). Without proper genetic counseling prior to testing, the diagnosis of having the genetic mutation can make one anxious, depressed, and possibly suicidal. This needs to be considered seriously as early diagnosis of a genetic disease at an asymptomatic stage can induce psychological stress. For example, preclinical and early diagnosis of Huntington's disease (HD) is associated with more suicidal behavior (Bird 1999). A survey of random participants in five

different European countries found that approximately two-thirds of respondents would like to know whether they would get AD before they had symptoms (2015). In the REVEAL study, participants who exhibited a high degree of emotional stress before undergoing genetic testing for carrying the *APOEε4* allele were more likely to have negative emotion after disclosure (Green et al. 2009). However, further investigation showed that attitudes of people toward early diagnosis of AD may vary with time. The accuracy of the tests, availability of effective treatment, and anonymity of results can all influence one's decision of going for early diagnosis (Huang et al. 2014). One way to reduce potential stress is to provide continuous counseling throughout the study or through social forums where open discussions can take place (Billings and Moos 1985). Public understanding of AD needs to be improved with public forums, and the disclosure of the diagnosis should be conducted by staff with specialty and skills, maybe in some specific procedure (Lingler and Klunk 2013; Kim et al. 2015; Roberts et al. 2013). Gauthier (Gauthier et al. 2013) and Pepersack (2008) propose a framework for diagnostic disclosure to reduce practice variation and improve average quality of care: before disclosure, determining the willingness of patients and their family members on the diagnosis, identifying the coping style of and the psychological profile of the patient and his or her entourage, and making an appointment to convey the diagnosis and related information. The disclosure phase includes establishing what the patient and his or her family want to know about AD using appropriate words. The diagnosis should be directed first and foremost to the patient, with the proviso that should the disease be in its initial stages, the patient's family should not be informed of the diagnosis without the patient's consent; after the disclosure, ensure that the patient understands the information presented, and provide contact information for psycho-education programs and scheduling of a follow-up meeting.

Social Stigma of the Disease

The social stigma of this disease is another potential issue which may affect persons at the pre-dementia stage of the disease, even when they have no symptoms, with almost normal behavior and social function. Worries about loss of or failure to obtain social and economic benefits such as employment and insurance may discourage people from seeking medical consult early, even though they may wish to know their diagnosis early or participate in a prevention trial. This may be the foremost ethical obstacle to be overcome, which involves social justice in terms of opportunities, insurance, and rights within a society. Furthermore, providing a label to the individual may elicit behavior that is perceived as belonging to this label, which is illustrated in a study where *APOEε4* carriers who were told had poorer performances on objective verbal memory tests compared to their nondisclosure counterparts who carried the same alleles (Lineweaver et al. 2014). As we educate the society and introduce laws, the benefits of these people will be protected and safeguarded.

Costs of Diagnostic Work-Up

Tests for early diagnosis of AD are not used in routine clinical practice and are not covered by insurance company (Frisoni and Hansson 2016). The cost of these tests will be high, especially for brain magnetic resonance imaging (MRI) and PET scan, and the one-off cost for a dementia screening may be up to US$5000 (£3,200;€3,800) (Le Couteur et al. 2013). Costs of diagnostic work-up will definitely be increased even when people use their own money without reimbursement (Frisoni and Hansson 2016). The quest for sustainability in health care, in which health-care expenditures will need to be restricted, gives added urgency to the ethical issue of justice. Besides this economic cost, the diagnostic processes can be distressing, alarming, and stigmatizing as well (Manthorpe et al. 2013).

Additional Workload for Memory Clinics and Cognitive Research Centers

Screening for preclinical AD would mean additional workload for memory clinics. In positive subjects, the educational and counseling burden will be tremendous, given the current standards for genetic counseling for AD genetic tests and similar counseling needs for biomarker test results (Goldman 2012).

Conclusions

Due to high prevalence of AD and the lack of disease-modifying drugs at present, health care in AD is facing a great challenge. With the availability of biomarkers for the pathology of AD, the diagnosis of AD at the pre-dementia stage is now possible. However, it is a dilemma for patients and physicians whether to know this diagnosis early. There are both benefits and risks. It is the duty of the physicians to recommend whether AD biomarkers are needed as part of the clinical evaluation due to the complexity of the dementia syndrome, and the patient has to decide whether or not to proceed with these tests. Once people decide to be diagnosed early, special communication skills for disclosure are needed followed by education and support.

Acknowledgments XL is supported by a fellowship program from Chongqing Medical University and the Medical Research Fund by Chongqing Municipal Health Bureau 20141007 (China).

KN is supported by the National Medical Research Council, Research Training Fellowship Grant (Singapore).

MB is funded by the Yantai Yuhuangding Hospital (China).

SG and PRN are funded by the Canadian Institutes for Health Research.

References

2015 Alzheimer's disease facts and figures. Alzheimers Dement. 7;11(3):332–84.
2015 [cited http://www.alzheimer-europe.org/Research/Value-of-Knowing].
Albert SM, Sano M, Marder K, Jacobs DM, Brandt J, Albert M et al (1997) Participation in clinical trials and long-term outcomes in Alzheimer's disease. Neurology 49(1):38–43
Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3):270–279
Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM et al (2011) Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res Ther 3(1):1
Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC et al (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367(9):795–804
Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 11(6):718–726
Billings AG, Moos RH (1985) Life stressors and social resources affect posttreatment outcomes among depressed patients. J Abnorm Psychol 94(2):140–153
Bird TD (1999) Outrageous fortune: the risk of suicide in genetic testing for Huntington disease. Am J Hum Genet 64(5):1289–1292
Blennow K, Hampel H (2003) CSF markers for incipient Alzheimer's disease. Lancet Neurol 2(10):605–613
Boustani M, Peterson B, Hanson L, Harris R, Lohr KN (2003) Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 138(11):927–937
Brunet MD, McCartney M, Heath I, Tomlinson J, Gordon P, Cosgrove J et al (2012) There is no evidence base for proposed dementia screening. BMJ (Clin Res ed) 345:e8588
Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC (2008) Health behavior changes after genetic risk assessment for Alzheimer disease: the REVEAL study. Alzheimer Dis Assoc Disord 22(1):94–97
Coast J, Kinghorn P, Mitchell P (2015) The development of capability measures in health economics: opportunities, challenges and progress. Patient Patient – Patient-Cent Outcome Res 8(2):119–126
Dempsey D (2013) Advance care planning for people with dementia: benefits and challenges. Int J Palliat Nurs 19(5):227–234
Derksen E, Vernooij-Dassen M, Gillissen F, Olde Rikkert M, Scheltens P (2006) Impact of diagnostic disclosure in dementia on patients and carers: qualitative case series analysis. Aging Ment Health 10(5):525–531
Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J et al (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 6(8):734–746
Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S et al (2016) Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. JALZ Alzheimers Dement: J Alzheimers Assoc 12(3):292–323
Dunn LB, Alici Y, Roberts LW (2015) Ethical challenges in the treatment of cognitive impairment in aging. Curr Behav Neurosci Rep Current Behav Neurosci Rep 2(4):226–233
Fields LM, Calvert JD (2015) Informed consent procedures with cognitively impaired patients: a review of ethics and best practices. PCN Psychiatry Clin Neurosci 69(8):462–471
Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A et al (2008) PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 29(10):1456–1465

Frisoni GB, Hansson O (2016) Clinical validity of CSF biomarkers for Alzheimer's disease: necessary indeed, but sufficient? Lancet Neurol 15(7):650–651
Garibaldi P, Martins JO, van Ours JC (2010) Ageing, health, and productivity: the economics of increased life expectancy. OUP Oxford, Oxford
Gauthier S, Leuzy A, Racine E, Rosa-Neto P (2013) Diagnosis and management of Alzheimer's disease: past, present and future ethical issues. Prog Neurobiol 110:102–113
Giacobini E, Gold G (2013) Alzheimer disease therapy – moving from amyloid-beta to tau. Nat Rev Neurol 9(12):677–686
Goldman JS (2012) New approaches to genetic counseling and testing for Alzheimer's disease and frontotemporal degeneration. Curr Neurol Neurosci Rep 12(5):502–510
Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T et al (2009) Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med 361(3):245–254
Hauser PS, Ryan RO (2013) Impact of apolipoprotein E on Alzheimer's disease. Curr Alzheimer Res 10(8):809–817
Head D, Bugg JM, Goate AM, Fagan AM, Mintun MA, Benzinger T et al (2012) Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch Neurol 69(5):636–643
Hooper M, Grill JD, Rodriguez-Agudelo Y, Medina LD, Fox M, Alvarez-Retuerto AI et al (2013) The impact of the availability of prevention studies on the desire to undergo predictive testing in persons at risk for autosomal dominant Alzheimer's disease. Contemp Clin Trials 36(1):256–262
http://www.alz.org/advocacy/global-efforts.asp [Internet].
Huang M-Y, Huston SA, Perri M (2014) Consumer preferences for the predictive genetic test for Alzheimer disease. J Genet Counsel J Genet Couns 23(2):172–178
International AsD (2013) Policy brief for heads of government: the global impact of dementia 2013–2050. The King's Fund, London
Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P et al (2013) Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement 9(1):e-1-16
Jongsma KR, van de Vathorst S (2015) Beyond competence: advance directives in dementia research. Monash Bioeth Rev 33:2–3
Joosten-Weyn Banningh L, Vernooij-Dassen M, Rikkert MO, Teunisse JP (2008) Mild cognitive impairment: coping with an uncertain label. Int J Geriatr Psychiatry 23(2):148–154
Kim SY, Karlawish J, Berkman BE (2015) Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. Neurology 84(14):1488–1494
Knopman DS, Jack CR Jr, Wiste HJ, Weigand SD, Vemuri P, Lowe V et al (2012) Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. Neurology 78(20):1576–1582
Le Couteur DG, Doust J, Creasey H, Brayne C (2013) Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis. BMJ (Clin Res ed) 347:f5125
Levey A, Lah J, Goldstein F, Steenland K, Bliwise D (2006) Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease. Clin Ther 28(7):991–1001
Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM et al (2010) Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol 68(3): 311–318
Lim YY, Villemagne VL, Pietrzak RH, Ames D, Ellis KA, Harrington K et al (2015) APOE epsilon4 moderates amyloid-related memory decline in preclinical Alzheimer's disease. Neurobiol Aging 36(3):1239–1244
Lineweaver TT, Bondi MW, Galasko D, Salmon DP (2014) Effect of knowledge of APOE genotype on subjective and objective memory performance in healthy older adults. Am J Psychiatry 171 (2):201–208

Lingler JH, Klunk WE (2013) Disclosure of amyloid imaging results to research participants: has the time come? Alzheimers Dement 9(6):741–4.e2

Lopponen M, Raiha I, Isoaho R, Vahlberg T, Kivela SL (2003) Diagnosing cognitive impairment and dementia in primary health care – a more active approach is needed. Age Ageing 32(6):606–612

Manthorpe J, Samsi K, Campbell S, Abley C, Keady J, Bond J et al (2013) From forgetfulness to dementia: clinical and commissioning implications of diagnostic experiences. Br J Gen Pract: J R Coll Gen Pract 63(606):e69–e75

Marcos G, Santabarbara J, Lopez-Anton R, De-la-Camara C, Gracia-Garcia P, Lobo E et al (2016) Conversion to dementia in mild cognitive impairment diagnosed with DSM-5 criteria and with Petersen's criteria. Acta Psychiatr Scand 133(5):378–385

Mormino EC, Betensky RA, Hedden T, Schultz AP, Ward A, Huijbers W et al (2014) Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease. Neurology 82(20):1760–1767

Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R et al (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet (London, England) 385(9984):2255–2263

OECD. Unleashing the power of big data for Alzheimer's disease and dementia research: main points of the OECD expert consultation on unlocking global collaboration to accelerate Innovation for Alzheimer's disease and dementia. No 233 [Internet]. 2014.

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M et al (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 15(7):673–684

Pepersack T (2008) Disclosing a diagnosis of Alzheimer's disease. Rev Med Brux 29(2):89–93

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 9(1):63–75.e2

Reiman EM, Quiroz YT, Fleisher AS, Chen K, Velez-Pardo C, Jimenez-Del-Rio M et al (2012) Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. Lancet Neurol 11(12):1048–1056

Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL et al (2010) Cognition, reserve, and amyloid deposition in normal aging. Ann Neurol 67(3):353–364

Riley JC (2001) Rising life expectancy: a global history. Cambridge University Press, Cambridge

Roberts JS, Dunn LB, Rabinovici GD (2013) Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues. Neurodegener Dis Manag 3(3):219–229

Roe CM, Fagan AM, Grant EA, Marcus DS, Benzinger TL, Mintun MA et al (2011) Cerebrospinal fluid biomarkers, education, brain volume, and future cognition. Arch Neurol 68(9):1145–1151

Roher AE, Palmer KC, Yurewicz EC, Ball MJ, Greenberg BD (1993) Morphological and biochemical analyses of amyloid plaque core proteins purified from Alzheimer disease brain tissue. J Neurochem 61(5):1916–1926

Scholl M, Lockhart SN, Schonhaut DR, O'Neil JP, Janabi M, Ossenkoppele R et al (2016) PET Imaging of Tau deposition in the aging human brain. Neuron 89(5):971–982

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM et al (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. Alzheimers Dement 7(3):280–292

Steinbart EJ, Smith CO, Poorkaj P, Bird TD (2001) Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. Arch Neurol 58(11):1828–1831

Valcour VG, Masaki KH, Curb JD, Blanchette PL (2000) The detection of dementia in the primary care setting. Arch Intern Med 160(19):2964–2968

van der Steen JT, Radbruch L, de Boer ME, Jünger S, Hughes JC, Larkin P et al (2016) Achieving consensus and controversy around applicability of palliative care to dementia. Int Psychogeriatr/IPA 28(1):133–145

Vellas B, Carrillo MC, Sampaio C, Brashear HR, Siemers E, Hampel H et al (2013) Designing drug trials for Alzheimer's disease: what we have learned from the release of the phase III antibody trials: a report from the EU/US/CTAD task force. Alzheimers Dement 9(4):438–444

Vernarelli JA, Roberts JS, Hiraki S, Chen CA, Cupples LA, Green RC (2010) Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. Am J Clin Nutr 91(5):1402–1407

Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O et al (2013) Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 12(4):357–367

Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA et al (2013) Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol 12(10):957–965

Wimo A, Jonsson L, Bond J, Prince M, Winblad B (2013) The worldwide economic impact of dementia 2010. Alzheimers Dement 9(1):1–11.e3

Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H et al (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 15(5):455–532

Wirth M, Haase CM, Villeneuve S, Vogel J, Jagust WJ (2014) Neuroprotective pathways: lifestyle activity, brain pathology, and cognition in cognitively normal older adults. Neurobiol Aging 35(8):1873–1882

Wu L, Rosa-Neto P, Gauthier S (2011) Use of biomarkers in clinical trials of Alzheimer disease: from concept to application. Mol Diagn Ther 15(6):313–325

Delirium

8

Walter J. Kilpatrick III and Benjamin Liptzin

Abstract

Currently, the elderly remain at high risk for the development of delirium and the significant morbidity and mortality associated with it in all care settings. While significant advancements have been made through research and collaboration among clinicians in diverse specialty fields, some controversies still remain. The initial literature search performed for the chapter revealed over 3000 articles published from January 1990 to May 2016. The initial list was refined to around 200 original research articles for review. This chapter summarizes the controversies, collaborations, and recent advancements in the management of delirium in the elderly.

Keywords

Delirium • Management • Prevention • Treatment • Elderly • ICU

Contents

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_9

Introduction

Delirium is a clinical syndrome characterized by an acute disturbance in attention, awareness, and cognition. Rates of delirium are highest among hospitalized older patients, making the geriatric population especially vulnerable to delirium sequelae, including loss of independence, increased morbidity and mortality, and increased health-care costs (Inouye 2006). An argument has been made for utilizing the term "acute brain failure" to capture the acute severity of the syndrome and the devastating outcomes associated with it (Maldonado 2015).

Delirium affects up to 50% of hospitalized seniors and has been shown to be preventable in 30–40% of cases. In general medical and geriatric wards, the overall occurrence rates of delirium range from 29% to 64% of patients. Delirium is present in 8–17% of all seniors on presentation to an emergency department and 40% of nursing home residents. In addition, delirium is associated with increased mortality rates spanning all nonsurgical patient populations, and among surgical patients, cognitive impairment is common and symptoms can persist up to 1 year after the procedure (Inouye et al. 2014). Given the heavy clinical and economic burden of this syndrome, delirium has been the focus of clinical research in the form of both pharmacological and nonpharmacological prevention and treatment studies. Recent advances have been made in prevention strategies, and many quality improvement initiatives and multidisciplinary approaches to the management of delirium have emerged.

Nosology: Revised DSM-V Criteria

The revised *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V), characterizes delirium as a neurocognitive disorder with disturbance in attention, awareness, and cognition. The DSM-IV previously referred to this as "disturbance in consciousness." In addition, specifiers have been added to further characterize delirium. The specifiers include the motoric subtypes of delirium including hyperactive, hypoactive, and mixed level of activity. Per the DSM-V, the hyperactive subtype is specified when there is a hyperactive level of psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to cooperate with medical care. The hypoactive subtype is specified when there is a hypoactive level of psychomotor activity that may be accompanied by sluggishness

and lethargy that approaches stupor. Finally, the mixed level of activity subtype is specified when there is a normal level of psychomotor activity even though attention and awareness are disturbed and also when activity level rapidly fluctuates. In addition, there are now specifiers for the duration of the delirious episode including acute (lasting a few hours or days) and persistent (lasting weeks or months) (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) (American Psychiatric Association 2013). The addition of these specifiers helps to better characterize both the duration and psychomotor activity of the delirious episode.

Delirium Subtypes

Hyperactive, Mixed, and Hypoactive Delirium

Previous work regarding the characterization of delirium subtypes was conducted utilizing an empirical study method examining elderly patients admitted to a general hospital. The *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition* (DSM-III), was used to detect symptoms of delirium. Of the patients meeting DSM-III criteria for delirium, 15% were rated as hyperactive type, 52% as mixed type, 19% as hypoactive type, and 14% as neither. A novel instrument called the Delirium Symptom Interview (DSI) was utilized to stratify symptoms of hyperactive and hypoactive delirium. Hyperactive symptoms were identified as hypervigilance, restlessness, fast or loud speech, irritability, combativeness, impatience, swearing, singing, laughing, uncooperativeness, euphoria, anger, wandering, easy startling, fast motor response, distractibility, tangentiality, nightmares, and persistent thoughts. Conversely, hypoactive delirium symptoms consisted of unawareness, decreased alertness, sparse or slow speech, lethargy, slowed movements, staring, and apathy (Liptzin and Levkoff 1992). Similarly, a longitudinal study of motoric subtypes of delirium was conducted utilizing the Delirium Motor Subtype Scale (DMSS), Delirium Rating Scale-Revised-98 (DRS-R98), and Cognitive Test for Delirium (CTD). The authors found that across all assessments, the occurrence of the hyperactive delirium subtype was 15%, mixed was 26%, hypoactive was 35%, and no subtype was 24% (Meagher et al. 2012). A review article including 38 studies was conducted in various clinical settings aimed at examining prevalence and correlations of hypoactive delirium. The prevalence of hypoactive delirium varied considerably among clinical settings, but hypoactive delirium was more common in critically ill patients and less common in patients examined by consultation-liaison psychiatric services and in mixed patient populations. C-L psychiatrists are more likely to be called when a patient is agitated and uncooperative. The presence of hypoactive delirium in ICU patients was associated with higher short- and long-term mortality and other adverse outcomes (Peritogiannis et al. 2015) perhaps because hypoactive patients are too sick to show hyperactive symptoms.

The typical antipsychotic medication, haloperidol, has been used as the primary agent of choice for the treatment of hyperactive- and mixed-type delirium.

The American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) published guidelines recommending haloperidol as the preferred agent for the treatment of delirium in critically ill patients. They also recommended that patients should be monitored for electrocardiographic changes such as arrhythmias and QTc interval prolongation when utilizing haloperidol (Jacobi et al. 2002). Consensus among clinicians regarding pharmacological treatment strategies for hypoactive delirium has been elusive. Methylphenidate has been shown to improve cognitive functioning in patients with advanced cancer and hypoactive delirium (Gagnon et al. 2005). Aripiprazole has also been examined and been shown to be a viable treatment option for patients with hypoactive delirium (Alao and Moskowitz 2006; Boettger and Breitbart 2011; Straker et al. 2006). Ramelteon demonstrated improvement in a patient with hypoactive delirium in a single case report (Miura et al. 2015). In addition, quetiapine was shown to reduce the duration of hypoactive delirium in critically ill adults (Michaud et al. 2015). Finally, low doses of haloperidol or risperidone have been recommended for the treatment of hypoactive delirium (Maldonado 2015).

Emergence Delirium

Emergence delirium is an acute confusional state lasting minutes to hours which occurs during or immediately after emergence from anesthesia (Gross and Stern 2014). A prospective, observational cohort study assessed adult patients emerging from general anesthesia in the operating room to determine incidence, predictors, and consequences of emergence delirium. The authors found that 3.7% of the patients showed signs of emergence delirium when emerging from anesthesia which declined to 1.3% once reevaluated in the postanesthesia care unit. They also determined that male sex, volatile anesthesia, and endotracheal tubes were factors significantly related to emergence delirium. Finally, the most notable clinical consequence was the need for additional staff to be called to maintain safety for agitation (Munk et al. 2016). Dexmedetomidine appears to be emerging as a potential effective treatment option. A case report described the successful treatment of emergence delirium in a 71-year-old post-ECT patient with a dexmedetomidine infusion (Cohen and Stewart 2013). Similarly, a systematic review and meta-analysis of 12 studies found that intravenous alpha-2-agonists greatly reduced the risk of emergence delirium in children after general anesthesia (Pickard et al. 2014). Further studies in adults are required to determine effective treatment strategies.

Delirious Mania

Delirious mania is a neuropsychiatric syndrome characterized by the rapid onset of delirium and mania co-occurring at the same time (Jacobowski et al. 2013). Fink and Taylor 2003, wrote “the presence of the complex syndrome of mania and delirium, with or without obvious catatonia, justifies the syndromal diagnosis of delirious

mania." Delirious mania may represent up to 15% of all acute mania cases (Jacobowski et al. 2013). The syndrome itself is severe, under-recognized, and potentially life threatening (Lee et al. 2012). It is often difficult to distinguish from excited catatonia (Detweiler et al. 2009). Symptoms tend to have an acute onset, rapid progression (hours to days), and fluctuating course. The patient can experience symptoms of both delirium (disorientation, fluctuating sensorium, severe cognitive dysfunction, altered consciousness) and mania (intense excitement, grandiosity, irritability, insomnia, psychomotor agitation, disorganization, hypersexuality), and neuropsychiatric complications can include psychosis and/or catatonia (Jacobowski et al. 2013).

Fink and Taylor described the features of delirious mania as: "The outstanding feature of a delirious mania is a nightmarish, dreamlike, derealization within an altered sensorium. The change in perception is profound, frightening the subject and leading to restlessness, agitation, and thrashing about. Patients harm themselves and others. Stereotypy, grimacing, posturing, echolalia, and echopraxia are common. Negativism and automatic obedience are almost always present. Patients sleep poorly, are unable to recall their recent experiences, or the names of objects or numbers given to them, and are disoriented. They confabulate, often with fantastic stories. The onset develops rapidly, within a few hours or a few days. Fever, rapid heart rate, elevated blood pressure, and rapid breathing are prominent. Patients hide in small spaces, close the doors and blinds on windows, and remove clothes and run nude from their home. Garrulousness, flights of ideas, and rambling speech alternate with mutism" (Fink and Taylor 2003).

The similarities to catatonia are clear. As such, nonmalignant and malignant delirious mania have been described with malignant delirious mania presenting with delirium, mania, and autonomic instability (tachycardia and hypertension) or hyperthermia, likened to a malignant catatonia. For nonmalignant delirious mania, benzodiazepines and/or ECT can be initiated with mood stabilizers, and, if necessary, atypical antipsychotics can be added adjunctively. Typical antipsychotics should be avoided as they can precipitate the malignant subtype, NMS, or malignant catatonia. If malignant delirious mania ensues, intensive support is warranted, and benzodiazepines and/or ECT should be immediately initiated with discontinuation of any antipsychotic medications. Delirious mania can quickly become life threatening. Early recognition is paramount as high-dose lorazepam and/or ECT are highly effective, first-line treatments which can significantly reduce morbidity and mortality (Jacobowski et al. 2013; Detweiler et al. 2009; Lee et al. 2012; Fink and Taylor 2003).

Subsyndromal Delirium

Subsyndromal delirium (SSD) has been described in the literature as a delirium subtype in which the presence of certain symptoms of delirium exists, but the patient does not meet full criteria for delirium (Cole et al. 2013; Meagher et al. 2014). Studies have been conducted to attempt to better define the characteristics of this

subtype. A systematic review of 12 studies focusing on older patients determined that the combined incidence of SSD was 13% (95% CI, 6–23%) and combined prevalence was 23% (95% CI, 9–42%) and that episodes were often recurrent. The authors defined SSD as the presence of one or more symptoms of delirium, not meeting criteria for delirium and not progressing to delirium. They identified four statistically significant risk factors including presence of dementia, admitted from an institution, increasing severity of medical illness, and vision impairment. Outcomes including rates of death and institutionalization were significantly worse for groups with SSD (Cole et al. 2013). A point prevalence study conducted of adult patients in a general hospital setting found that SSD was found in 7.7% when utilizing a DRS-R98 score of 7–11 and 13.2% when utilizing a two fourth Confusion Assessment Method (CAM) criteria score. The authors also reported that SSD with inattention had greater disturbance with multiple delirium symptoms than subjects without. They argued that inattention should be central to SSD definitions (Meagher et al. 2014). A prospective cohort study of patients 65 years or older undergoing major noncardiac surgery was conducted to determine SSD's prognostic significance. SSD was defined as the presence of at least one tenth symptoms of delirium defined by CAM criteria. The authors found that a patient with one SSD feature was 1.07 times more likely to have delirium the following day (95% CI: 0.42–2.53), 3.32 times more likely with two SSD features (95% CI: 1.42–7.57), and 8.37 times more likely if greater than two SSD features were present (95% CI: 4.98–14.53). They also reported a significant relationship between the number of SSD features present and increased length of hospital stay and worsened functional status at 1 month after surgery (Shim et al. 2015). Treatment studies have yielded mixed results. Administration of low-dose oral risperidone (0.5 mg every 12 h) to elderly patients who experienced SSD after on-pump cardiac surgery was associated with significantly lower incidence of delirium compared to controls (Hakim et al. 2012). Conversely, low-dose, scheduled, intravenous haloperidol (1 mg every 6 h), initiated early in the ICU stay, did not prevent delirium and had little therapeutic advantage in mechanically ventilated, critically ill adults with SSD (Al-Qadheeb et al. 2016). Further research is warranted to better characterize this syndrome and develop effective prevention and treatment strategies.

Imaging and Delirium

Recently, several studies have examined the relationship between brain imaging findings and delirium. A retrospective chart review was conducted to examine if there was an association between delirium and cerebral white-matter hyperintensities (WMH) on magnetic resonance imaging (MRI) in patients who underwent cardiac surgery. The authors reported that the prevalence of severe WMH (Fazekas score = 3) was significantly higher in patients with delirium, and this suggested that white-matter abnormality was an important risk factor for the development of delirium after cardiac surgery (Hatano et al. 2013). A retrospective medical record review in a large academic center was conducted to determine the diagnostic yield of head computed

tomography when evaluating a hospitalized medical patient with delirium. The authors found that the diagnostic yield was low and that head imaging was unnecessary in the majority of cases of delirium (Theisen-Toupal et al. 2014). A prospective cohort study utilized perioperative brain magnetic resonance imaging (MRI) to determine the relationship between MRI findings and postoperative delirium in patients undergoing elective off-pump coronary artery bypass grafting (OPCAB). The authors found that magnetic resonance imaging findings of new cerebral ischemic lesions, carotid stenosis, and deep subcortical white-matter hyperintensity correlated significantly with postoperative delirium in patients who had undergone OPCAB surgery (Omiya et al. 2015). A prospective cohort study was conducted to determine the feasibility of functional magnetic resonance imaging (fMRI) assessments in survivors of critical illness and analyze potential associations between delirium and brain activation patterns observed during a working memory task (N-back) at hospital discharge and 3-month follow-up. The authors reported that no association was observed between delirium duration in the hospital and brain region activity in any brain region at discharge or at 3 months after adjusting for relevant covariates (Jackson et al. 2015).

A prospective cohort study investigated the association of magnetic resonance imaging (MRI)-derived quantitative measures of white-matter damage, global brain, and hippocampal volume with the incidence and severity of delirium in subjects aged 70 years or older who were undergoing elective surgery. The authors found no statistically significant differences in white-matter hyperintensities, whole brain, or hippocampal volume between subjects with and without delirium (Cavallari et al. 2015). A prospective observational trial was conducted to examine the association between brain MRI characteristics potentially associated with delirium vulnerability and the development of postoperative delirium in patients who had brain MRI after cardiac surgery. The authors found that increased brain ventricular size was independently associated with delirium after cardiac surgery and hypothesized that cerebral atrophy may contribute to increased vulnerability for postoperative delirium (Brown et al. 2015). A prospective study in a university hospital of subjects undergoing elective cardiac surgery found that magnetic resonance imaging revealed a statistically significant reduction in the gray-matter volume of patients with delirium in the defined gyri of the temporal and limbic lobes. The authors concluded that decreased volume of gray matter could be associated with the vulnerability to delirium after surgery (Shioiri et al. 2016). Finally, a subsample of an ongoing prospective cohort study of older adults undergoing elective major noncardiac surgery revealed that presurgical diffusion tensor imaging (DTI) abnormalities of the cerebellum, cingulum, corpus callosum, internal capsule, thalamus, basal forebrain, and occipital, parietal, and temporal lobes, including the hippocampus, were associated with delirium incidence and severity. The authors concluded that the finding of an association of premorbid DTI abnormalities with delirium incidence and severity supports the hypothesis that structural dysconnectivity and microstructural tissue changes can predispose to delirium under the stress of surgery (Cavallari et al. 2016). It is likely that further imaging studies exploring the relationship of structural changes in the brain to incidence, prevalence, and severity of delirium will

continue as technology in this area continues to develop. It is unclear whether identification of risk on imaging studies would change the management of patients.

Advances in Delirium Management

Over the past decade, a number of trials aimed to advance our approach to the management of delirium have focused on both pharmacological and non-pharmacological prevention and treatment strategies. The majority of clinical trials reviewed here focus on these prevention strategies; however, some studies focusing on treatment have been included for completeness. A significant number of screening tools for the detection of delirium have also emerged and been utilized in these studies. The use of varied tools to detect delirium has not been found to bias results across studies.

Melatoninergic Agents: Melatonin and Ramelteon

The use of melatonin and its synthetic analog, ramelteon, has garnered recent interest as potential pharmacological agents that could be utilized in the prevention or treatment of delirium, particularly in the elderly in acute care settings. Melatonin or diurnal dysregulation has been identified as a potential hypothesis regarding the neuropathogenesis of delirium and has been extensively reviewed (Maldonado 2013).

A randomized controlled double-blind study examining the role of perioperative melatonin in both prevention and treatment of delirium was performed in patients aged >65 undergoing hip arthroplasty under spinal anesthesia. The patients were randomly assigned to four groups including control, melatonin (5 mg), midazolam (7.5 mg), and clonidine (100 ug). The intervention groups received their respective medications at bedtime the night before their procedure and 90 min prior to their procedure at the above doses. Patient's receiving melatonin demonstrated a statistically significant decrease in the percentage of postoperative delirium (32.65% control group vs. 9.43% melatonin group; ($P = 0.003$) vs. 44% midazolam group vs. 37.25% clonidine group). In addition, of the patients who did develop postoperative delirium in the study 58.06% experienced resolution of delirium symptoms after treatment with melatonin. The author concluded that preoperative administration of melatonin was successful in decreasing postoperative delirium and was also effective in treating postoperative delirium when given for three consecutive postoperative nights (Sultan 2010). Similarly, a randomized, double-blind, placebo-controlled study was performed to evaluate the efficacy of low-dose exogenous melatonin in decreasing delirium in patients aged 65 years or older who were admitted to a medical unit in a tertiary care hospital. The patients were randomized to receive either placebo or melatonin (0.5 mg) nightly for 14 consecutive days or until discharge. The melatonin group saw significantly lower percentage rates of delirium (12.0%) versus the placebo group (31.0%; $P = 0.014$). In addition, after

excluding patients who were delirious at enrolment, melatonin was still associated with a lower risk of delirium (3.6% in the melatonin group vs. 19.2% in the placebo group, $P < 0.02$). The authors concluded that administration of low-dose melatonin nightly to elderly patients in acute care settings may play a protective role against the development of delirium (Al-Aama et al. 2011).

A multicenter, double-blind, randomized controlled trial examined the effect of melatonin on the incidence of delirium among patients aged 65 or older with emergent hip fractures in one academic and two nonacademic hospitals. The patients in the trial received either melatonin 3 mg or placebo in the evening for five consecutive days, starting within 24 h of admission. However, in this trial, there was no difference in the incidence of delirium in the melatonin group (29.6%) versus the placebo group (25.5%; $P = 0.4$). The authors also followed the two groups for 3 months following the primary trial and found no differences in cognitive outcomes, functional outcomes, or mortality rates between the two treatment groups (de Jonghe et al. 2014). A multicenter, rater-blinded, randomized placebo-controlled trial examined the effect of ramelteon, a synthetic analog of melatonin, on the incidence of delirium among patients aged 65 or older admitted to intensive care units and regular acute wards of four university hospitals and one general hospital. The patients in the trial received either ramelteon 8 mg or placebo nightly for 7 days. The incidence of delirium in the ramelteon group (3%) was significantly less than the placebo group (32%; $P = 0.003$). Thus, ramelteon was associated with a lower risk of delirium, with a relative risk of 0.09 (95% CI, 0.01–0.69). The authors concluded that nightly ramelteon administration to elderly patients admitted to acute care settings may provide protection against the development of delirium (Hatta et al. 2014).

A prospective single-center observational nonrandomized study was performed to determine if prophylactic treatment with melatonin could reduce the incidence of postoperative delirium in elective or urgent cardiac surgery patients. The treatment group received melatonin 5 mg the evening before the operation, and the treatment was continued until postoperative day 3. The authors found that the incidence of delirium was 8.4% in the melatonin group versus 20.8% in the control group ($P = 0.001$). They concluded that prophylactic treatment with melatonin decreased the incidence of postoperative delirium after cardiac surgery (Artemiou et al. 2015). A randomized double-blind study involving patients with mean age of 60 examined the effect of melatonin versus oxazepam on post-cardiac surgery sleep disorder. The patients were randomized to receive either melatonin 3 mg or oxazepam 10 mg 1 h before sleep time, from 3 days before surgery until the time of discharge. The authors found that patients in the oxazepam group demonstrated significantly higher disturbance in their mean postoperative quality of sleep versus the melatonin group. They did not find a statistically significant difference in the incidence of delirium between the two groups (Dianatkhah et al. 2015).

A systematic review examining melatonin treatment on circadian rhythm disturbances in dementia found that melatonin improved sundowning and agitated behavior in patients with dementia and argued that melatonin treatments could be effective in patients with delirium (de Jonghe et al. 2010). An editorial commenting on the above studies argued that melatonin and ramelteon prevent delirium in acutely ill

medical, elective surgical, and ICU patients (de Rooij et al. 2014). A meta-analysis of randomized controlled trials examining the role of melatonin for delirium prevention, including the above four RCTs, concluded that melatonin supplementation had a significant preventive effect in decreasing the incidence of delirium in elderly patients that were presented to medical wards but not surgical wards (Chen et al. 2015). A systematic review of pharmacological interventions for preventing delirium in the elderly, including melatonin and ramelteon, found that the above trials suggested a potential role for melatonin in preventing and treating delirium in older adults (Ford and Almeida 2015). A review examining circadian rhythm disruption in the critically ill also examined the above studies and argued for further testing of lighting and melatoninergic interventions in full-scale trials (Oldham et al. 2016). Finally, a recent systematic review was performed of randomized controlled trials to assess the effectiveness of interventions for the prevention of delirium in hospitalized non-intensive care unit patients. The authors concluded that there was no clear evidence to support the effectiveness of melatonin or ramelteon in reducing delirium incidence compared to placebo in hospitalized non-intensive care unit patients (Siddiqi et al. 2016). At this time, further large-scale randomized controlled trials are warranted to assess the effectiveness of melatonin for the prevention or treatment of delirium.

Acetylcholinesterase Inhibitors: Rivastigmine and Donepezil

Acetylcholinesterase inhibitors have also been studied as potential pharmacological agents that could reduce the incidence of delirium. Donepezil and rivastigmine have each been studied in randomized controlled trials examining their potential use for the prevention of delirium.

A retrospective cohort study examined the efficacy of chronic rivastigmine usage in patients with dementia on incidence of delirium. In the study, patients who were treated by a geriatrics consultation service in a general teaching hospital were screened for chronic rivastigmine usage and compared with a randomly selected subgroup of all patients not treated with rivastigmine. 45.5% of subjects in the rivastigmine group developed delirium compared to 88.9% in the control group ($p < 0.05$). The authors concluded that chronic rivastigmine usage may be associated with a lower incidence of delirium in elderly hospitalized patients with dementia (Dautzenberg et al. 2004). A prospective study was conducted to determine if rivastigmine had an effect on delirium in patients with vascular dementia. Patients between the ages of 65–80 who were diagnosed with vascular dementia were included in the study and randomized to receive rivastigmine 6 mg or cardioaspirin. The authors found that 40% of the patients receiving rivastigmine developed delirium versus 62% ($p < 0.001$) in the cardioaspirin treatment group. They concluded that rivastigmine may help in reducing the frequency of delirium episodes in this patient population (Moretti et al. 2004).

A prospective open-label study was conducted to assess the feasibility and safety profile of rivastigmine in elderly patients who developed delirium after a recent

stroke. Patients found to be delirious were treated with orally administered rivastigmine with a total dose between 3 and 12 mg/day. The authors reported there was a considerable decrease in severity and duration of delirium. No major side effects were recorded. They concluded that rivastigmine was safe in stroke patients with delirium, even after rapid titration, and that in the majority of patients the delirium improved after treatment (Oldenbeuving et al. 2008). A double-blind, randomized, placebo-controlled trial was conducted to determine if rivastigmine could reduce the incidence of delirium in elderly patients undergoing elective cardiac surgery. Patients aged 65 years or older undergoing elective cardiac surgery with cardiopulmonary bypass in a university hospital were included in the study. The patients were randomly assigned to receive three doses of rivastigmine 1.5 mg per day or three doses of placebo per day, starting the evening preceding surgery and continuing until postoperative day number six. Delirium developed in 32% of the patients in the rivastigmine group and 30% of the patients in the placebo group. The difference was not statistically significant between the two groups. The authors concluded that this was a negative trial that did not support the short-term prophylactic use of rivastigmine to prevent postoperative delirium in elderly patients who underwent elective cardiac surgery (Gamberini et al. 2009).

A large, double-blind, randomized placebo-controlled trial was initiated to study the effect of rivastigmine on duration of delirium in critically ill patients. Patients, aged 18 years or older, were enrolled from six different intensive care units. They were randomized to receive either placebo or an increasing dose of rivastigmine, as an adjunct to usual care with haloperidol. The authors reported that the data safety and monitoring board recommended that the trial be halted because the percentage of mortality in the rivastigmine group (22%) was higher than in the placebo group (8%; $p = 0.07$). The authors also commented that median duration of delirium was longer in the rivastigmine group (5.0 days) versus the placebo group (3.0 days; $p = 0.06$). They concluded that rivastigmine did not decrease duration of delirium and might have increased mortality. They recommended against the use of rivastigmine to treat delirium in critically ill patients (van Eijk et al. 2010). A double-blind, randomized, placebo-controlled, pilot clinical trial was conducted to study the effect of transdermal rivastigmine on the incidence of postoperative delirium. Patients aged 70 years or older undergoing major surgery were included in the study. Patients received rivastigmine 5-cm^2 transdermal patch or a placebo patch preoperatively. The study was halted because of a warning letter issued by Novartis, the rivastigmine manufacturer, indicating the possibility of increased mortality associated with oral administration of the drug in critically ill patients (van Eijk et al. 2010) as mentioned in the above study. The authors found that 18% of the patients in the rivastigmine group developed delirium versus 23% ($p = 0.075$) in the placebo group. The authors concluded that the difference in incidence of postoperative delirium in the rivastigmine group versus the placebo group was not statistically significant (Zaslavsky et al. 2012).

A double-blind, randomized, placebo-controlled trial was conducted to study the effects of donepezil on the prevention and treatment of postoperative delirium. Patients aged 50 years or older undergoing elective total knee or hip arthroplasty

in a major academic hospital were included in the study. Patients were randomly assigned to receive either donepezil (5 mg) or placebo daily for 14 days prior to surgery and 14 days after surgery. The authors found that 20.5% of the patients receiving donepezil developed postoperative delirium versus (17.1%; $p = 0.69$) in the placebo group. The difference in incidence of delirium between the two groups was not statistically significant. They concluded that the study did not demonstrate a benefit for donepezil in preventing or treating this cohort of patients undergoing elective orthopedic surgery (Liptzin et al. 2005).

A double-blind, placebo-controlled, parallel-group randomized trial was conducted to determine the efficacy of donepezil in preventing postoperative delirium. Patients with mean age of 67 years old undergoing elective total hip replacement surgery were included in the study and were randomly assigned to receive either donepezil (5 mg) or placebo immediately after surgery and then every 24 h following for 3 days. The authors found that 9.5% of the patients receiving donepezil developed postoperative delirium versus 35.7% ($p = 0.08$) of the patients receiving placebo. The difference was not statistically significant perhaps because of the small sample size. They concluded that donepezil did not reduce the incidence of delirium (Sampson et al. 2007). A pilot, double-masked, randomized, placebo-controlled trial was conducted to determine if donepezil could be effective in reducing the prevalence and severity of delirium after hip fracture. Patients aged 70 years or older undergoing hip fracture repair in an academic medical center were included in the study and were randomly assigned to receive either donepezil (5 mg) or placebo. The authors reported that in longitudinal models, there were no significant differences between the treatment groups (donepezil vs. placebo) with regard to delirium presence over time. They concluded that donepezil had no significant benefit (Marcantonio et al. 2011).

The use of acetylcholinesterase inhibitors for the prevention of delirium remains controversial. The current evidence suggests that they are not effective agents for reducing the incidence of delirium in elderly patients. In addition, the fact that one trial involving rivastigmine was halted for concerns regarding increased mortality should give providers pause if considering this agent for delirium prevention. A recent systematic review analyzing the randomized controlled trials discussed above concluded that the current evidence did not suggest efficacy of acetylcholinesterase inhibitors for the prevention or management of delirium (Tampi et al. 2016).

Alpha-2 Agonists: Dexmedetomidine and Clonidine

Recently, considerable research has been conducted by intensivists and anesthesiologists examining the role of the central acting alpha-2 adrenergic receptor agonists, dexmedetomidine and clonidine, in intensive care unit settings and postoperative settings, regarding their efficacy in the prevention of delirium. In these trials, patients were typically screened for delirium utilizing the Intensive Care Delirium Screening Checklist (ICDSC) or the Confusion Assessment Method for the ICU (CAM-ICU),

and sedation was typically measured using the Richmond Agitation and Sedation Scale (RASS).

A double-blind, randomized controlled trial (MENDS trial) was conducted in two tertiary care centers to study the effects of dexmedetomidine (DEX) on duration of delirium and coma, while providing adequate sedation in ICU patients who were mechanically ventilated. Patients were randomly assigned to receive sedation with DEX (0.15–1.5 ug/kg/h) or lorazepam (1–10 mg/h) for up to 120 h. The authors reported that the patients who received DEX for sedation experienced more days alive without delirium or coma (median days, 7.0 vs. 3.0; $p = 0.01$) and had a lower prevalence of coma (63% vs. 92%; $p < 0.001$) compared to lorazepam. Patients sedated with DEX also spent more time at sedation goals ($p = 0.04$) (Pandharipande et al. 2007). A large, prospective, double-blind, randomized trial (SEDCOM Trial) was conducted in ICUs in 68 centers in five countries comparing the efficacy and safety of dexmedetomidine (DEX) with midazolam (MID) for prolonged sedation in mechanically vented patients. Patients were randomly assigned to receive light sedation (RASS scores −2 to +1) with DEX (0.2–1.4 ug/kg/h) or MID (0.02–0.1 mg/kg/h) from enrollment until extubation or 30 days. The authors reported that the prevalence of delirium during treatment was lower in the DEX treatment group (54%) versus the MID treatment group (76.6%; $p < 0.001$). Patients receiving DEX experienced shorter median time to extubation (3.7 days vs. 5.6 days, $p = 0.01$), less likelihood of tachycardia (25.4% vs. 44.3%, $p < 0.001$), and less hypertension requiring treatment (18.9% vs. 29.5%; $p = 0.02$) (Riker et al. 2009).

A randomized, open-label, parallel-group, pilot trial was conducted in a university hospital ICU to compare the efficacy of dexmedetomidine (DEX) and haloperidol (HAL) in facilitating extubation in delirious, agitated, mechanically ventilated patients. Patients were randomly assigned to receive an infusion of DEX (0.2–0.7 ug/kg/h) or HAL (0.5–2.0 mg/h). The authors reported that DEX shortened medium time to extubation (42.5 vs. 19.9 h; $p = 0.016$) and decreased ICU length of stay (6.5 vs. 1.5 days; $p = 0.004$), and for patients who required ongoing propofol sedation, DEX halved the proportion of time that propofol was required by (79.5% vs. 41.2%; $p = 0.05$) (Reade et al. 2009). An open-label, prospective, randomized clinical trial was conducted in a tertiary care university medical center to examine the effects of postoperative sedation utilizing dexmedetomidine (DEX), propofol (PROP), or midazolam (MID) on the development of delirium in patients undergoing cardiac valve operations with cardiopulmonary bypass. Patients were randomly assigned to receive one of three sedation protocols in the postoperative period including DEX (loading dose: 0.4 ug/kg, maintenance drip: 0.2–0.7 ug/kg/h), PROP (25–50 ug/kg/min), and MID (0.5–2.0 mg/h). The authors reported that the incidence of delirium in the DEX sedation protocol group was 3% versus the PROP group (50%; $p < 0.001$) versus the MID group (50%; $p < 0.001$). In addition, the number of delirious days was significantly lower in the DEX sedation protocol group (1%) versus the PROP group (16%; $p < 0.001$) versus the MID group (29%; $p < 0.001$). They concluded that sedation with DEX was associated with a significantly reduced incidence of postoperative delirium in patients undergoing cardiac valve operations with cardiopulmonary bypass (Maldonado et al. 2009).

A double-blind, randomized, controlled clinical trial (DEXCOM trial) was conducted in two tertiary referral university-affiliated hospitals to examine the effects of dexmedetomidine (DEX) compared to morphine, at equivalent levels of sedation and analgesia, on the prevalence of delirium. Patients aged 60 years or older undergoing pump cardiac surgery were randomized to receive either DEX (0.1–0.7 ug/kg/h) or morphine (10–70 ug/kg/h). The authors reported that delirium incidence was comparable between the DEX treatment group (8.6%) and the morphine group (15%; $p = 0.088$) but that the duration of delirium was significantly less in the DEX group compared to the morphine group (2 vs. 5 days; $p = 0.0317$). They concluded that DEX reduced the duration but not the incidence of delirium after cardiac surgery in this cohort of patients (Shehabi et al. 2009).

Two phase 3 multicenter, randomized, double-blind trials were conducted to compare dexmedetomidine (DEX) with midazolam (MID) (MIDEX trial) in ICUs of 44 centers in nine European countries and DEX with propofol (PROP) (PRODEX trial) in ICUs in 31 centers in six European countries and two centers in Russia, to determine efficacy in maintaining sedation, reducing duration of mechanical ventilation, and improving patients' interaction with nursing care. Adult ICU patients receiving mechanical ventilation who needed light to moderate sedation for more than 24 h were randomly assigned to receive sedation with DEX (0.2–1.4 ug/kg/h) versus MID (0.03–0.2 mg/kg/h) (MIDEX trial) or DEX (0.2–1.4 ug/kg/h) versus PROP (0.3–4.0 mg/kg/h) (PRODEX trial). With regard to delirium, the authors reported that in the MIDEX trial, rates of neurocognitive adverse events, including delirium, were not different between patients receiving DEX or MID. In the PRODEX trial, DEX was associated with fewer neurocognitive disorders, including delirium, than PROP (18%, vs. 29%; $p = 0.008$), respectively. They added that DEX was not inferior to MID and PROP in maintaining light to moderate sedation; DEX reduced duration of mechanical ventilation compared with MID; and DEX improved patients' ability to communicate pain compared to MID and PROP (Jakob et al. 2012). Finally, a prospective, randomized, single-blinded, controlled clinical trial was conducted in a single center to compare dexmedetomidine (DEX)- and propofol (PROP)-based postoperative sedation regimens on the incidence of postoperative delirium after cardiac surgery. Patients aged 60 years or older who underwent cardiac surgery were randomly assigned to receive either DEX (loading dose: 0.4 ug/kg, maintenance drip: 0.2–0.7 ug/kg/h) or PROP (25–50 ug/kg/min) in the postoperative period. The authors reported that sedation with DEX reduced the incidence of postoperative delirium when compared with PROP (17.5% vs. 31.5%; $p = 0.028$), respectively. The median onset of postoperative delirium was on postoperative day 2 for the DEX group versus postoperative day 1 in the PROP group ($p = 0.027$), and duration of postoperative delirium in the DEX group was 2 days compared to 3 days in the PROP group ($p = 0.04$). They concluded that postoperative administration of a DEX-based sedation regimen resulted in reduced incidence, delayed onset, and shortened duration of postoperative delirium in elderly patients after cardiac surgery (Djaiani et al. 2016).

A meta-analysis of ten RCTs examining dexmedetomidine (DEX) versus propofol in adult ICU patients found that DEX may offer advantages over propofol in

terms of risk of delirium and decreased length of stay in the ICU. The authors also reported that bradycardia and hypertension were notable side effects associated with administration of DEX (Xia et al. 2013). A meta-analysis of 14 RCTs versus any comparator in the ICU setting was also conducted. The authors reported that DEX reduces the incidence of delirium in critically ill patients. This was particularly evident in the general ICU setting and in the subgroup of patients requiring noninvasive mechanical ventilation. They added that the advantages were very encouraging when DEX was compared with midazolam (Pasin et al. 2014). Finally, a meta-analysis of 16 RCTs examined the efficacy and sedation of DEX with comparators (propofol, midazolam, and lorazepam) in critical care patients. The authors found that DEX was associated with a 48-h reduction in ICU length of stay and duration of mechanical ventilation. DEX was also associated with a significant reduction in incidence of delirium. They also reported that DEX was associated with an increase in bradycardia and hypotension which was consistent with other studies (Constantin et al. 2016).

At this point, there is strong evidence that DEX lowers the incidence of delirium, reduces duration of mechanical ventilation, and shortens length of stay in intensive care units. Larger, multicenter, randomized, clinical trials will help to further define the role of DEX in the prevention of delirium. Further advantages of DEX include its ability to provide sedation, reduce concurrent analgesic requirements, and maintain patient arousability without inducing respiratory depression. One of its limitations is that it is only available in intravenous formulations. This prompted examination of clonidine, an alpha-2 receptor agonist, which can be administered in intravenous or enteral formulations.

A prospective, randomized, pilot trial was conducted to examine the effect of IV clonidine on incidence and severity of delirium in patients undergoing surgery for acute type A aortic dissection. Patients were prospectively randomized to receive either clonidine (0.5 ug/kg bolus, followed by continuous infusion at 1–2 ug/kg/h) or placebo (normal saline) upon starting and throughout the weaning period from mechanical ventilation. The authors reported that there was no significant difference between the clonidine group and the placebo group (33% vs. 40%; $p = 0.705$) with regard to incidence of delirium, respectively. They did report that the severity of delirium was less in the clonidine group compared to the placebo group. They concluded that the use of clonidine during the weaning period after surgery reduced the severity of postoperative delirium (Rubino et al. 2010). A novel, single academic center, prospective, observation, pilot study was conducted to assess the efficacy, safety, and cost of transitioning selected ICU patients from dexmedetomidine (DEX) to enteral clonidine. The authors reported that 75% of the patients were successfully transitioned from DEX within 48 h of starting clonidine. Clonidine was the sole alpha-2 receptor agonist administered for 45 h while in the ICU and 54 h outside the ICU. They reported that patients who were receiving clonidine alone as the sole alpha-2 receptor agonist had lower fentanyl requirements compared to DEX alone (387 ug/day vs. 891 ug/day; $p = 0.03$), respectively. They reported that the potential drug acquisition cost avoidance was between $819 and $2338 per patient during the 3-month study. They concluded that transitioning from DEX to clonidine may be

safe, efficacious, and a less costly method of maintaining treatment with alpha-2 receptor agonists in critically ill adults (Gagnon et al. 2015).

Clonidine does appear to have a potential role in the management of delirium in ICUs and on general medical/surgical floors, indicating that alpha-2 receptor agonists should continue to be studied. At this time, further larger, randomized, controlled trials are warranted to determine clonidine's efficacy and potential role in the management of delirium.

Antiepileptic Drugs: Valproic Acid and Gabapentin

A case series was published in which the authors described the management of delirium or psychotic agitation in six patients with either the intravenous or liquid oral form of VPA (dose ranges: 500–2500 mg daily in divided doses). VPA was used in these cases due to either ineffectiveness or side effects of antipsychotic medications or benzodiazepines used as first-line therapies. Treatment with VPA adjunctive to conventional therapies led to improvement in behavioral symptoms in all six cases. In addition, there were no significant side effects associated with VPA use in these cases. The authors concluded that VPA can be an effective treatment for delirium when conventional treatments are ineffective or cause concerning side effects (Bourgeois et al. 2005). A retrospective chart analysis was conducted on 16 patients in an academic hospital to examine the effectiveness of VPA as an adjunctive treatment for patients presenting with hyperactive delirium who were not responding to conventional treatment with antipsychotic medications. The authors reported that complete resolution of delirium was achieved in 13 of the 16 patients after treatment with VPA. The average daily dose of VPA through day 4 of treatment was 1133–1258 mg which was given in two or three divided doses. The average time from starting treatment with VPA to complete resolution of symptoms of delirium was 6.2 days. They stated that adjunctive treatment with VPA resulted in significant improvement in symptoms of hyperactive delirium and that the agent was well tolerated and had minimal adverse effects. They concluded that VPA may represent a promising treatment modality for hyperactive delirium and called for randomized controlled trials to further determine efficacy of this agent in this patient population (Sher et al. 2015).

A double-blind, placebo-controlled, randomized, pilot clinical trial was conducted in an academic hospital to examine the effect of gabapentin on the incidence of delirium in patients receiving spinal surgery. Patients undergoing surgery involving their spine were randomly assigned to receive either gabapentin (900 mg) or placebo, 1–2 h before surgery and anesthesia and then daily for the first three postoperative days. The authors reported that the gabapentin treatment group experienced a lower incidence of delirium compared to the placebo group (0% vs. 42%; $p = 0.045$), respectively. They concluded that treatment with gabapentin produced a significantly lower incidence of postoperative delirium (Leung et al. 2006). A randomized, double-blind, placebo-controlled study was conducted to examine if perioperative gabapentin could improve in-hospital rehabilitation and

physical function after total knee arthroplasty. Two hours prior to surgery, patients received celecoxib 400 mg and were then randomly assigned to receive either gabapentin (600 mg) or placebo, followed by gabapentin (200 mg) or placebo three times per day for 4 days. The authors reported that use of gabapentin decreased postoperative analgesic requirements and improved knee range of motion (Clarke et al. 2014). A post hoc analysis of this study was conducted to examine rates of postoperative delirium in the two treatment groups. The authors found that there was no difference in the incidence of delirium between the gabapentin or placebo treatment groups (12% vs. 9%; $p = 0.53$) respectively. They concluded that there was no difference between treatment with gabapentin or placebo on the incidence of delirium in patients receiving TKA (Dighe et al. 2014).

To date, no randomized controlled studies have been conducted examining the role of valproic acid (VPA) in the management of delirium. Despite this, VPA is commonly used in intensive care units and on medical/surgical floors for the treatment of delirium, often when antipsychotic medications are contraindicated or have been ineffective. There is a clear need for randomized controlled trials to further explore VPA's effectiveness in the management of delirium. Similarly, the contrasting results of the studies examining gabapentin's role in the management of delirium also warrant further, larger, randomized controlled trials. At this time, these agents remain potential adjunctive treatments for delirium. Their function as glutamate antagonists and calcium channel modulators may help to explain their potential benefits in the treatment of delirium from a pathophysiological perspective (Maldonado 2013, 2015).

Antipsychotic Agents: Prevention Studies

The typical antipsychotic medication, haloperidol, has been recognized as the primary agent of choice for the treatment of hyperactive- and mixed-type delirium as noted above. Recently, though, several studies examined the role of antipsychotic medications for the prevention of delirium, representing a potential shift and advance in delirium management. It is important to note, however, that a black box warning exists for conventional or atypical antipsychotics due to increased mortality risk in elderly dementia patients utilizing these medications. As such, it is imperative to discontinue these medications at time of discharge if they are utilized for the treatment or prevention of delirium in dementia patients.

A randomized, double-blind, placebo-controlled trial in a medical school-affiliated general hospital was conducted to examine the effect of haloperidol on incidence, severity, and duration of postoperative delirium. Patients aged 70 years or older who were undergoing hip surgery were randomly assigned to receive haloperidol (1.5 mg/day) or placebo on admission with a maximum delay to surgery of 72 h and continued until 3 days after surgery. The authors reported there was no statistically significant difference in the incidence of delirium between the haloperidol treatment group (15.1%) versus the placebo group (16.5%). They did find that, on average, delirium severity was less in the haloperidol group versus the placebo group

and the mean duration of delirium was shorter in the haloperidol group compared to the placebo group. In addition, the mean length of stay until discharge was shorter in the haloperidol group versus placebo (Kalisvaart et al. 2005). A randomized, double-blind, placebo-controlled trial was conducted to examine the efficacy of risperidone on incidence of delirium in patients undergoing cardiac surgery with cardiopulmonary bypass. Patients aged 40 years or older were randomly assigned to receive a single dose of either sublingual risperidone (1 mg) or sublingual placebo, when they regained consciousness from the surgical procedure. The authors reported that the incidence of delirium was lower in the risperidone treatment group (11.1%) versus the placebo group (31.7%; $p = 0.009$) (Prakanrattana and Prapaitrakool 2007).

A randomized, double-blind, placebo-controlled trial was conducted in an orthopedic teaching hospital to examine the effect of prophylactic administration of olanzapine on the incidence of postoperative delirium. Patients aged 65 years or older undergoing elective knee or hip replacement surgery were randomly assigned to receive orally disintegrating olanzapine (5 mg) or orally disintegrating placebo, one dose just before and after surgery (10 mg total). The authors reported that the incidence of delirium was lower in the olanzapine treatment group (14.3%) versus the placebo group (40.2%; $p < 0.0001$) for the entire sample. They concluded that prophylactic, perioperative administration of olanzapine significantly lowered the incidence of postoperative delirium in this patient population (Larsen et al. 2010). A prospective, randomized, double-blind, placebo-controlled trial was conducted in two tertiary teaching hospitals to examine the effect of prophylactic administration of haloperidol on the incidence of postoperative delirium. Patients aged 65 years or older who were admitted to the intensive care unit after noncardiac surgery were randomly assigned to receive either haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1mg/h for 12 h) or intravenous placebo. The authors reported that the haloperidol group experienced a lower incidence of delirium during the first 7 postoperative days compared to the placebo group (15.3% vs. 23.2%; $p = 0.031$), respectively (Wang et al. 2012).

A before and after evaluation of a delirium prevention protocol targeting critically ill patients considered to be high risk for delirium was conducted in a single intensive care unit to determine if the protocol produced improved delirium outcomes. Patients with a predicted risk for delirium of $\geq$50% or with a history of alcohol abuse or dementia received intravenous haloperidol (1 mg/8 h) within a 24-h period after ICU admission and were compared to a historical control group who did not receive haloperidol prophylaxis. The authors reported that the incidence of delirium was lower in the haloperidol group (65%) compared to the control group (75%; $p = 0.01$) (van den Boogaard et al. 2013). A randomized, open-label prospective trial was conducted to examine the effectiveness of prophylactic treatment with haloperidol on the incidence of postoperative delirium. Patients aged 75 years or older who underwent orthopedic or abdominal surgery were randomly assigned to receive intravenous haloperidol (2.5 mg/day) from postoperative days 1–3 or no treatment (control group). The authors

reported that the incidence of postoperative delirium did not significantly differ between the haloperidol group (42.4%) and the control group (33.3%; $p = 0.309$). The authors concluded that prophylactic administration of haloperidol did not significantly decrease the incidence or severity of postoperative delirium (Fukata et al. 2014).

Several systematic reviews and meta-analyses have examined the efficacy of antipsychotic medications for the prevention of delirium. A meta-analysis of five studies examined whether antipsychotic prophylaxis with haloperidol (three studies), risperidone (one study), and olanzapine (one study) prevented delirium. The authors reported that in patients who received prophylactic administration of antipsychotic medications, the pooled relative risk of the five studies resulted in a 50% reduction in the relative risk of delirium compared with placebo ($p < 0.01$). They concluded that in elderly patients, prophylactic administration of antipsychotic medications in the perioperative period may reduce the overall risk of postoperative delirium (Teslyar et al. 2013). A meta-analysis examining six studies (haloperidol [three studies], risperidone [two studies], and olanzapine [one study]) produced similar results, with the authors reporting that prophylactic administration of antipsychotics demonstrated significant efficacy in reducing delirium occurrence (RR = 0.50, $p = 0.0003$). The authors performed further sensitivity analysis and found that second-generation antipsychotics were superior to placebo (RR = 0.36, $p < 0.00001$), but haloperidol did not show superiority to placebo. They concluded that second-generation antipsychotic medications were more beneficial than placebo for preventing the incidence of delirium (Hirota and Kishi 2013).

A systematic review examining 15 studies on pharmacological interventions to treat or prevent delirium in intensive care units found that the use of antipsychotic medications for surgical ICU patients as a preventive strategy may reduce the prevalence of delirium in the ICU (Serafim et al. 2015). A systematic review examining three of the larger delirium prevention trials (haloperidol [two studies] and olanzapine [one study]) found that pooled analysis of the trials was inconclusive regarding an effect of prophylactic antipsychotic treatment on the incidence of delirium (Siddiqi et al. 2016). Finally, a systematic review and meta-analysis examined seven studies which compared prophylactic antipsychotic administration with placebo or no treatment for the prevention of delirium. The authors also found that antipsychotic medications had no significant effect on delirium incidence (OR = 0.56, 95% CI = 0.23–1.34, $I^2 = 93\%$). They concluded that the current evidence did not support the use of antipsychotics for the prevention of delirium (Neufeld et al. 2016).

Despite several early positive trials and meta-analyses demonstrating efficacy for the prevention of delirium with prophylactic administration of antipsychotic medications, the practice has not been widely established. In addition, more recent systematic reviews and meta-analyses have presented contradictory evidence regarding the effectiveness of this practice. Given concerns regarding the use of antipsychotic medications in the elderly, there is a need for larger and more rigorous studies examining the efficacy of this potential intervention.

Nonpharmacological Prevention Studies: General Medical and Intensive Care Unit Settings

Nonpharmacological management strategies for the prevention of delirium have been explored in both general medical and intensive care unit settings. A number of positive studies have emerged in the literature.

A controlled clinical trial was conducted to determine if a nonpharmacological multicomponent intervention strategy could prevent the onset of delirium in elder hospitalized patients. Patients aged 70 years or older ($n = 852$) who were admitted to a general medicine service in a single teaching hospital were enrolled in the study. The study was conducted on one intervention unit and two usual care units, and patients were enrolled utilizing a prospective matching strategy. Standardized intervention protocols targeted cognitive impairment, visual impairment, hearing impairment, sleep deprivation, immobility, and dehydration. Delirium was measured daily utilizing Confusion Assessment Method (CAM) criteria. The authors reported that the incidence of delirium was significantly lower in the intervention group (9.9%) compared to the usual care group (15%; $p = 0.02$). In addition, the intervention significantly lowered the total number of days of delirium compared to usual care (105 vs. 161 days; $p = 0.02$), respectively, and significantly lowered the total number of episodes of delirium compared to usual care (62 vs. 90 episodes; $p = 0.03$), respectively. The authors added that the intervention did not significantly affect the severity of delirium nor the recurrence rates of delirium. They concluded that a multicomponent, targeted intervention strategy could effectively prevent delirium in older, hospitalized, medical patients (Inouye et al. 1999). This novel model of care came to be described as the Hospital Elder Life Program (HELP) (Inouye et al. 2000). The study has been successfully replicated in various care settings and has been shown to be both sustainable and cost-effective (Rubin et al. 2011; Zaubler et al. 2013; Strijbos et al. 2013).

Two randomized controlled trials have examined nonpharmacological interventions on elderly patients receiving orthopedic surgery. A prospective, blinded, randomized controlled trial was conducted to examine the effect of proactive geriatrics consultation on delirium incidence in patients aged 65 years or older receiving emergent surgical repair of hip fracture. The authors reported that the intervention significantly reduced the incidence of delirium compared to the usual care group (32% vs. 50%; $p = 0.04$), respectively (Marcantonio et al. 2001). Similarly, a randomized, controlled intervention trial was conducted to examine the effect of receiving postoperative care on a geriatric ward versus an orthopedic ward on incidence of delirium in patients aged 70 years or older after femoral neck fracture repair. The authors found that the intervention reduced the incidence of delirium compared to the usual care group (54.9% vs. 75.3%; $p = 0.003$), respectively (Lundstrom et al. 2007). These studies represented positive trials in hospitalized surgical patients.

The National Institute of Health and Clinical Excellence published a set of guidelines aimed at the prevention of delirium in at risk elderly patients. Thirteen guidelines were produced aimed at delirium prevention and included:

1. Ensuring that persons at risk for delirium are cared for by clinicians who are familiar with the person at risk.
2. Providing a tailored, multicomponent intervention package.
3. Instituting that package by a specialized multidisciplinary team competent in delirium prevention.
4. Address cognitive impairment or disorientation.
5. Address dehydration and constipation.
6. Address hypoxia.
7. Address infection.
8. Address mobility.
9. Address pain.
10. Perform a medication review.
11. Address poor nutrition.
12. Address sensory impairment.
13. Address sleep hygiene.

The authors emphasized that delirium is a neglected condition that too often goes unrecognized and underdiagnosed. They argued that approximately one third of all delirium episodes could be prevented and that delirium prevention would represent a cost-effective strategy (O'Mahony et al. 2011).

Nonpharmacological intervention trials have also been conducted in the ICU setting. A novel randomized controlled trial conducted in two university hospitals examined the effects of daily interruption of sedation with occupational therapy on functional outcomes. Patients aged 18 years or older in the ICU were randomly assigned to receive early exercise and mobilization (physical and occupational therapy) versus daily interruption of sedation with therapy as ordered by the primary care team. The authors reported that the intervention group had shorter duration of delirium compared to the control group (median 2.0 vs. 4.0 days; $p = 0.02$), respectively. They added that the intervention also resulted in statistically better functional outcomes at discharge and more ventilator-free days (Schweickert et al. 2009). A two-stage prospective observational study was conducted to assess the impact of a reorientation strategy in an ICU setting on occurrence of delirium. Older patients admitted to a single medical-surgical ICU were included in the study. Phase 1 of the study was observational and phase 2 consisted of the intervention in which patients underwent both a reorientation strategy and environmental, acoustic, and visual stimulation. The authors reported that delirium occurrence was significantly lower in the intervention group compared to the observational group (22% vs. 35.5%; $p < 0.020$), respectively (Colombo et al. 2012).

As part of the Society of Critical Care Medicine's pain, agitation, and delirium guidelines, nonpharmacological recommendations were proposed including the following: (1) maintain a light enough level of sedation to allow the patient to participate in care activities, and (2) promote early mobility to prevent physical deterioration and lower the risk of delirium. They argued that while they recognize that implementing practice guidelines can be challenging, the growing data demonstrating significant morbidities in survivors of critical illness warrants taking on that

challenge (Davidson et al. 2013). Despite evidence that nonpharmacological management strategies for delirium are efficacious in both general medical and intensive care unit settings, these strategies have yet to be implemented on a broader level.

Delirium Sequelae: Cognition, Post-traumatic Stress Disorder, and Depression

Recent advances in delirium research have come from a closer examination of the post-delirious period. Researchers have closely examined the relationship between delirium and the development of neurologic and psychiatric sequelae. A new spotlight has also been placed on family members of patients with delirium and the effect of delirium on the caregiver.

Several studies have examined the effect of delirium on cognition in the elderly. A secondary analysis from a large prospective cohort, the Massachusetts Alzheimer's Disease Research Center's patient registry, examined the impact of delirium on cognitive functioning in patients with Alzheimer's disease (AD) who developed delirium versus those who did not. Cognitive performance was measured by change in score on the Information-Memory-Concentration (IMC) subtest of the Blessed Dementia Rating Scale. The authors found that among patients who developed delirium, the average decline at baseline was 2.5 points per year, but after an episode of delirium, there was further decline to an average of 4.9 points per year ($p = 0.001$). This represented a significant acceleration in the slope of cognitive decline following an episode of delirium in patients with AD, and the rate of change in IMC score occurred about three times faster compared to patients who did not develop delirium (Fong et al. 2009). Further prospectively collected longitudinal data from the same cohort of hospitalized patients with AD found that 56% of the patients developed delirium. The authors reported that in the year following hospitalization, patients who developed delirium experienced greater cognitive deterioration (3.1 IMC points/year, 95% CI: 2.1,4.1) compared to patients who did not (1.4 IMC points/year, 95% CI: 0.2,2.6). They added that the ratio of these changes suggested that cognitive deterioration proceeds at 2.2 times the rate in patients who develop delirium compared to those who do not in the year after hospitalization. In addition, the delirium group maintained a more rapid pace of cognitive deterioration throughout the 5-year period following hospitalization (Gross et al. 2012). A systematic review and meta-analysis examined critically ill patients in 42 studies and found that nearly a third of patients admitted to an ICU develop delirium. In addition, patients who developed delirium had significantly higher mortality during admission, longer durations of mechanical ventilation, longer lengths of stay in the ICU and in hospital, and cognitive impairment after discharge (Salluh et al. 2015).

The effect of critical illness and delirium on the development of post-traumatic stress disorder (PTSD) and depression has also been examined. A prospective cohort study was conducted in medical and coronary intensive care units in a university-based medical center to identify risk factors associated with the development of PTSD symptoms in patients following critical illness who required mechanical

ventilation. Forty-three patients who were CAM-ICU positive were screened for PTSD symptoms utilizing the Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) 6 months after discharge. At time of follow-up, 14% of patients had high levels of PTSD symptoms. In addition, the authors found that PTSD symptoms were more likely to occur in female patients and those receiving high doses of lorazepam. Interestingly, they also reported that high levels of PTSD symptoms were less likely to occur in older patients (Girard et al. 2007).

A systematic review was conducted of 15 eligible studies to further clarify data on the prevalence of PTSD in general ICU survivors and identify risk factors for post-ICU PTSD and the effect of this on health-related quality of life. The authors reported that the median point prevalence of questionnaire-ascertained "clinically significant" PTSD was 22% and the median point prevalence of clinician-diagnosed PTSD was 19%. They also found that consistent predictors of post-ICU PTSD included prior psychopathology, greater ICU benzodiazepine administration, and post-ICU memories of in-ICU frightening and/or psychotic experiences. They also found that female sex and younger age were less consistent predictors, and severity of clinical illness was consistently not a predictor. They did find that post-ICU PTSD was associated with a substantially lower health-related quality of life (Davydow et al. 2008).

A prospective cohort study of elderly patients undergoing hip fracture surgery investigated whether in-hospital delirium was associated with increased anxiety and depressive levels, along with PTSD symptoms, 3 months after discharge. Fifty-three patients were included in the study and 23 (43.4%) developed in-hospital delirium. The authors reported that patients who experienced in-hospital delirium showed more depressive symptoms at 3-month follow-up than patients who did not develop delirium, but the level of anxiety and symptoms of PTSD did not differ between the two groups (Slor et al. 2013). A prospective, multisite cohort study was conducted to characterize depression, post-traumatic stress disorder, and functional disability in medical/surgical ICU patients with respiratory failure or shock. Critical care survivors were assessed at 3- and 12-month intervals after discharge. The authors reported that at the 3- and 12-month follow-up intervals, 37% and 33% of patients reported at least mild depression, respectively, driven primarily by somatic rather than cognitive symptoms. In addition, at either the 3- or 12-month interval, only 7% of patients presented with symptoms consistent with PTSD. The authors also found that disabilities in basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs) were present at 3 months (32% and 26%) and at 12 months (27% and 23%), respectively. They concluded that depression is more common than PTSD after critical illness and is driven by somatic symptoms indicative of physical disabilities rather than by cognitive symptoms (Jackson et al. 2014).

A literature review examined ten prospective cohort studies to investigate the relationship between depression and delirium. The authors reported that three studies involving patients undergoing hip fracture repair demonstrated more severe depressive symptoms both during delirium and after delirium ended. They reported that the remainder of the studies did not produce any statistically significant correlations between depression and delirium. They recommended closer monitoring of depressive

symptoms in patients with delirium undergoing surgical repair of hip fractures and called for further research to be performed exploring this relationship (Nelson et al. 2016). In addition, O'Sullivan et al. (2014) argued that in elderly populations, the interrelationship between symptoms of delirium and depression might include more complex interactions such as shared pathogenesis and pathophysiology. The authors added that the fact that depression and delirium are both defined as syndromes may account for some clinical overlap. They also called for further prospective studies to explore the contributions of cognitive and affective symptoms pre and post the delirious episode to clarify the features of depression versus delirium (O'Sullivan et al. 2014).

Finally, the adverse effect on family members of hospitalized patients with delirium has been studied. A literature review exploring the effect of delirium on patients, relatives, and staff found that some patients recall delirium and that recollections are generally distressing. In addition, distress may be greater in relatives witnessing delirium and is also reported in professional staff. The distress may also result in longer-term psychological sequelae (Partridge et al. 2013). An observational, cross-sectional analysis of caregivers of hospitalized patients with delirium found that they were at elevated risk for experiencing severe acute traumatic and depressive symptoms (Lloyd and Rosenthal 2015). Finally, a literature review explored the experiences of caregivers of patients with delirium in palliative care settings. The authors found that caregivers of patients with delirium experience high levels of distress which is heightened in palliative care settings because of the uncertainty around whether the caregiver-patient relationship can be re-established before death. They called for future interventions aimed at reducing caregiver distress (Finucane et al. 2016).

Conclusion

Research on delirium has expanded dramatically in recent years. However, many questions still remain on the best preventive and treatment interventions as well as the psychosocial consequences of an episode of delirium. As our elder population continues to remain at high risk for the development of delirium, it is hoped that further research will clarify these issues.

References

Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M (2011) Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry 26(7):687–694. doi:10.1002/gps.2582

Alao AO, Moskowitz L (2006) Aripiprazole and delirium. Ann Clin Psychiatry 18(4):267–269

Al-Qadheeb NS, Skrobik Y, Schumaker G, Pacheco MN, Roberts RJ, Ruthazer RR, Devlin JW (2016) Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol: a double-blind, placebo-controlled pilot study. Crit Care Med 44(3):583–591. doi:10.1097/CCM.0000000000001411

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing, Washington, DC

Artemiou P, Bily B, Bilecova-Rabajdova M, Sabol F, Torok P, Kolarcik P, Kolesar A (2015) Melatonin treatment in the prevention of postoperative delirium in cardiac surgery patients. Kardiochir Torakochirurgia Pol 12(2):126–133. doi:10.5114/kitp.2015.52853

Boettger S, Breitbart W (2011) An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. Palliat Support Care 9(4):351–357. doi:10.1017/S1478951511000368

Bourgeois JA, Koike AK, Simmons JE, Telles S, Eggleston C (2005) Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. J Neuropsychiatry Clin Neurosci 17(2):232–238

Brown CH 4th, Faigle R, Klinker L, Bahouth M, Max L, LaFlam A, Neufeld KJ, Mandal K, Gottesman RF, Hogue CW Jr (2015) The association of brain MRI characteristics and postoperative delirium in cardiac surgery patients. Clin Ther 37(12):2686–2699.e9. doi:10.1016/j.clinthera.2015.10.021

Cavallari M, Hshieh TT, Guttmann CR, Ngo LH, Meier DS, Schmitt EM, Marcantonio ER, Jones RN, Kosar CM, Fong TG, Press D, Inouye SK, Alsop DC, SAGES Study Group (2015) Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia. Neurobiol Aging 36(6):2122–2129. doi:10.1016/j.neurobiolaging.2015.02.024

Cavallari M, Dai W, Guttmann CR, Meier DS, Ngo LH, Hshieh TT, Callahan AE, Fong TG, Schmitt E, Dickerson BC, Press DZ, Marcantonio ER, Jones RN, Inouye SK, Alsop DC, SAGES Study Group (2016) Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. Brain 139(Pt 4):1282–1294. doi:10.1093/brain/aww010

Chen S, Shi L, Liang F, Xu L, Desislava D, Wu Q, Zhang J (2015) Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials. Mol Neurobiol. [Epub ahead of print]

Clarke HA, Katz J, McCartney CJ, Stratford P, Kennedy D, Pagé MG, Awad IT, Gollish J, Kay J (2014) Perioperative gabapentin reduces 24 h opioid consumption and improves in-hospital rehabilitation but not post-discharge outcomes after total knee arthroplasty with peripheral nerve block. Br J Anaesth 113(5):855–864. doi:10.1093/bja/aeu202

Cohen MB, Stewart JT (2013) Treatment of post-electroconvulsive therapy agitation with dexmedetomidine. J ECT 29(2):e23–e24. doi:10.1097/YCT.0b013e31827e56a7

Cole MG, Ciampi A, Belzile E, Dubuc-Sarrasin M (2013) Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. Int J Geriatr Psychiatry 28(8):771–780. doi:10.1002/gps.3891

Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, Raimondi F (2012) A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. Minerva Anestesiol 78(9):1026–1033

Constantin JM, Momon A, Mantz J, Payen JF, De Jonghe B, Perbet S, Cayot S, Chanques G, Perreira B (2016) Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 35(1):7–15. doi:10.1016/j.accpm.2015.06.012

Dautzenberg PL, Mulder LJ, Olde Rikkert MG, Wouters CJ, Loonen AJ (2004) Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage. Int J Geriatr Psychiatry 19(7):641–644

Davidson JE, Harvey MA, Bemis-Dougherty A, Smith JM, Hopkins RO (2013) Implementation of the pain, agitation, and delirium clinical practice guidelines and promoting patient mobility to prevent post-intensive care syndrome. Crit Care Med 41(9 Suppl 1):S136–S145. doi:10.1097/CCM.0b013e3182a24105

Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ (2008) Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry 30(5):421–434. doi:10.1016/j.genhosppsych.2008.05.006

de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE (2010) Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. Int J Geriatr Psychiatry 25(12):1201–1208. doi:10.1002/gps.2454

de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, van Velde R, Levi M, de Haan RJ, de Rooij SE, Amsterdam Delirium Study Group (2014) Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ 186(14):E547–E556. doi:10.1503/cmaj.140495

de Rooij SE, van Munster BC, de Jonghe A (2014) Melatonin prophylaxis in delirium: panacea or paradigm shift? JAMA Psychiatry 71(4):364–365. doi:10.1001/jamapsychiatry.2013.4532

Detweiler MB, Mehra A, Rowell T, Kim KY, Bader G (2009) Delirious mania and malignant catatonia: a report of 3 cases and review. Psychiatr Q 80(1):23–40. doi:10.1007/s11126-009-9091-9

Dianatkhah M, Ghaeli P, Hajhossein Talasaz A, Karimi A, Salehiomran A, Bina P, Jalali A, Ghaffary S, Shahmansouri N, Vejdani S (2015) Evaluating the potential effect of melatonin on the post-cardiac surgery sleep disorder. J Tehran Heart Cent 10(3):122–128

Dighe K, Clarke H, McCartney CJ, Wong CL (2014) Perioperative gabapentin and delirium following total knee arthroplasty: a post-hoc analysis of a double-blind randomized placebo-controlled trial. Can J Anaesth 61(12):1136–1137. doi:10.1007/s12630-014-0235-5

Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, Katznelson R (2016) Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: a randomized controlled trial. Anesthesiology 124(2):362–368. doi:10.1097/ALN.0000000000000951

Fink M, Taylor MA (eds) (2003) Catatonia: a clinician's guide to diagnosis and treatment. Cambridge University Press, Cambridge

Finucane AM, Lugton J, Kennedy C, Spiller JA (2016) The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. Psychooncology. doi:10.1002/pon.4140. [Epub ahead of print]

Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, Yang FM, Kiely DK, Inouye SK (2009) Delirium accelerates cognitive decline in Alzheimer disease. Neurology 72(18):1570–1575. doi:10.1212/WNL.0b013e3181a4129a

Ford AH, Almeida OP (2015) Pharmacological interventions for preventing delirium in the elderly. Maturitas 81(2):287–292. doi:10.1016/j.maturitas.2015.03.024

Fukata S, Kawabata Y, Fujisiro K, Katagawa Y, Kuroiwa K, Akiyama H, Terabe Y, Ando M, Kawamura T, Hattori H (2014) Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial. Surg Today 44(12):2305–2313. doi:10.1007/s00595-014-0859-7

Gagnon B, Low G, Schreier G (2005) Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. J Psychiatry Neurosci 30(2):100–107

Gagnon DJ, Riker RR, Glisic EK, Kelner A, Perrey HM, Fraser GL (2015) Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study. Pharmacotherapy 35(3):251–259. doi:10.1002/phar.1559

Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, Filipovic M, Seeberger MD, Pargger H, Siegemund M, Carrel T, Seiler WO, Berres M, Strebel SP, Monsch AU, Steiner LA (2009) Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery – a randomized controlled trial. Crit Care Med 37(5):1762–1768. doi:10.1097/CCM.0b013e31819da780

Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, Dittus RS, Bernard GR, Ely EW (2007) Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care 11(1):R28

Gross AF, Stern TA (2014) Neuropsychiatric conditions associated with anesthesia exposure. Psychosomatics 55(1):21–28. doi:10.1016/j.psym.2013.06.020

Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L, Schmitt E, Yap L, Inouye SK (2012) Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med 172(17):1324–1331. doi:10.1001/archinternmed.2012.3203

Hakim SM, Othman AI, Naoum DO (2012) Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology 116 (5):987–997. doi:10.1097/ALN.0b013e31825153cc

Hatano Y, Narumoto J, Shibata K, Matsuoka T, Taniguchi S, Hata Y, Yamada K, Yaku H, Fukui K (2013) White-matter hyperintensities predict delirium after cardiac surgery. Am J Geriatr Psychiatry 21(10):938–945. doi:10.1016/j.jagp.2013.01.061

Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, Nakamura H, DELIRIA-J Group (2014) Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 71(4):397–403. doi:10.1001/jamapsychiatry.2013.3320

Hirota T, Kishi T (2013) Prophylactic antipsychotic use for postoperative delirium: a systematic review and meta-analysis. J Clin Psychiatry 74(12):e1136–e1144. doi:10.4088/JCP.13r08512

Inouye SK (2006) Delirium in older persons. N Engl J Med 354(11):1157–1165

Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr (1999) A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 340(9):669–676

Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr (2000) The hospital elder life program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital elder life program. J Am Geriatr Soc 48(12):1697–1706

Inouye SK, Westendorp RG, Saczynski JS (2014) Delirium in elderly people. Lancet 383 (9920):911–922. doi:10.1016/S0140-6736(13)60688-1

Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, Pun BT, Vasilevskis EE, Morandi A, Shintani AK, Hopkins RO, Bernard GR, Dittus RS, Ely EW, Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators (2014) Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2(5):369–379. doi:10.1016/S2213-2600(14)70051-7

Jackson JC, Morandi A, Girard TD, Merkle K, Graves AJ, Thompson JL, Shintani AK, Gunther ML, Cannistraci CJ, Rogers BP, Gore JC, Warrington HJ, Ely EW, Hopkins RO, VISualizing Icu SurvivOrs Neuroradiological Sequelae (VISIONS) Investigation (2015) Functional brain imaging in survivors of critical illness: a prospective feasibility study and exploration of the association between delirium and brain activation patterns. J Crit Care 30(3):653.e1–653.e7. doi:10.1016/j.jcrc.2015.01.017

Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD, Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30(1):119–141

Jacobowski NL, Heckers S, Bobo WV (2013) Delirious mania: detection, diagnosis, and clinical management in the acute setting. J Psychiatr Pract 19(1):15–28. doi:10.1097/01.pra.0000426324.67322.06

Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J, Dexmedetomidine for Long-Term Sedation Investigators (2012) Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 307(11):1151–1160. doi:10.1001/jama.2012.304

Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, Eikelenboom P, van Gool WA (2005) Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 53(10):1658–1666

Larsen KA, Kelly SE, Stern TA, Bode RH Jr, Price LL, Hunter DJ, Gulczynski D, Bierbaum BE, Sweeney GA, Hoikala KA, Cotter JJ, Potter AW (2010) Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics 51(5):409–418. doi:10.1176/appi.psy.51.5.409

Lee BS, Huang SS, Hsu WY, Chiu NY (2012) Clinical features of delirious mania: a series of five cases and a brief literature review. BMC Psychiatry 12:65. doi:10.1186/1471-244X-12-65

Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P (2006) Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology 67(7):1251–1253

Liptzin B, Levkoff SE (1992) An empirical study of delirium subtypes. Br J Psychiatry 161:843–845

Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R (2005) Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry 13(12):1100–1106

Lloyd RB, Rosenthal LJ (2015) Acute traumatic and depressive symptoms in family members of hospitalized individuals with delirium. Int J Psychiatry Med 50(2):191–202. doi:10.1177/0091217415605033

Lundström M, Olofsson B, Stenvall M, Karlsson S, Nyberg L, Englund U, Borssén B, Svensson O, Gustafson Y (2007) Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. Aging Clin Exp Res 19(3):178–186

Maldonado JR (2013) Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 21(12):1190–1222. doi:10.1016/j.jagp.2013.09.005

Maldonado JR (2015) Delirium: neurobiology, characteristics, and management. In: Fogel BS, Greenberg DB (eds) Psychiatric care of the medical patient, 3rd edn. Oxford University Press, New York, pp 823–907

Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA (2009) Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics 50(3):206–217. doi:10.1176/appi.psy.50.3.206

Marcantonio ER, Flacker JM, Wright RJ, Resnick NM (2001) Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 49(5):516–522

Marcantonio ER, Palihnich K, Appleton P, Davis RB (2011) Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. J Am Geriatr Soc 59(Suppl 2):S282–S288. doi:10.1111/j.1532-5415.2011.03691.x

Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT (2012) A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. J Psychosom Res 72(3):236–241. doi:10.1016/j.jpsychores.2011.11.013

Meagher D, O'Regan N, Ryan D, Connolly W, Boland E, O'Caoimhe R, Clare J, Mcfarland J, Tighe S, Leonard M, Adamis D, Trzepacz PT, Timmons S (2014) Frequency of delirium and subsyndromal delirium in an adult acute hospital population. Br J Psychiatry 205(6):478–485. doi:10.1192/bjp.bp.113.139865

Michaud CJ, Bullard HM, Harris SA, Thomas WL (2015) Impact of quetiapine treatment on duration of hypoactive delirium in critically ill adults: a retrospective analysis. Pharmacotherapy 35(8):731–739. doi:10.1002/phar.1619

Miura S, Furuya M, Yasuda H, Miyaoka T, Horiguchi J (2015) Novel therapy with ramelteon for hypoactive delirium: a case report. J Clin Psychopharmacol 35(5):616–618. doi:10.1097/JCP.0000000000000370

Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G (2004) Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. Am J Alzheimers Dis Other Demen 19(6):333–339

Munk L, Andersen G, Møller AM (2016) Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences. Acta Anaesthesiol Scand. doi:10.1111/aas.12717. [Epub ahead of print]

Nelson S, Rustad JK, Catalano G, Stern TA, Kozel FA (2016) Depressive symptoms before, during, and after delirium: a literature review. Psychosomatics 57(2):131–141. doi:10.1016/j.psym.2015.11.003

Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM (2016) Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc 64(4):705–714. doi:10.1111/jgs.14076

Oldenbeuving AW, de Kort PL, Jansen BP, Kappelle LJ, Roks G (2008) A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative. BMC Neurol 8:34. doi:10.1186/1471-2377-8-34

Oldham MA, Lee HB, Desan PH (2016) Circadian rhythm disruption in the critically ill: an opportunity for improving outcomes. Crit Care Med 44(1):207–217. doi:10.1097/CCM.0000000000001282

O'Mahony R, Murthy L, Akunne A, Young J, Guideline Development Group (2011) Synopsis of the national institute for health and clinical excellence guideline for prevention of delirium. Ann Intern Med 154(11):746–751. doi:10.7326/0003-4819-154-11-201106070-00006

Omiya H, Yoshitani K, Yamada N, Kubota Y, Takahashi K, Kobayashi J, Ohnishi Y (2015) Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. Can J Anaesth 62(6):595–602. doi:10.1007/s12630-015-0327-x

O'Sullivan R, Inouye SK, Meagher D (2014) Delirium and depression: inter-relationship and clinical overlap in elderly people. Lancet Psychiatry 1(4):303–311. doi:10.1016/S2215-0366(14)70281-0

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW (2007) Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 298(22):2644–2653

Partridge JS, Martin FC, Harari D, Dhesi JK (2013) The delirium experience: what is the effect on patients, relatives and staff and what can be done to modify this? Int J Geriatr Psychiatry 28(8):804–812. doi:10.1002/gps.3900

Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A (2014) Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 28(6):1459–1466. doi:10.1053/j.jvca.2014.03.010

Peritogiannis V, Bolosi M, Lixouriotis C, Rizos DV (2015) Recent insights on prevalence and corelations of hypoactive delirium. Behav Neurol 2015:416792. doi:10.1155/2015/416792

Pickard A, Davies P, Birnie K, Beringer R (2014) Systematic review and meta-analysis of the effect of intraoperative α_2-adrenergic agonists on postoperative behaviour in children. Br J Anaesth 112(6):982–990. doi:10.1093/bja/aeu093

Prakanrattana U, Prapaitrakool S (2007) Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 35(5):714–719

Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R (2009) Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care 13(3):R75. doi:10.1186/cc7890

Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG, SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group (2009) Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 301(5):489–499. doi:10.1001/jama.2009.56

Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK (2011) Sustainability and scalability of the hospital elder life program at a community hospital. J Am Geriatr Soc 59(2):359–365. doi:10.1111/j.1532-5415.2010.03243.x

Rubino AS, Onorati F, Caroleo S, Galato E, Nucera S, Amantea B, Santini F, Renzulli A (2010) Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. Interact Cardiovasc Thorac Surg 10(1):58–62. doi:10.1510/icvts.2009.217562

Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, Serafim RB, Stevens RD (2015) Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 350:h2538. doi:10.1136/bmj.h2538

Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J, Blanchard MR, Bruce A, Blizard R, Ritchie CW (2007) A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry 22(4):343–349

Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373(9678):1874–1882. doi:10.1016/S0140-6736(09)60658-9

Serafim RB, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, Salluh JI (2015) Pharmacologic prevention and treatment of delirium in intensive care patients: a systematic review. J Crit Care 30(4):799–807. doi:10.1016/j.jcrc.2015.04.005

Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, Chen J (2009) Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology 111(5):1075–1084. doi:10.1097/ALN.0b013e3181b6a783

Sher Y, Miller AC, Lolak S, Ament A, Maldonado JR (2015) Adjunctive valproic acid in management-refractory hyperactive delirium: a case series and rationale. J Neuropsychiatry Clin Neurosci 27(4):365–370. doi:10.1176/appi.neuropsych.14080190

Shim J, DePalma G, Sands LP, Leung JM (2015) Prognostic significance of postoperative subsyndromal delirium. Psychosomatics 56(6):644–651. doi:10.1016/j.psym.2015.05.002

Shioiri A, Kurumaji A, Takeuchi T, Nemoto K, Arai H, Nishikawa T (2016) A decrease in the volume of gray matter as a risk factor for postoperative delirium revealed by an atlas-based method. Am J Geriatr Psychiatry 24(7):528–536. doi:10.1016/j.jagp.2015.09.002

Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA (2016) Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 3: CD005563. doi:10.1002/14651858.CD005563.pub3

Slor CJ, Witlox J, Jansen RW, Adamis D, Meagher DJ, Tieken E, Houdijk AP, van Gool WA, Eikelenboom P, de Jonghe JF (2013) Affective functioning after delirium in elderly hip fracture patients. Int Psychogeriatr 25(3):445–455. doi:10.1017/S1041610212001962

Straker DA, Shapiro PA, Muskin PR (2006) Aripiprazole in the treatment of delirium. Psychosomatics 47(5):385–391

Strijbos MJ, Steunenberg B, van der Mast RC, Inouye SK, Schuurmans MJ (2013) Design and methods of the Hospital Elder Life Program (HELP), a multicomponent targeted intervention to prevent delirium in hospitalized older patients: efficacy and cost-effectiveness in Dutch health care. BMC Geriatr 13:78. doi:10.1186/1471-2318-13-78

Sultan SS (2010) Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anaesth 4(3):169–173. doi:10.4103/1658-354X.71132

Tampi RR, Tampi DJ, Ghori AK (2016) Acetylcholinesterase inhibitors for delirium in older adults. Am J Alzheimers Dis Other Demen 31(4):305–310. doi:10.1177/1533317515619034

Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S (2013) Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. Psychosomatics 54(2):124–131. doi:10.1016/j.psym.2012.12.004

Theisen-Toupal J, Breu AC, Mattison ML, Arnaout R (2014) Diagnostic yield of head computed tomography for the hospitalized medical patient with delirium. J Hosp Med 9(8):497–501. doi:10.1002/jhm.2198

van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P (2013) Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care 17(1): R9. doi:10.1186/cc11933

van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ (2010) Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet 376(9755):1829–1837. doi:10.1016/S0140-6736(10)61855-7

Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, Chen KS, Gu XE, Zhu SN (2012) Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. Crit Care Med 40(3):731–739. doi:10.1097/CCM.0b013e3182376e4f

Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX (2013) Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. J Surg Res 185(2):833–843. doi:10.1016/j.jss.2013.06.062

Zaslavsky A, Haile M, Kline R, Iospa A, Frempong-Boadu A, Bekker A (2012) Rivastigmine in the treatment of postoperative delirium: a pilot clinical trial. Int J Geriatr Psychiatry 27(9):986–988. doi:10.1002/gps.2801

Zaubler TS, Murphy K, Rizzuto L, Santos R, Skotzko C, Giordano J, Bustami R, Inouye SK (2013) Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. Psychosomatics 54(3):219–226. doi:10.1016/j.psym.2013.01.010

Depression in Late Life: Etiology, Presentation, and Management

9

C. Power, E. Greene, and B. A. Lawlor

Abstract

Depression in late life is common with a community prevalence of approximately 15%. The figures are higher among hospital inpatients (20–25%) and patients in long-term care (10–40%). It is the most frequent cause of emotional suffering in the elderly and can have a significant impact on a person's physical health and cognitive and social functioning. Suicide among older adults is more often associated with depression than at any other age, and suicide attempts are more likely to be fatal. Depression in late life may refer to either depression with first onset in later life (late-onset depression) or depression that occurs for the first time in younger years and recurs in later life (early-onset depression). The two syndromes differ in terms of etiology, presentation, and natural history. Late-onset depression can be considered to be a geriatric syndrome similar to frailty, falls, or incontinence. Affective symptoms may be less to the fore with motivational-type symptoms and somatic complaints relatively more prominent. The

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_10

physiological and psychological effects of poor physical health and the organic changes of the aging brain are fundamental considerations in this age group. Successful management of depression in late life, regardless of the subtype, requires a flexible and thoughtful multidisciplinary approach. While pharmacotherapy undoubtedly plays a vital role in moderate to severe cases, it must be used cautiously given the increased risk of adverse side effects in the elderly. Physical health, social disconnection, and functional or occupational decline must also be identified and targeted according to the individual needs and abilities of the patient.

Keywords

Late life depression • Comorbidities • Dementia • Cognitive impairment • Social network • Psychological factors • Antidepressant • Prevention

Contents

Introduction

When considering many of the factors associated with later life – personal loss, physical ill health, and cognitive decline – the onset of a depressive syndrome could seem to be almost an inevitability. However, with community prevalence rates of between 8% and 16% for a clinically significant depression (Blazer 2003; Kirby et al. 1997), it is clear that the majority of the older population are not depressed and depression cannot, therefore, be seen as part of the normal aging process. Late life depression is associated with poorer physical and cognitive health, impaired social functioning, increased suicide risk, and higher overall mortality. It is hugely distressing for patients and impacts widely on families and friends.

One of the greatest challenges faced by clinicians when treating patients with late life depression is unpicking the etiological and clinical heterogeneity of the condition. Increasingly, however, we are seeing that the successful management of late life depression requires a multidisciplinary approach that takes advantage of this very heterogeneity. The aim of this chapter is to explore our current understanding of the etiology, presentation, and management of late life depression. By drawing from the rapidly expanding knowledge base in this area, we hope to provide a framework for how late life depression may be formulated and managed in order to improve outcomes and enhance the quality of life of patients.

Definitions

"Depression" refers to a disorder of mood that causes persistent feelings of sadness or loss of interest that impact negatively on a person's quality of life and normal occupational or social functioning. DSM-5 and ICD-10 have classified and defined depressive episodes as summarized in Figs. 1 and 2. In milder forms of depression, where the symptom count falls below the threshold required for a diagnosis of major depression, the terms "minor depression," "subsyndromal depression," or "subthreshold depression" are used interchangeably.

"Depression in late life" refers to a major depressive episode that occurs in later years. The debate as to when "later life" begins, however, is contentious with age thresholds differing significantly between countries, cultures, and health services. Traditionally, an age cutoff of 65 years is used to determine access to specialist geriatric care. However, 65 is no longer considered to be "old" in many developed countries where life expectancy now exceeds 80 years and the general health of the population is better than ever before. Studies which address specific age-related issues, such as physical frailty, increasingly draw from populations of the "old old," a term used more frequently now to describe those aged over 80 or 85 years of age. By and large, however, "late life" is still taken, by convention, to refer to those aged 65 years and older and will be used in that way throughout this chapter unless stated otherwise.

"Depression in late life" encompasses both depression with first onset in younger years that recurs in later life and depression that occurs for the first time in later years. Approximately half of the older depressed population experience their first depressive episode in later life. This will be referred to as late-onset depression (LOD), while depression of earlier life that recurs in later years will be referred to as early-onset depression (EOD).

Etiology

Successful treatment of depression in late life requires an approach that carefully considers all of the potential biological, psychological, and social factors which contribute to the individual's experience of depressive illness and a

A. At least 5 of the following symptoms present during the same 2-week period, representing a change from previous functioning. One of the symptoms must be either depressed mood or loss of interest or pleasure
   - Depressed mood most of the day, nearly every day
   - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
   - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
   - Insomnia or hypersomnia nearly every day
   - Psychomotor agitation or retardation nearly every day
   - Fatigue or loss of energy nearly every day
   - Feelings of worthlessness or excessive or inappropriate guilt nearly every day (which may be delusional)
   - Diminished ability to think or concentrate, or indecisiveness, nearly every day
   - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation or a suicide attempt or specific plan for committing suicide

B. There is significant distress or impairment in social, occupational or other important areas of functioning due to these symptoms
C. The episode is not attributable to the effects of a substance or another medical condition
D. The episode is not better explained by a schizophrenia spectrum or other psychotic disorder
E. There has never been a manic or hypomanic episode

Fig. 1 DSM-5 diagnostic criteria for major depressive disorder (Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*)

multidimensional treatment plan that targets them. Figure 3 illustrates the interplay of these multiple factors in the etiology of depression in late life.

Biological Factors

The pathophysiology of depression in late life can be conceptualized, in part, as a series of dysfunctional physiological processes that lead to disruption of the neural networks responsible for mood. Of the multiple neural networks implicated in the experience, regulation, and expression of mood, cortical and limbic structures appear to be of most significance. The prefrontal cortex, cingulate cortex, amygdala, hippocampus, and hypothalamus are each densely interconnected, and disruption at any level can cause a range of emotional, behavioral, and cognitive disturbances

Symptoms Group A	Symptoms Group B
Depressed Mood	Reduced concentration & attention
Loss of interest & enjoyment	Reduced self-esteem and self-confidence
Reduced energy and activity	Ideas of guilt and unworthiness
	Disturbed sleep
	Diminished appetite

F32.0 Mild Depressive Episode

At least 2 symptoms from Group A and 2 from Group B present to a mild degree for a minimum duration of 2 weeks

F32.1 Moderate Depressive Episode

At least 2 symptoms from Group A and at least 3 from Group B present to a marked degree for a minimum duration of 2 weeks

F32.2 Severe Depressive Episode without Psychotic Symptoms

All 3 symptoms from Group A and at least 4 from Group B should be present, some with severe intensity. Symptoms should be present for at least 2 weeks but an earlier diagnosis may be justified if symptoms are particularly severe or of very rapid onset

F32.3 Severe Depressive Episode with Psychotic Symptoms

A severe depressive episode which meets the criteria for F32.2 and in which delusions, hallucinations or depressive stupor are present

Fig. 2 ICD-10 criteria for depression (Adapted from the International Statistical Classification of Diseases and Related Health Problems 10th Revision)

that produce the clinical depression phenotype. Figure 4 depicts how the biological factors discussed below may interact as potential insults to the fragile neural networks of the aging brain.

Medical Illness

Medical ill health and late life depression are intimately related. Poor physical health is implicated in both the onset and persistence of depression and presages a poorer outcome, while depression adversely affects medical outcomes. It is uncertain whether this relationship is propelled by the illness entity or by the symptom experience though the likelihood is that a combination of both psychological and physiological factors is at play.

A wide array of illnesses has long been known to be associated with depression (Table 1), and many are screened for routinely as part of the initial work-up process. Disorders which are common in elderly populations such as chronic obstructive

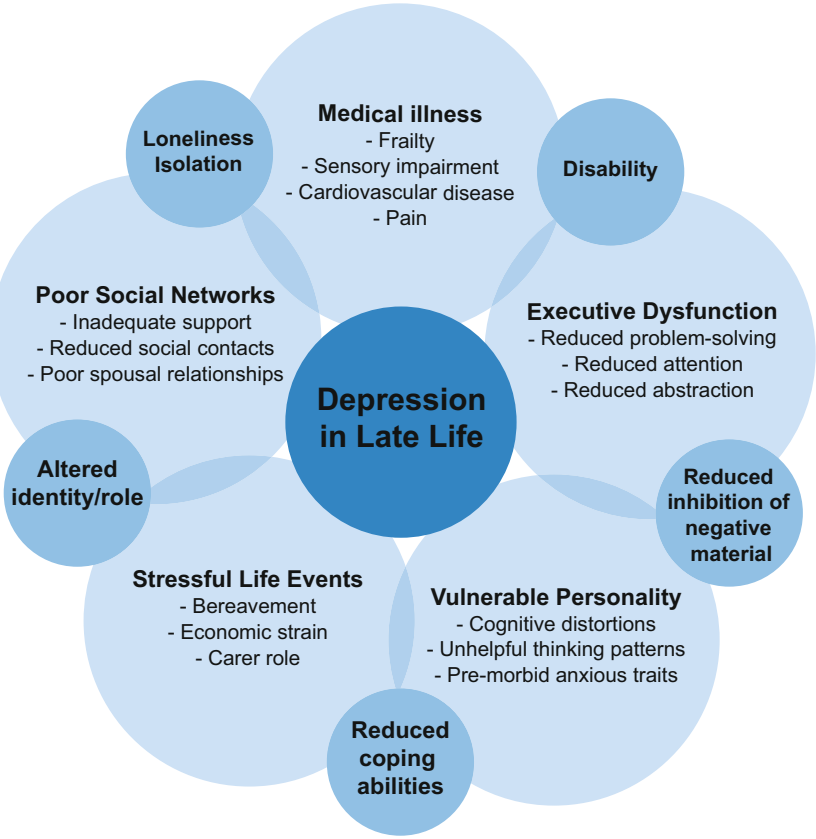

Fig. 3 Biopsychosocial model of depression in late life

pulmonary disease (COPD), osteoporosis, arthritis, type 2 diabetes, chronic pain, and obstructive sleep apnea (OSA) are frequently comorbid with depression. The link between Parkinson's disease and depression is particularly notable with a 2008 systematic review finding major depression among 19% of Parkinson's patients and clinically significant depressive symptoms in another 35% (Reinjders et al. 2008). Depression and stroke are highly comorbid also with pooled data from a systematic review showing a prevalence of 21.7% for major depression in stroke patients (Robinson and Spalletta 2010), while depression was seen to increase stroke risk among a large sample of 85-year-olds in Sweden when followed for 3 years (Liebetrau et al. 2008).

The relationship between cardiovascular disease (CVD) and late life depression has been extensively explored and can serve as a paradigm for the bidirectional association between poor physical and mental health. Large, multicenter studies have conclusively shown that CVD increases the risk of depression over time, while those who are depressed are at higher risk of suffering cardiovascular events. Even after correction for other cardiovascular risk factors, major depression has been

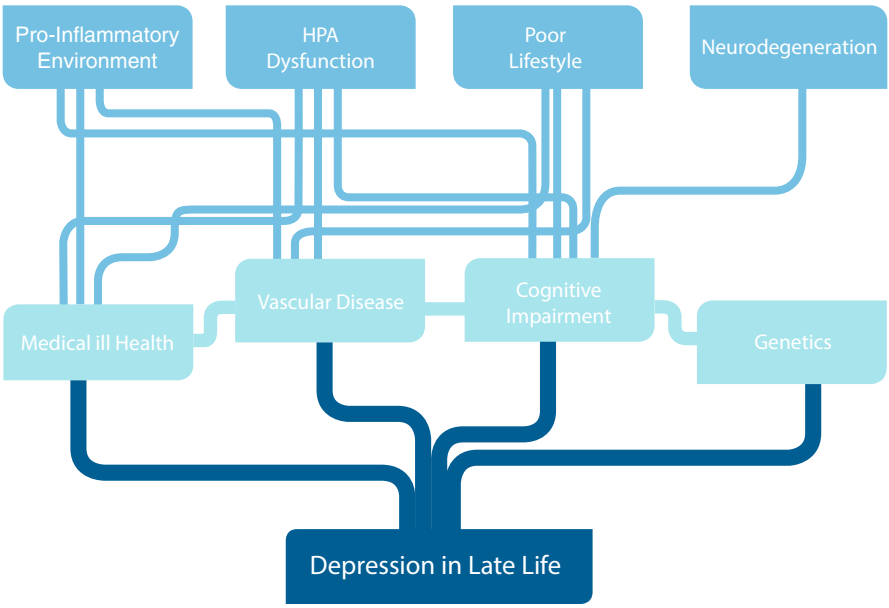

Fig. 4 The interplay of biological factors in the etiology of depression in late life

Table 1 Medical conditions associated with depression

Medical conditions	
Endocrine/metabolic	Hypo-/hyperthyroidism
	Type 2 diabetes
	Pernicious anemia
	Hypercalcemia
	Cushing's disease
	Addison's disease
Malignancy	Pancreas
	Lung
	Breast
	Bowel
Infections	Hepatitis
	HIV
	Mononucleosis
	Brucellosis
Hematological disease	Anemia
	Lymphoma
	Leukemia
Organic brain disease	Cerebrovascular disease/stroke
	Parkinson's disease
	Alzheimer's and vascular dementia

shown to confer an 80% increased risk of CVD on older adults, and outcomes for each disease are worse when comorbid (Choi et al. 2014; Gallagher et al. 2012). A meta-analysis of over 10,000 postinfarction patients (mean age 61 years) which adjusted for cardiac disease severity showed that depression was associated with a 22% increased risk of all-cause mortality (including cardiac mortality) and 13% increased risk for cardiovascular events (Meijer et al. 2013).

An underlying genetic vulnerability common to both conditions would be plausible to explain the degree of reciprocity between depression and cardiovascular disease. Physiological factors such as increased platelet reactivity, reduced heart rate variability, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated inflammatory markers, and activated cytokine and chemokine cascades are common to both, implicating a pro-inflammatory physiological environment as common to their etiology. Psychological stress and poor lifestyle habits contribute to hypertension, vascular damage, and a weakened immune system, and depression is associated with poor maintenance of cardiovascular risk factors at a population level (Choi et al. 2014).

The physiological mechanisms underlying the relationship between depression and medical illness are, therefore, manifold. It is essential, however, to be cognizant, also, of the psychological and social effects that physical illness and disability can have on mental health, particularly in the elderly. These factors will be discussed in further depth at a later point but should be borne in mind when considering the research literature on late life depression and medical illness. The highest rates of depressive symptoms in older people are to be found among those receiving high-level home support, hospital, or institutional care. This could be interpreted purely as a function of the medical burden seen invariably in this cohort of patients. However, it is important to be aware of the wider meaning and impact of the particular illness on the individual patient and to appropriately contextualize the contribution of biology when considering the etiology of depression.

Vascular Risk

The strong association between vascular risk factors, white matter lesions (WMLs), and depression led to the development of the vascular depression hypothesis which proposes that cerebrovascular disease can predispose, precipitate, or perpetuate a distinct clinical phenotype of depression in late life (Alexopoulos et al. 1997). It is thought that damage to the vasculature supplying cortico-striato-pallido-thalamic pathways disrupts the neural circuitry responsible for the regulation of mood. Fronto-striatal dysfunction may impair executive cognitive processes also, and the common co-occurrence of depressive symptoms and executive dysfunction in older adults, particularly those experiencing depression for the first time in later life, gave rise to the so-called depression-executive dysfunction syndrome. Neuroimaging findings bolster these propositions by demonstrating that white matter change is associated with incident depression in later life, higher scores on depression scales, and lower remission rates with treatment (Firbank et al. 2012; Gunning-Dixon et al. 2010). Opinions diverge on whether WML location or volume is of greater clinical import in the pathogenesis of these syndromes.

The vascular depression hypothesis implies a unidirectional relationship between vascular risk factors and depression, but this is likely an overly simplistic view. For example, WMLs are seen in an array of nonvascular conditions such as multiple sclerosis and hydrocephalus. In addition, not everyone with significant white matter disease burden is depressed. There must, therefore, be other factors mediating the relationship between cerebrovascular disease and depression.

The threshold hypothesis provides a useful model to conceptualize this. It proposes that after crossing an initial vulnerability threshold, vascular or other processes, e.g., inflammatory or endocrine, may serve as one of the multitude of factors that increase susceptibility to depression through disruption of affective and cognitive neural circuits (Taylor et al. 2013).

Cognitive Impairment

The dementia prodrome hypothesis is based on the findings of longitudinal studies that demonstrate an increased risk of progression to cognitive impairment among those with late-onset depression (Baldwin et al. 2006). It is thought in these cases that the emergence of depressive symptoms may be the first manifestation of the neurodegenerative processes responsible for the later effects on cognition. Consistent with this is the finding that depression in earlier or midlife does not seem to confer the same level of risk, though it is additive for a person who suffers both early and late life episodes (Barnes et al. 2012). Progression to both Alzheimer's dementia and vascular dementia is increased when compared to the nondepressed population, and the severity of depressive symptoms is linked to a greater risk of cognitive decline. Emerging data suggests that the risk of later dementia may be predicted by the particular course that depressive symptoms take over time. A recent study that followed over 3,000 depressed but dementia-free patients aged over 55 for 11 years monitored the trajectories of depressive symptoms and assessed for incident Alzheimer's dementia. Those whose depressive symptoms followed a course of persistently increasing severity over time had a significantly higher risk of transitioning to dementia compared with those whose symptoms followed a trajectory of lower severity as measured on the Center for Epidemiologic Studies Depression Scale (CES-D) (Mirza et al. 2016).

Given the link between depression and Alzheimer's disease, amyloid plaque deposition is coming under increasing scrutiny as potentially contributory to the etiology of certain types of depression. A postmortem examination of the brains of patients with cognitive impairment and major depression showed that Alzheimer's pathology predominated (Sweet et al. 2004). Another study using amyloid PET imaging to investigate amyloid deposition in patients with remitted major depression showed that half of the patients who met the criteria for MCI had amyloid patterns in the range of Alzheimer's patients (Butters et al. 2008). These are small studies, however, which are still a long way from establishing a causal link.

Cerebrovascular, neuroendocrine, and inflammatory processes are also implicated in the link between depression in late life and later dementia. For example, the hippocampus, which is integral to both mood regulation and memory

functioning, has been identified as an area which is particularly vulnerable to the effects of elevated circulating glucocorticoids and ischemia.

These factors – poor vascular health, amyloid deposition, and a chronic pro-inflammatory environment – are not mutually exclusive, and a threshold model can be useful in this context, also, to conceptualize the accumulation of various neuropathological insults which may account for the link between late life depression and dementia.

Genetics

A family history of depression is significantly less likely in late-onset depression than in depression of earlier onset (Gallagher et al. 2010). Studies are inconsistent as to the contribution of genetics to the overall variance of depression, but the interplay of genes with the environment and protective factors in later life is an active area of research nonetheless.

Brain-derived neurotrophic factor (BDNF) plays a key role in synaptic regulation and plasticity and is coded for by the BDNF gene on chromosome 11. The met66 allele of the BDNF gene may be associated with an increased risk of late life depression, a higher burden of WMLs, and, interestingly, higher rates of remission with treatment. Animal models suggest that BDNF expression is associated with stress and higher remission rates are hypothesized to be due, in part, to the effects of antidepressants on a dysregulated HPA axis (Dwivedi 2013).

The serotonin transporter is an important site of action for many antidepressants, and polymorphisms in the promoter region of the serotonin transporter gene (5HTTLPR) are thought to be relevant to both the pathogenesis and treatment of late life depression. There is evidence to suggest that carriers of the S/S genotype who have experienced childhood trauma bear an increased vulnerability to depression in adulthood – and by extension into later life. The HPA axis is once again implicated in this gene-stress association. The S/S genotype is also thought to confer lower treatment response rates with the L/L allele linked to better treatment outcomes (Naismith et al. 2012).

The role of the APO E gene – and the E4 allele in particular – is well established in the pathogenesis of Alzheimer's disease and is now coming to attention as potentially important in late life depression. A recent study of a sample of 800 patients aged over 70 without either depression or dementia at study entry showed that the APO E4 allele was associated with incident depression when the sample was followed for 5 years. The association remained even after those who became depressed and later developed dementia were removed from the analysis (Skoog et al. 2015). Studies looking at whether the E4 allele is associated with early- versus late-onset depression have produced inconsistent results.

Psychological Factors

By and large, the psychological factors which are implicated in the development of depression in later life are similar to those relevant to earlier onset illness. A person's personality traits and cognitive characteristics are central to their response to adversity,

be that in a protective capacity or a more maladaptive pattern. The stress-vulnerability model proposes that depression arises when environmental stressors and a negative or highly stressful experience impact on a vulnerable personality (Goldberg and Huxley 1992). The nature of these triggering events may differ in late-onset depression from those commonly associated with depression in earlier life. Physical ill health, loneliness, and bereavement are in general more pertinent in late-onset depression.

Personality Factors

Neuroticism confers a well-established vulnerability to depressive symptoms and major depression. Longitudinal studies have shown that neuroticism predicts the recurrence of depression in later life and the severity of symptoms (Steunenberg et al. 2010; Koorevaar et al. 2013).

Cluster C personality disorders seem to predominate among the older depressed with avoidant and dependent personalities particularly prevalent and associated with a poorer treatment response.

There is also a strong association between low scores on measures of personal mastery and risk of depression. Low mastery is associated with negative affect, anxiety, and depression with higher mastery protective against negative life events. The risk of recurrence of depression in patients aged over 55 years at study outset was increased threefold among those who scored poorly on measures of mastery when followed for 6 years (Steunenberg et al. 2010).

Cognitive Style

The cognitive model of depression proposes that cognitive distortions may be a cause of depression. Catastrophization and overgeneralization are more likely to be associated with depressive symptoms than more positive thinking processes such as positive reappraisal. Cognitive styles that lead to difficulties inhibiting the processing of negative material are associated with greater rumination among the depressed, and executive dysfunction, which is closely aligned with late life depression, may be a mediator in this relationship (Von Hippel et al. 2008). Depressed elderly patients have been shown to feel a greater negative impact of life events in the preceding year than dysthymic or euthymic controls (Devanand et al. 2002). However, depression itself can give rise to negative thinking patterns, and the direction of the relationship between cognitive style and depression remains an ongoing source of debate. Nonetheless, it is widely accepted that there is a cohort of people across all age groups, who are caught in a cycle of unhelpful cognitive processes, with an overemphasis on negative material, who are particularly vulnerable to the onset of a depressive episode.

Social Factors

Stressful Life Events

Each of the 36 participants in a 2011 study of the meaning of depressed mood to older adults attributed the onset of their depression to a precipitating life event

despite demonstrating an awareness of the importance of biological mechanisms to the etiology of a depressive episode (Gustavson 2011). This underlines the salience given to life stressors, on a personal level, in crafting an interpretation of one's experience of depression.

Debate exists around whether depression is more likely to arise in the context of the cumulative effect of a number of stressors or in response to a sudden, severe negative event such as a bereavement or relationship breakdown. It has been proposed that exposure to specific negative experiences earlier in life, for example, childhood abuse, increases the vulnerability to depression in later life due to changes in the biology of stress management which confer vulnerability to depression onset in response to a triggering event. "Allostatic load" has been proposed as a measure of dysregulation of multiple physiological systems including the HPA axis. It has been shown to increase in response to the buildup of stress across the life cycle and is associated with impaired physical and mental health and functional decline in older adults (Karlamangla et al. 2002).

The relationship between chronic strain and depression is clearly illustrated in studies of caregivers which consistently show that they are particularly vulnerable to depression. An assessment of 100 informal carers of community-dwelling patients of a geriatric psychiatry service revealed a prevalence of depression of 21%. Higher scores were associated with more problem behaviors or functional disability in those they were caring for (Molyneux et al. 2008).

Socioeconomic adversity is an established source of chronic stress with longitudinal studies showing an inverse relationship between social gradient and the prevalence and persistence of depression (McCrory et al. 2013; Mojtabai and Olfson 2004).

Retirement brings about very significant life changes with effects on daily occupation, personal relationships, and identity. The literature on the impact of retirement on mental health is inconsistent, reflecting the complexities associated with such a significant transition. It is likely that certain additional factors will increase the risk of depression postretirement as seen in a group of older Irish adults where involuntary or forced retirement or retirement due to ill health was associated with a negative and statistically significant effect on mental health (Mosca and Barrett 2016).

Bereavement is one of the life events that are experienced with increased frequency in later years. It is argued that the elderly may be more prepared for significant loss than younger adults for whom bereavement may be more unexpected and difficult to accept. Nonetheless, for many older people, grief represents a significant challenge to their psychological resources and coping abilities. A large meta-analysis of people aged over 50 showed that bereavement had the greatest effect size of all the factors studied, more than tripling the risk for the onset of depression (Cole and Dendukuri 2003). Death of a spouse or partner is particularly linked to depression with loneliness appearing to underlie the excess risk (Golden et al. 2009).

Social Support

Social network size and composition, frequency of social contacts, and instrumental/emotional support were some of the parameters found to be associated with

depression in a study of community-dwelling elderly in Hong Kong. Satisfaction with social support was found to be the most important predictor of depression severity with both inadequate and excessive support linked to late life depression (Chi and Chou 2001; Nolen-Hoeksema and Ahrens 2002). This may reflect varying personal attitudes on concepts such as personal independence, social role, and identity as well as differences in individual psychological makeup. Unsurprisingly, spousal relationships play a key role in moderating psychological well-being with poor quality of partner interactions associated with depression, anxiety, and suicidal ideation in older adults (Ivan Santini et al. 2015).

The role of loneliness in the etiology of late life depression cannot be underestimated, though it is often overlooked. Social loneliness and emotional loneliness are thought to represent two distinct manifestations of the experience of loneliness with emotional loneliness, which occurs due to the loss of an intimate bond, being perhaps more important in older populations whose close relationships are thinning out due to aging and death (Luanaigh and Lawlor 2008). Thirty-five percent of older adults were identified as lonely in a 2009 community-based study, with highest rates among women, the widowed, and the physically disabled. There was a clear relationship to depression with a population attributable risk of 61% (Golden et al. 2009). Loneliness is associated with more severe depression, lower remission rates, and an increased risk of suicide in the elderly (Holvast et al. 2015; Waern et al. 2003).

Presentation

Depression in late life is a heterogeneous condition that encompasses late-onset depression and early-onset, recurrent depression, and the presentation varies accordingly. See Table 2. Patients with late-onset depression present as less clearly affectively disturbed, more preoccupied somatically, and more agitated. Amotivation, anhedonia, and hopelessness are commonly endorsed. Cognitive impairment is more pronounced and less likely to resolve. Patients with late-onset depression tend to be physically frailer with a high burden of chronic and disabling illnesses. A past history or family history of depression is less likely in late-onset depression, possibly implying a stronger genetic influence in early-onset illness.

A lack of clarity in the literature on whether depression in late life is in fact a phenomenologically distinct condition may be explained, in part, by the fact that most studies do not specifically distinguish between late- and early-onset illness. Studies which categorize patients according to age of onset of the first depressive episode are, unfortunately, relatively few in number.

Studies also differ in their participant populations, age cutoffs, diagnostic tools, and methods of classification. Overlap of somatic symptoms common to both depression and age-related physical illnesses (pain, fatigue, sleep disturbance) may lead to under- or overdiagnosis of depression resulting in a phenomenological depiction of an "impure" cohort. Diagnostic accuracy may also be limited by sociocultural differences between generations which affect the perception and

Table 2 Characteristics of early-onset/recurrent depression and late-onset depression

	Early Onset/Recurrent Depression	Late Onset Depression
Biological Factors		
Past Psychiatric History	Common	Less common
Family History	Likely	Less likely
Medical History	Closer to population norms for age	Multiple co-morbidities
		Chronic, disabling conditions
		Physically frail
Neurocognitive Factors		
Neuropathology	Closer to population norms for age	Increased white matter lesions
		Cerebrovascular disease
		Possibly increased amyloid deposition
		Hippocampal atrophy
Cognitive Impairment	Relatively milder attentional and executive deficits	Marked attentional and executive deficits
		Slowed psychomotor processing speed
	Temporal association with depression onset	
	Insight into deficits may be present	Less insight
	More likely to resolve	May not fully resolve
		Association with later dementia
Presentation		
Symptom profile	Prominent affective symptoms	Affective symptoms may be less prominent

(*continued*)

Table 2 (continued)

	Early Onset/Recurrent Depression	Late Onset Depression
	Feelings of worthlessness and guilt may be relatively more prevalent	Agitation, sleep disturbance, anhedonia may be relatively more prevalent
	Less somatic preoccupation	Somatic preoccupation and somatic delusional themes common
	Anxiety highly co-morbid - work, finances, interpersonal relationships common themes	Anxiety highly co-morbid - family, physical health, disability common themes. May increase risk of cognitive decline.
	Clear precipitants may be less obvious	Poor health, grief, loneliness, changing role common precipitants
Suicide	Recurrent suicidal behaviour and para suicide seen more commonly	Suicidal behaviour less common
		High level of intent
		Methods of high lethality used
		More likely to succeed

expression of depression. Additionally, many studies fail to account for what are proposed to be age-specific subtypes of depression, such as vascular depression or non-dysphoric depression, which, as a result of organic changes of the aging brain, are thought to be neurobiologically distinct from early-onset depression.

The vascular depression phenotype is typified by significant psychomotor retardation with less agitation and guilt and poorer insight than depression without vascular risk factors. MRI-defined vascular depression groups are older at age of the first onset, endorse more apathy and anhedonia, and are less likely to have a family history of depression (Krishnan et al. 2004). Executive cognitive impairment is prominent ("depression-executive dysfunction syndrome") with impaired

planning, organization, sequencing, problem-solving, and set-shifting as well as reduced speed of information processing. Contrary to the long-held assumption that cognitive deficits resolve as depressive symptoms remit, studies are demonstrating that some degree of cognitive dysfunction tends to persist even after successful treatment of the mood symptoms.

It has long been recognized that elderly people may minimize feelings of sadness – possibly a reflection of a generation raised in an era when emotional or mental difficulties were not openly discussed and were viewed as evidence of personal weakness. Non-dysphoric depression characterizes those elderly patients who deny sadness but endorse hopelessness, anhedonia, and a lack of interest in personal care. Though lacking a core diagnostic feature of operationalized depression (sadness), the syndrome was associated with increased psychological distress, disability, and mortality in a 13-year interval follow-up study (Gallo et al. 1997). A 2010 study of 787 elderly primary care patients demonstrated that those with vegetative symptoms of depression without mood disturbance showed poorer cognitive and functional performance, highlighting a need for vigilance for depression in the absence of clear-cut mood changes (Paradiso et al. 2010).

The link between late life depression and dementia was explored previously. However, the nature of a dementing illness can make the diagnosis of a superimposed or comorbid depression quite challenging due to the overlap of certain symptoms (apathy, sleep disturbance) and impaired recognition and expression of an emotionally disturbed state. Olin et al. have proposed criteria to assist in the diagnosis of depression of Alzheimer's disease. Three or more features of major depression are required, excluding poor concentration, but including more non-somatic symptoms such as irritability and withdrawal (Olin et al. 2002). Depression in the context of dementia can present as increased behavioral disturbance, wandering, and an impairment of ADLs out of keeping with the degree of cognitive impairment.

Because these less "typical" presentations do not necessarily cleave strictly to the core DSM and ICD criteria for a depressive disorder, it is likely that they are under-recognized and undertreated. They may be dismissed as an "understandable" and therefore "normal" reaction to age-related life events. Overlooking a depression, however, will exclude people from access to treatment, leading to prolonged suffering both for patients and their families and increasing the risk of other adverse outcomes such as functional decline, deterioration in physical and cognitive health, and suicide.

Anxiety

Anxiety is highly comorbid with depression and contributes substantially to levels of distress and functional disability. A large study ($n = 14{,}200$) assessing older adults in seven European countries demonstrated that clinically significant anxiety symptoms were present in 87% of those with case-level depression and 67% of those with

subthreshold depression. Anxiety symptoms were associated with increased severity of depressive symptoms and higher functional disability (Braam et al. 2014). In a sample of community-living elderly, comorbid anxiety was found at case level in 17.3% of those who were depressed with sub-case level anxiety found in a further 59.9% (Kirby et al. 1997). While anxiety is highly comorbid in both early- and late-onset depression, the themes are thought to differ (see Table 2). Late life depression is more persistent and difficult to treat when combined with anxiety. Somatic symptom expression is more frequent, and there is a significantly higher risk of suicide. Organic depression, in particular, is thought to be associated with more anxiety, and anxiety may also increase the risk of cognitive decline among older adults with treated depression.

Pseudodementia

The term "pseudodementia" refers to a clinical picture characterized by a reversible dementia syndrome arising due to depression. Organic causes such as vitamin B12 deficiency and hypothyroidism must be ruled out prior to this diagnosis being made. In general, patients are said to be aware of and distressed by their memory impairment and can often date the onset of their problems in contrast to the more insidious onset of a neurodegenerative dementia. Assessment of cognitive function often leads to frequent "I don't know" answers which also differs from those with dementia who try their best but are simply unable to answer accurately. A history which clearly identifies the onset of a mood disturbance as preceding the cognitive symptoms can point toward the diagnosis. In certain respects, however, the term "pseudodementia" is now seen to be slightly outmoded, as we now know that cognitive deficits in the context of depression may not, in fact, be fully reversible and may presage the later onset of a true dementia syndrome. It serves well, however, to identify people who bear monitoring for cognitive decline over time once the initial depression has been treated.

Suicidality

Suicide among older adults is more likely to be associated with depression than suicide at any other age. Suicidal behavior and repeated acts of self-harm are uncommon among older adults, who are also less likely than younger age groups to verbally express suicidal ideation. They are, however, the age cohort most likely to use an immediately lethal means of self-harm and the most likely to complete suicide. More than any other age group, therefore, a suicide attempt in an older adult needs to be recognized as a grave event signaling a severe depression requiring immediate and aggressive treatment. Elderly people attempting suicide are more likely to be widowed, live alone, have a poorer perception of their health status, experience poor sleep quality, lack a confidant, and experience stressful life events

(Conwell et al. 2002). Neurotic personality styles and executive dysfunction are also associated with suicide in later life. Comorbid anxiety increases the risk of suicide in older adults as do comorbid alcohol or substance misuse, each of which is an important therapeutic target when identifying and treating elderly suicidal patients.

Management

A detailed history and collateral information are key to identifying elderly people who may be at risk for or are struggling with depression. Successful management requires a holistic approach. While pharmacotherapy can play a vital role in moderate to severe cases of depression, it must be used with caution in this group who are particularly vulnerable to adverse side effects and the risks of polypharmacy. Physical health, social disconnection, and functional/occupational decline are vital therapeutic targets which demand multimodal treatment plans tailored to the individual needs and abilities of the patient.

Pharmacotherapy

Placebo-controlled studies and meta-analyses support the efficacy of antidepressants in late life depression. However, the benefits are modest with high placebo response rates and smaller treatment effects relative to placebo in patients over 65 compared to younger populations (Cleare et al. 2015). The rate of an adequate response to first-line medication is approximately 50% in the elderly. Medications appear to have greater value in the treatment of moderate to severe cases, and older patients may require longer treatment trials than considered sufficient in younger groups. It is vital to be cognizant also of the potential for reduced tolerability of medications in older people due to age-related physiological changes that affect pharmacokinetics and pharmacodynamics. With that in mind, guidelines are consistent in their advice to initiate treatment at lower doses than used in younger patient groups and to be aware of comorbid medical conditions and co-prescribed medications that may affect drug efficacy and metabolism (NICE 2009; APA 2010).

Treatment Strategies

Accurately elucidating presenting symptoms, previous treatments, medical comorbidities, and patient preference in a comprehensive history should guide decisions around pharmacotherapy. Monotherapy with a safe and effective agent is the ideal, but in cases where the clinical response is suboptimal or absent, consensus opinion suggests a number of possible strategies. See Table 3.

Antidepressant Classes

Table 4 summarizes the effects of the various antidepressant classes in the elderly. Selective serotonin reuptake inhibitors (SSRIs) are generally considered to be the first-line agents in the treatment of moderate to severe late life depression. They are

Table 3 Pharmacologic strategies in suboptimal response or treatment failure

Strategy	Example
Optimization	Dose increase
	Longer treatment course
Substitution	SSRI to another SSRI
	SSRI to a different antidepressant class
Augmentation	Lithium
	Atypical antipsychotic (data for mid-age groups only)
Combination	SSRI and mirtazapine
	Mirtazapine + venlafaxine

Table 4 Medication classes and effects in the elderly

	Advantages in elderly	Disadvantages in elderly
SSRIs	Effective	Hyponatremia
	Clinician confidence	Falls
	Better tolerated than SNRIs or TCAs	GI bleeding
		Serotonin syndrome
	Sertraline safe in cardiac disease (mixed-age data only)	Prolongation of QTc with citalopram and escitalopram
SNRIs	Efficacy comparable to SSRIs	Falls
		Postural hypotension
		Hyponatremia
TCAs	Efficacy comparable to SSRIs	Anticholinergic effects
		Postural hypotension
	Can be helpful in sleep disturbance	Sedation
	Useful in comorbid neuropathic pain	Weight gain
	Side effect profile varies within class	Cardiotoxicity
Mirtazapine	Anxiolytic effects	Sedation
	Helpful in sleep disturbance and anorexia	Falls
		Weight gain
	May be useful in hyponatremia	
Bupropion	Limited evidence supports efficacy	Possibly improves energy and motivation
Lithium	Effective as augmentation strategy	Renal impairment over time
	Reduces suicide risk	
	Possibly neuroprotective	Optimal plasma ranges less clear
		Increased vulnerability to neurotoxicity
Antipsychotics	Effective as adjunctive treatment (data in mixed-age samples only)	Metabolic side effects
		Increased cerebrovascular risk and mortality in dementia
	Useful in sleep disturbance	
	Anxiolytic effects	Movement disorders
	Effects seen within days	Akathisia

effective, with a 2008 meta-analysis of randomized, placebo-controlled trials in older people demonstrating a higher likelihood of response for SSRIs when compared to placebo (OR = 1.36, 95% CI 1.19–1.56). Response rates were significantly higher in trials of longer duration (10–12 weeks vs. 6–8 weeks). Discontinuation rates and adverse effects were also higher in the treatment groups with pooled mean adverse event dropout rates of 12% for those in the treatment arms compared to 7% of those receiving placebo (Nelson et al. 2008). A 2014 literature review quotes response rates of 30–60% for SSRIs versus 20–40% for placebo with remission rates of 32–44% for SSRIs compared to 19–26% for placebo (Taylor 2014). Although studies comparing SSRIs and tricyclic antidepressants (TCAs) demonstrate largely equivalent efficacy, SSRIs are associated with a lower risk of adverse effects and are therefore considered preferable as first-line agents.

Common adverse effects associated with SSRIs include headache, sleep disturbance, sexual dysfunction, and gastrointestinal (GI) upset. These are usually mild and resolve within 14 days of treatment or dose increase. More serious adverse effects that are particularly associated with older populations include serotonin syndrome, hyponatremia, falls, and GI bleeding. Diuretics, aspirin, and NSAIDS, commonly prescribed for older people, increase vulnerability to these adverse effects. The period of highest risk for side effects is within the first 28 days of treatment. Citalopram and escitalopram have been implicated in prolongation of the QTc interval at higher doses, and limiting maximum treatment doses to 20 mg and 10 mg, respectively, is now advised in the elderly. Evidence from mixed-age samples supports the safety of sertraline in cardiac patients with depression though there is no data on this specifically in the elderly. SSRIs are considered relatively safe in overdose with the possible exception of citalopram and escitalopram due to QTc prolongation. SSRIs have the potential to cause significant drug-drug interactions via inhibition of the hepatic cytochrome-P450 isoforms.

Serotonin-noradrenaline reuptake inhibitors (SNRIs) are a common second choice when a patient fails to respond to an SSRI. There is no clear difference in efficacy between the two classes, but adverse events may be more common with SNRIs. In particular, postural hypotension, with its attendant risks of falls and cerebrovascular compromise, is a cause for concern in older populations, where physical frailty, autonomic fragility, and polypharmacy are commonplace.

TCAs are as efficacious as SSRIs and may be prescribed either as monotherapy or augmentation if SSRIs and SNRIs are ineffective. Anticholinergic effects, postural hypotension, sedation, and weight gain are particularly associated with the use of TCAs in the elderly though the side effect profile of the individual drugs within the class can vary considerably. They are considered dangerous in overdose due to cardiotoxicity but can be helpful in the management of sleep disturbance or comorbid neuropathic pain. Secondary amines, e.g., nortriptyline, are generally better tolerated with less anticholinergic effects and less sedation. Lofepramine, a tertiary amine, is considered to be less cardiotoxic and is preferred in cardiac disease where treatment with a TCA is unavoidable.

Mirtazapine and bupropion are considered reasonable alternatives. Data with respect to their use in the elderly specifically is limited but points to their being effective in the

relief of depressive symptoms (Hewett et al. 2010; Roose et al. 2003). Bupropion may also improve energy and motivation and reduce functional limitations. Mirtazapine has anxiolytic, appetite stimulant, and sedative properties that can be useful where anxiety, anorexia, or sleep disturbance are features, though falls, sedation, and weight gain are important considerations also. Cases of hyponatremia have been attributed to mirtazapine though the impact on sodium levels appears to be less than that of SSRIs, and, as such, mirtazapine may be a reasonable alternative in these situations.

Lithium augmentation of unipolar major depression in younger depressives is established as effective and well tolerated. Its use in older adults arises from this experience, but studies addressing its efficacy and safety in this age group are scarce. A review of extant studies in older people indicates that lithium augmentation of either SSRIs or TCAs improves response rates in older partial or nonresponders to monotherapy (Maust et al. 2013); however, there are no randomized controlled trials to definitively determine its efficacy. Lithium has additional advantages beyond its antidepressant properties: it reduces suicide risk and could be neuroprotective.

However, up to 50% of older adults on lithium may experience side effects, most commonly tremor, polyuria, dizziness, and renal impairment over time. Optimal plasma ranges are unclear as the correlation between serum level and CNS bioavailability is less reliable in older adults. A 2009 study demonstrated that in patients aged over 50 years, brain lithium levels were associated with impairments on tests of executive functioning, a relationship that was not seen in the younger participants. However, the association was not present for serum lithium levels and suggests that serum measurements, alone, may be insufficient to determine early signs of lithium neurotoxicity in older adults (Forester et al. 2009). Age-related deterioration in renal function, polypharmacy, and medical comorbidity render older adults particularly vulnerable to lithium toxicity.

Discontinuation of lithium augmentation is associated with a substantial risk of relapse. In a naturalistic study of older adults attending a lithium clinic, over 50% relapsed following discontinuation of lithium therapy with a mean time to relapse of 7.8 months. Those that were on lithium for longer and had had more hospitalizations were at significantly higher risk of relapse. In the majority of cases, remission following relapse was achieved upon reinstitution of lithium treatment (Fahy and Lawlor 2001).

Antipsychotics

The role of antipsychotics in the management of psychotic depression is well established with combined antidepressant and antipsychotic treatment more effective than the use of either agent alone. However, second-generation antipsychotics are increasingly being used in mixed-age samples as adjunctive therapy in the treatment of nonpsychotic depression. A therapeutic response is sometimes seen within days of initiation, thought perhaps to be due to their anxiolytic and sedative properties which can provide rapid relief from distress and help to regulate sleep patterns. A 2011 pooled subpopulation analysis that assessed the efficacy and safety of adjunctive aripiprazole in mid-age adults (aged 50–67) showed higher remission rates versus placebo (32.5% vs. 17.1%) though discontinuation rates due to adverse effects were

also higher in the treatment group (5.2% vs. 2%) with akathisia the most common adverse effect experienced (Steffens et al. 2011). There is no data on its efficacy in the elderly specifically. Optimum dosing remains to be determined, though it is felt that lower doses than typically used in primary psychotic illnesses are effective in this context. The long-term effects of antipsychotic augmentation are also unclear with justifiable concern about the metabolic side effects, in particular. Consensus opinion, therefore, advises withdrawal of the antipsychotic when possible after 4–6 months of treatment (Alexopoulos et al. 2001).

Duration of Treatment

The elderly are particularly vulnerable to the risks of relapse and recurrence. Balancing the possibility of relapse with the particular hazards of long-term pharmacotherapy in an older population becomes a question, therefore, of significant import. The 2001 Expert Consensus Guideline, compiled from the collated opinions of 50 experts in late life depression, recommends treating a first episode of major unipolar depression for at least 1 year. One to 3 years of treatment is advised in the case of two episodes. For those experiencing a third episode, treatment is likely to be necessary for longer than 3 years (Alexopoulos et al. 2001). As mentioned previously, gradually tapering antipsychotics after 4–6 months of dual antidepressant-antipsychotic treatment is advisable in the case of psychotic depression or adjunctive treatment.

Electroconvulsive Therapy (ECT)

ECT is the most effective option in the management of acute depression, and it is the treatment of choice for psychotic depression. It can be of particular utility in the management of late life depression where physical frailty, sensitivity to side effects, or the organic changes of the aging brain may limit aggressive treatment with antidepressants or the achievement of a complete therapeutic response. Additionally, as discussed previously, suicidal ideation in old age indicates immediate and particular risk, and in this context the rapid therapeutic response induced by ECT can be particularly welcome.

ECT has been shown to be more effective than antidepressants in the elderly with remission rates of 50–85% quoted in a 2013 review of the literature. Remission rates are even higher in psychotic depression, approaching 90%. There is evidence to suggest that older people may respond better to ECT than their younger counterparts, though this is inconsistent (Ramos-Garcia and González-Salazar 2013).

ECT is safe and well tolerated in the elderly. Mortality rates for ECT across all age groups are very low (1:80,000), and safety appears to be independent of age. Respiratory and cardiovascular disease and issues to do with anesthesia appear to confer increased risk, underscoring the need to carefully assess patients for suitability, regardless of age.

The cognitive effects of ECT, however, are of particular relevance to the elderly where impairment of cognition may be comorbid with, compounded by, or directly attributable to the depressive episode. However, the relationship between mood,

cognition, and ECT in late life depression has yet to be fully teased apart by the literature. From mixed-age studies, we know that anterograde amnesia for the period immediately preceding treatment generally resolves within days. Retrograde amnesia for personal or autobiographical events has also been described, though proponents of ECT would argue that studies investigating this phenomenon fail to control for the normal loss of autobiographical memory with time as well as persisting depressive symptoms. Controversy exists as to whether the elderly are particularly vulnerable to these effects though it does appear that they are more susceptible to a prolonged postictal confusion. By contrast, the cognitive impairment associated with the so-called depressive pseudodementia syndrome is likely to improve with successful treatment with ECT. This is supported by studies that show that within 2 weeks of ECT, certain cognitive domains such as processing speed, working memory, and some aspects of executive functioning will improve beyond the pre-ECT baseline (Semkovska and McLoughlin 2010). However, where there is a concern about a preexisting, organic cognitive impairment or a prior history of an adverse cognitive outcome with ECT, variations in ECT technique can attenuate the incidence and severity of cognitive side effects. Increasing the time between treatment sessions or using unilateral rather than bilateral electrode placement has been shown to reduce the risk of cognitive side effects, though treatment response may be less rapid. An important recent study addressed this issue by establishing that high-dose unilateral ECT (6 × seizure threshold) was non-inferior to moderate-dose bitemporal ECT (1.5 × seizure threshold) in terms of response and remission or 6-month relapse status with less adverse cognitive side effects noted with the high-dose unilateral treatment (Semkovska et al. 2016).

Although ECT is extremely effective in the acute treatment of depression, relapse rates approach 80% within 6 months without continued active treatment. Individual patient factors will determine the preferred mode of continued therapy. At a minimum, patients will require antidepressant therapy. However, for those who cannot tolerate medication or who fail to maintain remission on antidepressants alone, maintenance ECT is a valid option. 2012 and 2013 reviews suggest that relapse and readmission rates are substantially lower for older patients receiving maintenance ECT versus antidepressants without evidence of serious or persistent adverse effects even when patients with comorbid cardiac or neurological conditions are treated (Ramos-Garcia and González-Salazar 2013; Van Schaik et al. 2012).

Psychological Interventions

A range of psychological treatments have been empirically determined to be effective in the treatment of late life depression. Common to many of these therapies is a behavioral component that addresses the problems of activity limitation, amotivation, or social disengagement – issues of particular relevance in depressed older people. Additionally, many of these treatments are “manualized” and

educational, rather than reflective, an approach which may be of more utility among certain groups of older people who, for sociocultural reasons, may find the exploration of emotional and psychological issues to be particularly challenging. Psychological interventions may be the first-line treatment in cases of mild to moderate depression. Patient factors such as the ability to commit to weekly therapy sessions and engage in a therapeutic relationship as well as the local availability of services will determine whether a psychological approach is likely to be feasible and of benefit.

Cognitive behavioral therapy (CBT) is based on the premise that reframing dysfunctional and unhelpful thoughts will lead to changes in behavior which increase social engagement and pleasure. It is effective in older people during acute depressive episodes and has benefits in the prevention of relapse, also. Best outcomes, however, are seen when CBT is combined with antidepressant treatment.

Interpersonal therapy (IPT) is another manualized treatment that targets four components that are proposed to precipitate and maintain depression: grief, role transitions, interpersonal deficits, and interpersonal disputes. The therapist guides an assessment of these areas and helps the patient to redirect the associated negative emotions in more positive ways. IPT has been specifically adapted for use in older people and has been shown to be effective, in combination with antidepressant treatment, in the treatment of depression and prevention of relapse.

The benefits of CBT and IPT are less clear among patients with cognitive impairment, a group that are also less responsive to antidepressant therapy. By contrast, problem-solving therapy (PST) effectively treats depression in older patients with executive dysfunction by training them to develop skills to cope with stressful life problems. The structured and practical approach of this treatment modality seems to be particularly helpful in the context of executive impairment with a reduction in disability when compared to supportive therapy and continued benefits following the completion of treatment (Alexopoulos et al. 2011).

Psychodynamic psychotherapy, reminiscence therapy, and mindfulness-based cognitive therapy are among some of the many other psychological treatments which have potential in the management of depression in late life. As yet, there is a lack of definitive evidence as to their efficacy in late life depression. However, they are likely to be beneficial for groups of patients who have been carefully selected according to their individual needs and abilities. This is an area where further high-quality research is required to guide best practice and treatment decisions.

Though psychotherapy may be employed as monotherapy in mild to moderate depression, combined treatment using psychotherapy and antidepressants appears to be most effective to induce and preserve recovery in moderate to severe cases. Patient-specific factors, as well as personal preference and the availability of resources, will guide decisions around the optimum treatment strategy for a particular individual.

It is difficult to empirically quantify the importance of interventions which target physical health, social disengagement, environmental disadvantage, and sensory impairment in late life depression. It is likely, however, that these strategies are often of the greatest value for older depressed people. Loneliness, loss of role, physical disability,

and executive impairment are very amenable to practical interventions designed to improve how the individual interacts with the environment and other people. Central to this multidisciplinary care model is the imperative to enable the individual to continue to enjoy a life of personal meaning and fulfillment while growing older.

Hard-to-Treat Subgroups

White matter hyperintensities on MRI and cognitive impairment are associated with increased disability, poorer response to antidepressants, and higher risk of relapse and recurrence (Alexopoulos et al. 2002). Executive dysfunction can impact negatively on engagement and compliance. Longitudinal studies show that depression in Alzheimer's dementia will tend to remit over time, but depressive symptoms in the context of vascular dementia can prove refractory to treatment. Comorbid alcohol or substance misuse and personality disorders also presage poorer outcomes (Koorevaar et al. 2013). Comorbid anxiety predicts a more severe illness course and is an independent risk factor for suicide. Up to one third of patients will experience a depressive episode in the 5 years following a stroke. Damage to the neural pathways important for the regulation of mood and residual functional disability contribute to the difficulty of achieving remission in this group.

The specific challenges of these patient subgroups demand a flexible and multimodal treatment approach aimed at reducing disability, optimizing quality of life, and minimizing risk. Successful management often requires a longer-term treatment plan with an emphasis on psychological and behavioral interventions. For example, psychosocial therapies with an emphasis on reducing disability and social isolation are effective, in conjunction with pharmacotherapy, for both the treatment and prevention of poststroke depression. Interventions that provide psychoeducation and support to family members have also been shown to be of benefit to the patients themselves. Similarly, engaging carers of dementia patients in structured treatment programs which focus on their personal skills, communication, and coping abilities improves outcomes for the patients.

New Treatments

Ketamine, a NMDA receptor antagonist, with effects on the glutamatergic neurotransmitter system, has been the source of considerable interest as a potential novel antidepressant agent. Used at sub-anesthetic doses for analgesia in certain settings, it has been shown to induce a rapid antidepressant response. Data on its use in the elderly is limited. Case reports suggest that the dramatic improvements seen in younger groups may be replicated in older patients. It appears to be well tolerated, even among the physically frail and those who were unsuitable for ECT because of medical contraindications. Cardiovascular side effects appear to be transient and generally do not require medical attention (George et al. 2016; Horr et al. 2014). Maximal therapeutic effect is seen within hours to days but longer follow-up data is

lacking. The clinical utility of ketamine, however, remains questionable. Therapeutic response is transient, it is administered intravenously, and there are concerns about its potential as a substance of abuse. It remains of interest in research settings, however, as a means of learning more about the role of the glutamatergic system in depressive disorders.

The role of anti-glucocorticoid drugs (e.g., ketoconazole, dehydroepiandrosterone), vasoactive agents (e.g., nimodipine), and stimulants (e.g., methylphenidate) in the pharmacological management of depression is unclear. Data specific to their use in the elderly is minimal. Maust summarizes the very limited data available on the use of methylphenidate to accelerate response to antidepressants in older adults. While improvement of depressive symptoms was seen within 2 weeks in two trials, numbers were small, and a subsequent comparison to placebo led to high dropout rates in the treatment group because of intolerable side effects (Maust et al. 2013).

Repetitive transcranial magnetic stimulation (rTMS) is a newer treatment for depression that uses a rapidly changing magnetic field to induce electrical currents in the brain. The electromagnetic field is generated by a coil held over the scalp. The treatment does not require anesthesia and there are no apparent cognitive side effects. Sessions are held five times per week over 4–6 weeks. While rTMS has been shown to be effective compared to placebo in the treatment of depression, it is inferior to ECT, particularly in severe illness. This is mirrored in the literature for rTMS in late life depression. Response rates for rTMS vary between 20% and 50% for non-psychotic depression in the elderly, but it is not as effective in psychotic depression with ECT far superior in terms of outcomes. Cognitive functioning does not appear to be adversely affected in the elderly, however, and although there have been no studies specifically designed to examine safety in this group, it appears well tolerated (Galvez et al. 2015).

Transcranial direct-current stimulation (tDCS) and vagus nerve stimulation (VNS) are other brain stimulation techniques that aim to produce brain changes by means of electrical currents. There are a small number of individual case reports that indicate favorable results for tDCS in the elderly, but there are no RCTs to date looking at its efficacy in older age groups. Neither are there any studies looking at the efficacy of VNS in the geriatric population. NICE does not currently recommend any of these three techniques for clinical use.

Physical exercise is effective in reducing depressive symptoms among the elderly depressed (Sjösten and Kivelä 2006). It is cheap, has advantages for physical and cognitive health, and can be a means of social engagement and integration. Studies exploring the benefits of exercise in depression have been criticized for poor quality methodology. Patients who are sufficiently motivated to engage in a structured exercise program likely represent a highly selected cohort who is unrepresentative of the general older depressed population. Despite these methodological flaws, however, with its manifold advantages on physical and general well-being, physical exercise should be considered an important therapeutic intervention that may offer multiple treatment benefits for specific patient groups.

Prevention of Depression in Late Life

Successful treatment of depression in late life is difficult. Preventing the onset of illness in the first place is, naturally, preferable as a means of averting emotional suffering as well as illness-related morbidity and mortality. Primary prevention must take a biopsychosocial approach that encompasses the physical, cognitive, psychological, and social aspects of late life depression. Public education has the potential to reduce stigma, improve awareness, and increase understanding of depression, anxiety, and addiction. Community initiatives designed to promote and maintain older peoples' resilience to adversity may offset the more severe mental health consequences of bereavement, physical illness, and loss. Community social groups and outreach programs can reduce the risks associated with loneliness and isolation. However, these interventions should be implemented in midlife so that support networks are well established and adaptive coping mechanisms entrenched prior to the onset of older age.

Secondary prevention should focus on identifying and intervening in at-risk groups. Subsyndromal depressive symptoms are associated with a 40% risk of depression with a number needed to treat of 5.8 (Schoevers et al. 2006), supporting the treatment of subsyndromal states. Stroke patients who receive preventative antidepressant medication are less likely to become depressed than those who receive placebo (Whyte et al. 2006). Intervening in poor physical health, chronic pain, and sensory impairment further reduces incident depression. Carers of ill or disabled people are very vulnerable to depression, but programs that enhance their caring skills and coping strategies as well as support groups are effective in reducing their risk of becoming depressed. As at all stages across the life cycle, managing alcohol and substance dependency is a challenging but essential component of preventative mental health care.

Tertiary prevention strategies identify cases of late life depression and treat them at an early stage to reduce the risk of illness-related morbidity, chronicity, and mortality.

Course and Prognosis

The prognosis of late life depression is poor. Early-onset depression is associated with more depressive episodes across the life-span, but the comparatively better response to medications in this group lends to a more characteristic relapsing-remitting course. Late-onset depression is associated with a chronic course, longer duration of illness, high risk of relapse, increased mortality, and increased risk of later dementia. A longitudinal study of 127 depressed older patients living in the community showed that at 3 years, 30% had died, 35% had persistent or relapsed depression, 25% had another mental illness, and only 10% had maintained a complete recovery (Denihan et al. 2000). In this older, physically frailer group, medical comorbidity is a risk factor for poor medication response and tolerability.

Cognitive impairment predicts a poor prognosis, and the depression-executive dysfunction syndrome is associated with particularly poor outcomes: poor response to treatment, long-term persistence of symptoms, disability, and higher rates of relapse and recurrence (Sheline et al. 2010; Alexopoulos et al. 2002). Complete resolution of cognitive deficits is rare, particularly in late-onset depression. Comorbid neurological disorders, anxiety, substance misuse, and personality disorders also predict poorer outcomes.

Conclusion

Depression in late life is an etiologically heterogeneous condition that leads to significant suffering, functional disability, and social disruption. It is associated with increased morbidity and mortality and may be a harbinger of neurocognitive decline. It is common, though under-recognized. The physiological and biochemical effects of the aging brain as well as physical illness and age-related psychosocial changes distinguish late-onset depression from early-onset, recurrent depression. Late-onset depression may present quite differently with less affective disturbance and more somatic preoccupation and executive dysfunction. Depression in later life is amenable to treatment, but successful management requires a comprehensive, integrated, and biopsychosocial approach that links patients and families to medical services, community resources, and social supports. Our knowledge of the etiology, presentation, and management of late life depression has expanded exponentially in very recent decades. As the populations of developed nations continue to age, we can expect the demand due to depression on geriatric and psychogeriatric services to increase also. An evidence-based care pathway for depression that considers every point along the illness trajectory, from population-level prevention to individual intervention, is a necessity if we are to meet this demand and provide the best care for our patients and their families.

References

Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M (1997) Clinically defined vascular depression. Am J Psychiatry 154(4):562–565

Alexopoulos GS, Katz IR, Reynolds 3rd CF, Carpenter D, Docherty JP (2001) The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. Postgraduate medicine Spec No Pharmacotherapy:1–86

Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML (2002) Clinical presentation of the "depression-executive dysfunction syndrome" of late life. Am J Geriatr Psychiatry 10(1):98–106

Alexopoulos GS, Raue PJ, Kiosses DN, MacKin RS, Kanellopoulos D, McCulloch C, Areán PA (2011) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. Arch Gen Psychiatry 68(1):33–41

APA (2010) Practice guideline for the treatment of patients with major depressive disorder. Internet

Baldwin RC, Gallagley A, Gourlay M, Jackson A, Burns A (2006) Prognosis of late life depression: a three-year cohort study of outcome and potential predictors. Int J Geriatr Psychiatry 21(1):57–63

Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA (2012) Midlife vs late-life depressive symptoms and risk of dementia. Arch Gen Psychiatry 69(5):493–498

Blazer DG (2003) Depression in late life: review and commentary. J Gerontol – Ser Biol Sci Med Sci 58(3):249–265

Braam AW, Copeland JRM, Delespaul PAEG, Beekman ATF, Como A, Dewey M, Fichter M, Holwerda TJ, Lawlor BA, Lobo A, Magnússon H, Prince MJ, Reischies F, Wilson KC, Skoog I (2014) Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action. J Affect Disord 155(1):266–272

Butters MA, Klunk WE, Mathis CA, Price JC, Ziolko SK, Hoge JA, Tsopelas ND, Lopresti BJ, Reynolds ICF, DeKosky ST, Meltzer CC (2008) Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh compound-B. Alzheimer Dis Assoc Disord 22(3):261–268

Chi I, Chou KL (2001) Social support and depression among elderly Chinese people in Hong Kong. Int J Aging Hum Dev 52(3):231–252

Choi NG, Kim J, Marti CN, Chen GJ (2014) Late-life depression and cardiovascular disease burden: examination of reciprocal relationship. Am J Geriatr Psychiatry 22(12):1522–1529

Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, Dickens C, Ferrier IN, Geddes J, Gilbody S, Haddad PM, Katona C, Lewis G, Malizia A, McAllister-Williams RH, Ramchandani P, Scott J, Taylor D, Uher R (2015) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol (Oxford, England) 29(5):459–525. doi:10.1177/0269881115581093

Cole MG, Dendukuri N (2003) Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry 160(6):1147–1156

Conwell Y, Duberstein PR, Caine ED (2002) Risk factors for suicide in later life. Biol Psychiatry 52(3):193–204

Denihan A, Kirby M, Bruce I, Cunningham C, Coakley D, Lawlor BA (2000) Three-year prognosis of depression in the community-dwelling elderly. Br J Psychiatry 176:453–457

Devanand DP, Kim MK, Paykina N, Sackeim HA (2002) Adverse life events in elderly patients with major depression or dysthymic disorder and in healthy-control subjects. Am J Geriatr Psychiatry 10(3):265-274

Dwivedi Y (2013) Involvement of brain-derived neurotrophic factor in late-life depression. Am J Geriatr Psychiatry 21(5):433–449

Fahy S, Lawlor BA (2001) Discontinuation of lithium augmentation in an elderly cohort. Int J Geriatr Psychiatry 16(10):1004–1009

Firbank MJ, Teodorczuk A, Van Der Flier WM, Gouw AA, Wallin A, Erkinjuntti T, Inzitari D, Wahlund LO, Pantoni L, Poggesi A, Pracucci G, Langhorne P, O'Brien JT (2012) Relationship between progression of brain white matter changes and late-life depression: 3-year results from the LADIS study. Br J Psychiatry 201(1):40–45

Forester BP, Streeter CC, Berlow YA, Tian H, Wardrop M, Finn CT, Harper D, Renshaw PF, Moore CM (2009) Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: a lithium-7 magnetic resonance spectroscopy study. Am J Geriatr Psychiatry: Off J Am Assoc Geriatr Psychiatry 17(1):13–23. doi:10.1097/JGP.0b013e318172b3d0

Gallagher D, Mhaolain AN, Greene E, Walsh C, Denihan A, Bruce I, Golden J, Conroy RM, Kirby M, Lawlor BA (2010) Late life depression: a comparison of risk factors and symptoms according to age of onset in community dwelling older adults. Int J Geriatr Psychiatry 25(10):981–987

Gallagher D, O'Regan C, Savva GM, Cronin H, Lawlor BA, Kenny RA (2012) Depression, anxiety and cardiovascular disease: Which symptoms are associated with increased risk in community dwelling older adults? J Affect Disorders 142(1–3):132–138

Gallo JJ, Rabins PV, Lyketsos KG, Tien AY, Anthony JC (1997) Depression without sadness: Functional outcomes of nondysphoric depression in later life. J Am Geriatr Soc 45(5): 570–578

Galvez V, Ho KA, Alonzo A, Martin D, George D, Loo CK (2015) Neuromodulation therapies for geriatric depression. Current Psychiatry Report 17(7):59. doi:10.1007/s11920-015-0592-y

George D, Kumar D, Hadzi-Pavlovic D, Leyden J, Wark H, Harper S, Brodaty H, Loo C (2016) Randomised controlled trial of ketamine in depressed elderly. Biol Psychiatry 79(9):156S

Goldberg DP, Huxley P (1992) Common mental disorders: a bio-social model. Routledge, London

Golden J, Conroy RM, Bruce I, Denihan A, Greene E, Kirby M, Lawlor BA (2009) Loneliness, social support networks, mood and wellbeing in community-dwelling elderly. Int J Geriatr Psychiatry 24(7):694–700

Gunning-Dixon FM, Walton M, Cheng J, Acuna J, Klimstra S, Zimmerman ME, Brickman AM, Hoptman MJ, Young RC, Alexopoulos GS (2010) MRI signal hyperintensities and treatment remission of geriatric depression. J Affect Disord 126(3):395–401

Gustavson KA (2011) Late life depressed mood: Crafting meaning from experience and knowledge. Am J Geriatr Psychiatry 19(3):S92–S93

Hewett K, Chrzanowski W, Jokinen R, Felgentreff R, Shrivastava RK, Gee MD, Wightman DS, O'Leary MC, Millen LS, Leon MC, Briggs MA, Krishen A, Modell JG (2010) Double-blind, placebo-controlled evaluation of extended-release bupropion in elderly patients with major depressive disorder. J Psychopharmacol 24(4):521–529

Holvast F, Burger H, De Waal MMW, Van Marwijk HWJ, Comijs HC, Verhaak PFM (2015) Loneliness is associated with poor prognosis in late-life depression: longitudinal analysis of the Netherlands study of depression in older persons. J Affect Disord 185:1–7

Horr TB, Dale R, Finnegan N, Frankel M (2014) Ketamine: a potential option for treatment-refractory depression in elder adults. J Am Geriatr Soc 62:S179

Ivan Santini Z, Koyanagi A, Tyrovolas S, Haro JM (2015) The association of relationship quality and social networks with depression, anxiety, and suicidal ideation among older married adults: findings from a cross-sectional analysis of the Irish Longitudinal Study on Ageing (TILDA). J Affect Disord 179:134–141

Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE (2002) Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. J Clin Epidemiol 55(7):696–710

Kirby M, Bruce I, Radic A, Coakley D, Lawlor BA (1997) Mental disorders among the community-dwelling elderly in Dublin. Br J Psychiatry 171:369–372

Koorevaar AML, Comijs HC, Dhondt ADF, Van Marwijk HWJ, Van Der Mast RC, Naarding P, Voshaar RCO, Stek ML (2013) Big five personality and depression diagnosis, severity and age of onset in older adults. J Affect Disord 151(1):178–185

Krishnan KRR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, Steffens DC (2004) Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry 55(4):390–397

Liebetrau M, Steen B, Skoog I (2008) Depression as a risk factor for the incidence of first-ever stroke in 85-year-olds. Stroke 39 (7):1960-1965

Luanaigh CÓ, Lawlor BA (2008) Loneliness and the health of older people. Int J Geriatr Psychiatry 23(12):1213–1221

Maust DT, Oslin DW, Thase ME (2013) Going beyond antidepressant monotherapy for incomplete response in nonpsychotic late-life depression: a critical review. Am J Geriatr Psychiatry 21(10):973–986

McCrory C, Gallagher D, Kenny RA (2013) Control orientation as a mediator of the social gradient in depression: a role for learned helplessness? Age Ageing 42:nn29

Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney RM, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Lane DA, Pilote L, Parakh K, Rafanelli C, Sato H, Steeds RP, Welin C, De Jonge P (2013) Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. Br J Psychiatry 203(2):90–102

Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, Ikram MA (2016) 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. Lancet Psychiatry 3:628

Mojtabai R, Olfson M (2004) Major depression in community-dwelling middle-aged and older adults: prevalence and 2- and 4-year follow-up symptoms. Psychol Med 34(4):623–634

Molyneux GJ, McCarthy GM, McEniff S, Cryan M, Conroy RM (2008) Prevalence and predictors of carer burden and depression in carers of patients referred to an old age psychiatric service. Int Psychogeriatr 20(6):1193–1202

Mosca I, Barrett A (2016) The impact of voluntary and involuntary retirement on mental health: evidence from older Irish adults. J Ment Health Policy Econ 19(1):33–44

Naismith SL, Norrie LM, Mowszowski L, Hickie IB (2012) The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog Neurobiol 98(1):99–143

Nelson JC, Delucchi K, Schneider LS (2008) Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. Am J Geriatr Psychiatry 16(7):558–567

NICE (2009) Depression: the NICE guideline on the treatment and management of depression in adults. Update Edition. Internet

Nolen-Hoeksema S, Ahrens C (2002) Age differences and similarities in the correlates of depressive symptoms. Psychol Aging 17(1):116–124

Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, Bruce ML, Caine ED, Cummings JL, Devanand DP, Krishnan KRR, Lyketsos CG, Lyness JM, Rabins PV, Reynolds Iii CF, Rovner BW, Steffens DC, Tariot PN, Lebowitz BD (2002) Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry 10(2):125–128

Paradiso S, Duff K, Vaidya JG, Hoth A, Mold JW (2010) Cognitive and daily functioning in older adutls with vegetative symptoms of depression. Int J Geriatr Psych 25(6):569-577

Ramos-Garcia MI, González-Salazar CF (2013) Electroconvulsive therapy: is there a role for treating older patients? Rev Clin Gerontol 23(4):283–294

Reinjders JSAM, Ehrt U, Weber WEJ, Aarskand D, Leentjens AFT (2008) A systematic review of prevalence studies of depression in Parkinson's disease. Movement Disorders 23(2):183–189

Robinson RG, Spalletta G (2010) Poststroke depression: A review. Can J Psychiat 55(6):341–349

Roose SP, Nelson JC, Salzman C, Hollander SB, Rodrigues H (2003) Open-label study of mirtazapine orally disintegrating tablets in depressed patients in the nursing home. Curr Med Res Opin 19(8):737–746

Schoevers RA, Smit F, Deeg DJH, Cuijpers P, Dekker J, Van Tilburg W, Beekman ATF (2006) Prevention of late-life depression in primary care: do we know where to begin? Am J Psychiatry 163(9):1611–1621

Semkovska M, McLoughlin DM (2010) Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry 68(6):568–577

Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, Noone M, Carton M, Lambe S, McHugh C, McLoughlin DM (2016) Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomized, non-inferiority trial. Am J Psychiatr 173(4):408–417

Sheline YI, Pieper CF, Barch DM, Welsh-Boehmer K, McKinstry RC, MacFall JR, D'Angelo G, Garcia KS, Gersing K, Wilkins C, Taylor W, Steffens DC, Krishnan RR, Doraiswamy PM (2010) Support for the vascular depression hypothesis in late-life depression: Results of a 20site, prospective, antidepressant treatment trial. Arch Gen Psychiat 67(3):277–285

Sjösten N, Kivelä SL (2006) The effects of physical exercise on depressive symptoms among the aged: a systematic review. Int J Geriatr Psychiatry 21(5):410–418

Skoog I, Waern M, Duberstein P, Blennow K, Zetterberg H, Börjesson-Hanson A, Östling S, Guo X, Kern J, Gustafson D, Gudmundsson P, Marlow T, Kern S (2015) A 9-year prospective population-based study on the association between the APOE∗E4 allele and late-life depression in Sweden. Biol Psychiatry 78(10):730–736

Steffens DC, Nelson JC, Eudicone JM, Andersson C, Yang H, Tran QV, Forbes RA, Carlson BX, Berman RM (2011) Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. Int J Geriatr Psychiatry 26(6):564–572

Steunenberg B, Beekman ATF, Deeg DJH, Kerkhof AJFM (2010) Personality predicts recurrence of late-life depression. J Affect Disord 123(1–3):164–172

Sweet RA, Hamilton RL, Butters MA, Mulsant BH, Pollock BG, Lewis DA, Lopez OL, DeKosky ST, Reynolds ICF (2004) Neuropathologic correlates of late-onset major depression. Neuropsychopharmacology 29(12):2242–2250

Taylor WD (2014) Depression in the elderly. N Engl J Med 371(13):1228–1236

Taylor WD, Aizenstein HJ, Alexopoulos GS (2013) The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry 18(9):963–974

Van Schaik AM, Comijs HC, Sonnenberg CM, Beekman AT, Sienaert P, Stek ML (2012) Efficacy and safety of continuation and maintenance electroconvulsive therapy in depressed elderly patients: a systematic review. Am J Geriatr Psychiatr 20(1):5–17

Von Hippel W, Vasey MW, Gonda T, Stern T (2008) Executive function deficits, rumination and late-onset depressive symptoms in older adults. Cogn Ther Res 32(4):474–487

Waern M, Rubenowitz E, Wilhelmson K (2003) Predictors of suicide in the old elderly. Gerontology 49(5):328–334

Whyte EM, Mulsant BH, Rovner BW, Reynolds CF (2006) Preventing depression after stroke. Int Rev Psychiatry 18(5):471–481

Anxiety in Late Life

10

Gerard J. Byrne

Abstract

This chapter focuses on anxiety disorders, which occur at high prevalence throughout the world. It summarizes contemporary findings on prevalence and risk factors. It deals with assessment issues, including rating scales. It explores the available evidence on effective management strategies in older people, including behavior therapy and antidepressant medication. Emphasis is given to the role of non-pharmacological interventions. The chapter deals with several controversial issues, including the limited evidence for the manual-based psychotherapies in late-life anxiety disorders and the role of benzodiazepines and antipsychotics. Anxiety disorders are often underestimated as causes of human distress and disability.

Keywords

Anxiety • Avoidance • Panic • Phobia • Agoraphobia • Exposure • Psychotherapy • Antidepressants

Contents

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_13

Introduction

Anxiety can be found in all animal species and is necessary for survival (Darwin 1872). Although mild to moderate levels of anxiety are often adaptive and may lead to improved performance (Yerkes and Dodson 1908), severe anxiety is maladaptive and may lead to anxiety disorder.

Biological Theory

The biological basis of the **fear response** in humans involves appraisal of threat by the prefrontal cortex; activation of the limbic system, including the amygdala, hippocampus, anterior cingulate, and insular cortex; and subsequent activation of the hypothalamo-pituitary-adrenal (HPA) axis. There is evidence that activation of the amygdala is particularly important for the generation of panic and that one function of the hippocampus is to dampen stress responses. Following activation of the limbic system and the HPA axis, stress hormones are secreted. Adrenaline (epinephrine) and noradrenaline (norepinephrine) come from the adrenal medulla, and cortisol comes from the adrenal cortex. Autonomic changes occur, including dilated pupils, dilated bronchi, and tachycardia. Behavioral changes follow rapidly, including the fight or flight response and, in some species, freezing. This biological system for dealing with threat is phylogenetically ancient and facilitates escape from present danger and preparation for rapid reactions to future threats.

It is clear from laboratory experiments in rodents (Liu et al. 2000) and observational studies in humans (Gilbertson et al. 2002) that both genetic and environmental factors are necessary for the genesis of maladaptive anxiety. About 30–40% of the variation in risk for anxiety disorder appears to be of genetic origin (Norrholm and Ressler 2009). No individual genes of large effect have been identified, so genetic effects are thought to be polygenic, with contributions from many genes of small effect.

The serotonin transporter gene has been investigated as a risk factor for both anxiety and depression, and polymorphisms in the promoter region of this gene (5-HTTLPR) have been linked to risk of anxiety disorder (Xie et al. 2009).

Although it might seem reasonable to assume that genetic effects are less important in later life, there is evidence to the contrary. In addition, some midlife and late-life genetic factors appear to be relevant only for women (Gillespie et al. 2004).

Genetic factors interact with environmental factors, particularly those present in early childhood. Evidence from studies in rats indicates that pups separated from their mothers shortly after birth exhibit increased biological reactions to stress and increased anxiety-related behaviors. Similarly, rat pups born to anxious mothers and who are then cross-fostered and reared by anxious foster mothers are much more prone to anxious behaviors than rat pups born to non-anxious mothers or rat pups reared by

non-anxious foster mothers. It is likely that some of these observations can be explained by epigenetic factors and may have implications for subsequent generations.

Psychological Theory

From a psychological perspective, anxiety is generally considered to be a dimensional construct rather than a categorical one. Within this framework, normal anxiety can be divided into **trait anxiety** and **state anxiety**. Levels of trait anxiety are relatively stable over time, reflecting genetic and early environmental influences, whereas state anxiety fluctuates over time, reflecting the vicissitudes of life. However, trait and state anxiety are highly correlated, and both result from a combination of genetic and environmental influences.

Certain personality traits are associated with anxiety disorders. In particular, high levels of **neuroticism** are associated with anxiety symptoms and with all anxiety disorders. Neuroticism is moderately heritable, and about one-third of the genetic influence on neuroticism is shared with generalized anxiety disorder. Low levels of extraversion are associated with social phobia, whereas high levels of conscientiousness are associated with obsessive-compulsive disorder and generalized anxiety disorder. It is also worth noting that dementia of the Alzheimer's type is associated with elevated neuroticism and symptoms of anxiety. In later life, anxiety is a better predictor of subsequent cognitive impairment and dementia than depression.

A fear response develops when a harmless cue or context (conditioned stimulus (CS)) is paired with an aversive event or exposure (unconditioned stimulus (US)). The fear response to the CS can be extinguished by habituation but is subject to rapid reinstatement by simultaneous or sequential exposure to the US and CS. **Avoidance behavior** leads to a temporary reduction in anxiety, which negatively reinforces (increases) avoidance behavior. However, avoidance is not a successful long-term strategy because it prevents habituation to the feared stimulus (Byrne 2013).

From a dimensional perspective, the point at which normal anxiety is considered pathological anxiety depends upon its consequences for an individual's function.

Burden of Disease

In 2010, anxiety disorders were the sixth leading cause of disability, in terms of years of life lived with disability (YLD), in both high-income and low- and middle-income countries (Baxter et al. 2014a). Anxiety disorders were associated with greater **burden** in women and in young and middle-aged people than in men and older people. Although the availability of informative data varies considerably across the world, and the measures employed might have cultural biases, it does appear that anxiety disorders are less prevalent in Asia and more prevalent in conflict areas (Baxter et al. 2014b). In people aged 65 years and over, the global prevalence of any anxiety disorder was 3.7% (Baxter et al. 2014a). Prevalence estimates from

population surveys are discussed in greater detail later in this chapter (see section "Epidemiology of Anxiety Disorders").

The Severity of Anxiety Disorders

Older people with anxiety disorders are rarely admitted to hospital. Patients with psychosis and severe mood disorders often dominate occupied bed days in in-patient psychiatric facilities. As a group, anxiety disorders are generally considered to be less severe than mood disorders and psychotic disorders. However, some specific anxiety disorders (panic disorder, agoraphobia, post-traumatic stress disorder) can sometimes be more severe than the average case of major depressive disorder.

Comorbid Mental Disorders

There is a myth that anxiety disorders with no associated psychiatric **comorbidity** are uncommon. In fact, about 60% of older people with a current anxiety disorder have no psychiatric comorbidity.

Anxiety Symptoms

Anxiety symptoms can be categorized as mental, emotional, or physical. Mental symptoms include worry, rumination, depersonalization, derealization, poor concentration, and impaired memory. Emotional symptoms include fear, dread, a sense of impending doom, anger, depression, emotional numbness, irritability, and tearfulness. Physical (or somatic) symptoms can be experienced in any bodily system. These include blushing, sweating, stomach churning, tremor, palpitations, muscle tension, fatigue, hyperventilation, sighing, frequent urination, diarrhea, and insomnia. Anxiety is frequently associated with behaviors such as avoidance of feared objects or situations and repetitive checking or washing.

Differential Diagnosis of Anxiety

There is an extensive differential diagnosis list for anxiety disorders. Mental disorders such as delirium, dementia, depression, and psychosis may masquerade as anxiety disorders. Substance use disorders, particularly those due to alcohol, benzodiazepines, caffeine, and amphetamines, may present with anxiety symptoms. A variety of general medical conditions may also be associated with anxiety. These include hyperthyroidism, asthma and chronic obstructive pulmonary disease, diabetes, heart disease, Parkinson's disease (Dissanayaka et al. 2010, 2016), and rare endocrine tumors (pheochromocytoma). Medications used to treat mental disorders

or general medical conditions may also cause anxiety. These include sympathomimetics, anticholinergics, and selective serotonin reuptake inhibitors.

Classification of Anxiety Disorders

Psychiatrists generally adopt a categorical approach to anxiety disorders, and this approach has facilitated the development of evidence-based treatments.

The tenth edition of the *International Classification of Diseases and Related Health Problems* (ICD-10) classifies anxiety disorders as neurotic, stress-related, and somatoform disorders (F40 – F48). ICD-10 includes post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) within this grouping, although the ICD-11 draft has PTSD and OCD in separate sections.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; APA 2013) has removed post-traumatic stress disorder PTSD) and obsessive-compulsive disorder OCD) from its Anxiety Disorders chapter and placed them in separate chapters.

As most of the extant scientific literature refers to ICD-10 or DSM-IV categories rather than to ICD-11 or DSM-V categories, in this chapter, PTSD and OCD will be considered to be anxiety disorders. It should be noted that many prevalence estimates, including those used to calculate disease burden, have used the concept of any anxiety disorder, which includes PTSD and OCD. In both psychiatric nosologies, anxiety disorders are not further categorized by age of onset, although most lifetime cases have their onset during childhood or early adult life.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD; F41.1) is characterized by multiple worries that are experienced by the patient as excessive and that have persisted for 6 months or more. Of all the anxiety disorders, it is GAD that could most readily be understood as a dimensional rather than a categorical construct. The median age of onset is in early adult life (Gonçalves and Byrne 2012) although many older people have subthreshold symptoms (Miloyan et al. 2015). GAD occurs commonly alongside major depression and worsens the prognosis of the latter.

Panic Disorder

Panic disorder (F41.0) is characterized by frequent unexpected panic attacks together with persistent worry about future panic attacks or with avoidance behavior. Panic attacks occur less commonly among older persons than among young and middle-aged persons, but subthreshold panicky episodes are common. Panic attacks occur also in people with delirium, alcohol withdrawal, generalized anxiety disorder, and major depression. Older people with isolated panic attacks or with panic disorder

are often seen in hospital emergency departments, mimicking asthma or acute coronary syndrome. Panic attacks and panic disorder commonly lead to agoraphobia.

Agoraphobia

Agoraphobia (F40.0) is characterized by fear and avoidance of situations from which escape might be difficult or embarrassing. People with agoraphobia tend to avoid crowded shopping malls and supermarkets. They are often able to enter feared situations if accompanied by another trusted person. At the time of presentation, older adults with agoraphobia have often had the disorder for more than a decade. One exception is when agoraphobia-like symptoms develop following a stroke or following the development of Parkinson's disease. Older people with agoraphobia generally have one or more persons who support them and assist to conceal their disability.

Specific Phobia

Specific (or simple) phobia (F40.2) is highly prevalent but rarely becomes a focus of clinical attention in older adults as most persons with this condition simply avoid the phobic stimulus (Coelho et al. 2010). Older people with **specific phobia** commonly fear and avoid situations such as elevators or flying or objects such as spiders or moths. Exposure to the phobic object causes severe distress. Fear of falling shares some features of specific phobia and some features of agoraphobia.

Social Phobia

In social phobia (F40.1), people experience fear, embarrassment, or humiliation in social situations, such as public speaking. Social phobia is a somewhat controversial diagnosis because of its overlap with normal shyness. Concerns have also been expressed that **social phobia** was an uncommon clinical diagnosis until drug treatment for this condition became available. Although social phobia occurs across the lifespan (Miloyan et al. 2014), it is infrequently a focus of clinical attention in older people.

Adjustment Disorder with Anxiety

Adjustment disorder with anxiety (F43.22) occurs following a wide variety of adverse life events, including assaults, disasters, traumatic bereavements, and major changes in social status or financial circumstances. It is often self-limiting but may

persist if the adversity persists or if the person has a personality vulnerability that reduces their resilience.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD; F43.1) occurs following exposure to one or more major traumatic events, such as combat, rape, or serious assault. About 15–20% of older people exposed to a life-threatening event develop PTSD. In older people, PTSD has often been present for many years since combat exposure in early adult life. However, PTSD can come on in later life following adverse life events. PTSD is characterized by intrusive reexperiencing of the traumatic event through flashbacks and nightmares. Patients also experience hyperarousal, emotional numbing, and avoidance behavior. PTSD is often associated with substance abuse and sometimes with dissociative phenomena. Older people with PTSD often also meet diagnostic criteria for major depression.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD; F42) is distinguished from obsessive-compulsive personality disorder by the presence of obsessional thoughts or images or by the presence of compulsive rituals. It generally has its onset in childhood or early adult life but is often a chronic disorder that persists into later life. It commonly fluctuates in severity in relation to internal or external stressors. It is highly variable in its manifestations and, when severe, can sometimes be difficult to distinguish from psychosis. Religious scrupulosity is usually a symptom of OCD. There is a subtype of hoarding that is associated with compulsive buying behavior, which has some features of OCD.

Epidemiology of Anxiety Disorders

The epidemiology of anxiety disorders in later life is complex and subject to debate. Prevalence estimates vary substantially between studies, in both developing and developed countries. While much of this variation is due to differences in study methodology and the diagnostic criteria employed, it is difficult to discount the possibility that the actual prevalence of anxiety disorders does vary substantially between places.

Data from the MentDis_ICF65+ study was used to investigate the prevalence of DSM-IV anxiety disorders in a random sample of 3,142 persons aged 65–84 years from six European countries (Andreas et al. 2016). The overall prevalence of current anxiety disorder was 11.4% (95% CI, 9.1–13.6), the prevalence of 12-month anxiety

disorder was 17.2% (95% CI, 14.0–20.4), and the prevalence of lifetime anxiety disorder was 25.6% (95% CI, 21.4–29.7).

Data from National Comorbidity Survey Replication (NCS-R) was used to investigate the prevalence of DSM-IV anxiety disorders in a random sample of 2,575 persons aged 55 years and older in the United States (Byers et al. 2010). The overall weighted prevalence of 12-month anxiety disorder was 11.6% (SE 0.7), although the prevalence declined significantly with advancing age.

Data from the National Survey of Mental Health and Wellbeing (NSMHWB) was used to investigate the prevalence of DSM-IV anxiety disorders in a random sample of 1,905 community-dwelling persons aged 65–85 years in Australia (Byrne 2013). The overall prevalence of 12-month anxiety disorder was 4.3% (95% CI, 3.3–5.2).

Data from the Hong Kong Mental Morbidity Survey was used to investigate the prevalence of ICD-10 anxiety disorder in a random sample of 1,158 community-dwelling persons aged 60–75 years (Fung et al. 2016). The overall weighted prevalence of 1-week anxiety disorder was 8% (95% CI, 6.5–9.6).

The 10/66 cross-national study of mental disorders surveyed the prevalence of anxiety in 15,021 people aged 65 years and over in seven countries: China, India, Cuba, Dominican Republic, Venezuela, Mexico, and Peru (Prina et al. 2011). Using the GMS/AGECAT system, the prevalence of clinically significant anxiety was found to vary greatly between countries and between rural and urban residents within individual countries. For example, the prevalence of anxiety was 0.1% in rural China and 0.2% in urban China. In contrast, the prevalence of anxiety was 2.2% in rural Peru and 9.6% in urban Peru.

In addition to transnational variations and urban/rural variations, there are major differences in the older persons identified using different sets of diagnostic criteria for anxiety disorder. For example, among 75-year-olds in Gothenburg, Sweden, the DSM-IV/5 and ICD-10 diagnostic criteria for generalized anxiety disorder identified mostly different individuals (Nilsson et al. 2012).

Prevalence estimates for individual anxiety disorders in older people vary enormously across the world and even between different sites in a single country. This appears to be due to local differences in the application of diagnostic criteria and large standard errors in population level data due to inadequate sample size.

The extent of variation found in the measured prevalence of anxiety disorders in older people in epidemiological surveys should give rise to concern about the reliability and validity of such data. Certainly, care should be taken when using such epidemiological data for clinical service planning. In some places, it is likely that older people with anxiety disorders are undercounted, whereas in others it is possible they are overcounted. Many national surveys only count individuals living in domestic dwellings and exclude those in hospitals, nursing homes, caravan parks, and homeless shelters.

Epidemiological data indicate that anxiety disorders often occur in comorbid relation to other anxiety disorders and other types of mental disorders.

Risk Factors for Anxiety

Prejudicial childhood experiences, including neglect, physical abuse, and sexual abuse, are all associated with anxiety in later life. Adverse life experiences in later life, including domestic violence, rape, assault, natural disaster, and combat exposure, are associated with anxiety disorders in later life. Substance use disorders, including alcohol use disorders, are associated with anxiety in later life.

Anxiety and Depression

There is considerable overlap between the common symptoms of anxiety and depression. For example, sleep disturbance is a common feature of both syndromes. In addition, there is overlap between the common syndromes, especially between generalized anxiety disorder and major depressive disorder (van der Veen et al. 2015). Longitudinal studies have shown that anxiety more often precedes depression in individuals with lifetime comorbid anxiety and depression. Post-traumatic stress disorder and major depression commonly co-occur. Panic attacks may complicate major depression. Some have argued for the existence of mixed anxiety and depression as a distinct disorder.

Anxiety and Alcohol

There is a bidirectional relationship between anxiety and alcohol. Some anxious individuals use alcohol in an attempt to ameliorate their anxiety symptoms. This strategy is of limited long-term benefit as alcohol withdrawal leads to an exacerbation of anxiety and reinforces the use of alcohol. Some individuals who consume excessive alcohol develop clinically significant anxiety symptoms that may mimic panic, generalized anxiety, or social phobia.

Anxiety and Bereavement

Although bereavement reactions are often considered analogous to depressive episodes, they also share many features of an anxiety disorder (Byrne and Raphael 1997). There is evidence that the emotional distress experienced by widowed older people can be separated into factors loading on anxiety, depression, and grief (Prigerson et al. 1996).

Anxiety and Cognitive Impairment

Anxiety occurs commonly in older people with cognitive impairment and appears to be a nonspecific response of the failing brain. The onset of anxiety symptoms for the first time in later life predicts the subsequent development of cognitive impairment

and dementia better than depression. There are substantial alterations in personality function in dementia. In people with dementia of the Alzheimer's disease (AD) type, neuroticism rises and conscientiousness falls (Robins Wahlin and Byrne 2011). In AD current levels of anxiety are associated with informant ratings of pre-morbid neuroticism (Archer et al. 2007).

Anxiety and Psychosis

Anxiety is a frequent concomitant of psychosis but is often under-recognized and undertreated. Even in community-residing older people, with no formal diagnosis of psychosis, the presence of delusion-like ideas is associated with anxiety disorder (Byrne et al. 2015).

Anxiety and Suicide

There is a strong association between anxiety disorders and **suicide**. Among adults reporting a lifetime history of suicide attempts in the US NESARC study, 70% met diagnostic criteria for an anxiety disorder. Those individuals with panic disorder or PTSD together with a personality disorder were at greatest risk of suicide (Nepon et al. 2010). In older adults, Voshaar et al. (2015) found that anxiety disorders were involved in one in six patients who died by suicide.

Anxiety and General Medical Disorders

When clinically significant anxiety occurs in relation to a general medical condition, such as Parkinson's disease, there are several ways of conceptualizing it. One way is as a psychological reaction to the symptoms of the general medical condition that, in principle, would resolve if the general medical condition resolved. Alternatively, the anxiety could be conceptualized as an anxiety disorder that, although precipitated by the general medical condition, has a life of its own and will persist despite resolution of the general medical condition unless it is treated in its own right. Finally, the treatment for the general medical condition, such as dopaminergic agents in Parkinson's disease, may have produced symptoms of an anxiety disorder.

Assessment of the Anxious Older Person

When dealing with older people, it is often useful to see them at home rather than in the clinic. While sometimes inconvenient for the clinician, a **domiciliary visit** does allow the collection of valuable data that are often missed during a clinic-based assessment. The family context and the physical environment can be observed during a domiciliary visit. Evidence of alcohol or drug use might be seen. The patient's

medication can be readily reviewed. The patient may be more cooperative when they are seen in their usual environment. The patient's family may be more accessible during a home visit. If two clinicians undertake a domiciliary visit, one can interview family members while the other interviews the identified patient.

History from the Patient and a Reliable Informant

Although protection of patient confidentiality is essential to the development and maintenance of a durable therapeutic alliance, it is important also to obtain information from reliable informants, particularly family members, where these are available.

It is sometimes only from an informant that the clinician is able to obtain a valid perspective on the extent of avoidance behavior associated with anxiety symptoms. In addition, the extent of any cognitive impairment that might be a concomitant of late-life anxiety can be estimated.

By conducting part of the assessment interview with the patient and a significant other (spouse, partner, sibling, adult child), the clinician often discovers useful information about relationship dynamics critical to an understanding of the cause or maintenance of the patient's anxiety problem.

It is important to interview the patient alone at some point to enable private material to be discussed, including any history of childhood abuse, domestic violence, or elder abuse.

A detailed list of history-taking components can be found in Table 1.

Table 1 Outline of history taking in anxiety disorders

Nature and periodicity of anxiety symptoms
Identification of phobic stimuli, if any
Quantification of avoidance behavior, if any
Age of onset of anxiety symptoms
Relationship to adverse life events
Use of stimulants such as amphetamine, caffeine, and nicotine
Use of sedatives such as alcohol and benzodiazepines
Relationship of anxiety symptoms to depressive symptoms, if any
Relationship of anxiety symptoms to psychotic symptoms, if any
Relationship of anxiety symptoms to cognitive impairment, if any
Past history of mental disorder, including treatment response
Family history of mental disorder
General medical history
Relationship of anxiety symptoms to pain or discomfort, if any
Personal and developmental history
History of childhood neglect or abuse
History of domestic violence
History of elder abuse
History of military service, including deployment status and combat exposure, if any

Mental State Examination

Older people with anxiety disorders often present relatively well on mental state examination, because their anxiety is relieved by their clinic attendance and the reassuring presence of the clinician. However, at interview they may exhibit tremor, sweating, coughing, sighing, fidgeting, hypervigilance, increased startle, and impaired attention. Those with severe anxiety may exhibit psychomotor agitation, including hand wringing and pacing. It is uncommon for patients with anxiety disorders to experience a panic attack in front of the clinician. Those with OCD may exhibit compulsive rituals. Some patients with agoraphobia will not leave home alone and may refuse to be interviewed alone, insisting on the presence of a support person.

Clinical Cognitive Screening

Although the Mini-Mental State Examination (MMSE; Folstein et al. 1975) is a commonly used screening instrument available in several languages, it has limited coverage of frontal executive functions, which are often associated with anxiety. Among brief screening instruments, the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) and the Addenbrooke's Cognitive Examination – Third Edition (ACE-III; Hsieh et al. 2013) are relatively brief instruments with better coverage of frontal executive functions than the MMSE. The MMSE also suffers from having an easy memory test. A more difficult memory test in the public domain is the Hopkins Verbal Learning Test – Revised (HVLT-R; Shapiro et al. 1999). The HVLT-R is an auditory verbal new learning test, with free recall, delayed recall, and recognition components.

Rating Scales for Anxiety in Older People

It is part of good clinical practice to routinely use a rating scale to measure dimensional elements of anxiety. The ideal instrument for rating anxiety in later life would employ straightforward syntax, minimal somatic symptoms, and dichotomous response scale. It would translate readily into other languages.

Several rating scales for anxiety in older people are now available. Among these, the **Geriatric Anxiety Inventory** (GAI) is in most common use (Pachana et al. 2007a). The GAI is a 20-item self-report measure with a dichotomous (agree/disagree) response scale. The GAI is available in more than 20 languages. In validation studies, scores of 9 or more on the GAI were associated with the diagnosis of DSM-IV generalized anxiety disorder. There is a shorter form of the GAI, the five-item GAI-SF, useful for screening in geriatric medical settings and for surveys (Byrne and Pachana 2011). The psychometric properties of the GAI have been examined by Gould et al. (2014).

Physical Examination

In the work-up of the older patient presenting with the recent onset of clinically significant anxiety symptoms, a general physical examination is recommended. Observation of posture and gait may reveal motor signs of cerebrovascular disease or Parkinson's disease or less common conditions such as Lewy body disease and Huntington's disease. Chest examination may reveal signs of cardiorespiratory disease. Abdominal examination may reveal constipation, which is a common cause of alterations in mental state and behavior in older people.

Review of Current Medications

As previously noted, sympathomimetics and anticholinergics may be associated with anxiety in older people. Sympathomimetics include drugs for asthma and rhinitis. Anticholinergics include drugs for parkinsonism and diarrhea, as well as older antidepressants and antipsychotics. Withdrawal from benzodiazepines is another potential cause of anxiety symptoms in later life. Urine drug screens are sometimes used in cases where the history is considered unreliable.

Laboratory Investigations

Anxiety in older people can be a nonspecific manifestation of general medical illness. Accordingly, screening blood tests are a justifiable component of the work-up of the anxious older person. Standard blood tests can be used to exclude anemia, electrolyte abnormalities, thyroid disease, diabetes, and vitamin deficiencies. Dipstick urinalysis can be performed in the clinic to screen for a urinary tract infection, another common cause of deteriorations in mental state and behavior in older people. Serology for syphilis, hepatitis, and HIV is not routinely performed unless the patient is in a high-risk category.

Electrocardiogram

An electrocardiogram (ECG) might reveal a cardiac arrhythmia causing palpitations or might reveal a prolongation of the QTc interval during antidepressant therapy. ECGs are commonly ordered in older people on psychotropic medication in the developed world but are not generally considered essential.

Structural Neuroimaging

The yield of structural neuroimaging (CT, MRI) in older people with early onset anxiety symptoms is low. While there is a higher yield from structural imaging in

older people with late-onset anxiety symptoms, such imaging rarely alters clinical management. CT and MRI brain scans can generally be reserved for cases with neurological symptoms or signs or for cases with atypical clinical features.

Functional Neuroimaging

There is currently little or no indication for functional neuroimaging (SPECT/PET) in the older person with anxiety, outside of the research setting.

Electroencephalogram

Electroencephalograms (EEGs) are useful in the work-up of suspected epilepsy or delirium and may contribute to the assessment of putative cases of Creutzfeldt-Jakob disease. However, there is little indication for the routine use of EEGs in older people with anxiety disorders.

Treatment of Anxiety Disorders

Late-life anxiety disorders of mild severity should usually be treated non-pharmacologically. The available evidence from short-term clinical trials indicates that the efficacy of non-pharmacological interventions is equivalent to that of pharmacological interventions, and they are associated with fewer adverse effects.

One limitation to the use of non-pharmacological interventions for late-life anxiety disorders is the availability of clinicians trained in the application of non-pharmacological methods in older people. Another limitation for many older people is accessibility, including the cost of non-pharmacological treatments. There is some evidence in adults for the use of internet-based psychotherapy and bibliotherapy, but little evidence in older people.

Moderate and severe late-life anxiety disorders often require treatment with a combination of psychological and drug treatment.

Non-pharmacological Treatment

Therapeutic Alliance

It is important for the clinician to build rapport with the patient and develop a therapeutic alliance, particularly because exposure paradigms are likely to seem counterintuitive to many patients and their families.

Table 2 Sleep recommendations

Ensure the bed and pillow are comfortable
Ensure the sleeping environment is a suitable temperature (colder rather than warmer)
Ensure the sleeping environment is shielded from light (even relatively small amounts of light can affect sleep onset and continuity)
Avoid using electronic screens (TV, iPad, smart phone, etc.) in the half hour before bedtime
Ensure the sleeping environment is shielded from excessive noise (this is less important than shielding from light)
Have a regular wind-down sequence before bedtime
Use the bed for sleep and sex, not other activities
Consider general medical problems that might contribute to poor sleep, including gastroesophageal reflux, nocturnal asthma, and chronic pain
Take regular exercise but avoid vigorous exercise within an hour or two of bedtime
Get out of bed and read a book or meditate if not asleep within 20 minutes
Don't be concerned about nocturnal awakenings – these are often normal in later life

Psychoeducation

The clinician should undertake careful psychoeducation about the nature of anxiety, the fear response, and avoidance behavior so that the patient and their family can better understand the nature of the illness. The patient should be counseled to reduce their stimulant intake, including their intake of nicotine and caffeine. They should be instructed about the key elements of good sleep hygiene (see Table 2).

Physical Activity

Regular aerobic exercise of moderate intensity for 150–300 minutes each week in adults is associated with improved general health and may help with the management of insomnia and other symptoms associated with anxiety disorder. The effective dose of aerobic and muscle-strengthening exercise in older people to maintain good health is subject to debate but is likely to be similar to the recommendations in adults. Physical exercise provides exposure to interoceptive stimuli such as sweating, palpitations, and dyspnoea. If physical exercise is conducted outside or in a public setting such as a gym, it will also provide exposure to exteroceptive stimuli, such as weather, animals, and the scrutiny of others. The regular nonspecific exposure associated with physical exercise assists with habituation and reduces avoidance.

Relaxation Training

Relaxation training is an essential component of most non-pharmacological approaches to anxiety management. Controlled breathing and reciprocal inhibition using visual imagery are the techniques most applicable in older adults.

Progressive muscular relaxation, while useful in younger adults, is often of limited use in older adults with reduced muscle bulk (sarcopenia) or arthritic joints.

Behavior Therapy

Behavior therapy is suitable for almost all older people with anxiety disorders and is particularly useful in those situations in which CBT and related techniques are not appropriate or feasible. Behavior therapy is effective even in people with limited education and low levels of psychological mindedness. The three most powerful ingredients of behavior therapy appear to be relaxation training (discussed separately above), behavioral activation, and graded exposure.

Behavioral activation emphasizes graded activity scheduling and aims to reduce avoidance behavior and increase response-contingent positive reinforcement. It has mainly been used in the treatment of depression, but there is preliminary evidence of its value in the treatment of anxiety (Pachana et al. 2007b).

Exposure is a powerful intervention that should be employed more frequently in older people with anxiety disorders, particularly in those with agoraphobia, social phobia, and specific phobia. Classically, exposure interventions in phobic disorders have involved either flooding or systematic desensitization. In practice, flooding is rarely used, and systematic desensitization is the method usually employed. After obtaining explicit consent from the patient, a hierarchical list of phobic cues is constructed. Exposure tasks are designed to allow the patient to work through the list of phobic stimuli from least aversive to most aversive. The aim of exposure therapy is for the patient to be able to repeatedly expose themselves to the phobic object or situation by themselves without experiencing significant distress. However, it is often necessary for a confederate to accompany the patient while they work through the initial part of their exposure hierarchy. In OCD, exposure is paired with response prevention.

Cognitive Therapy

Cognitive behavior therapy (CBT) has been tested in several clinical trials in older people with generalized anxiety disorder. The findings have been summarized in a meta-analysis (Gonçalves and Byrne 2013), which demonstrated that CBT was superior to control conditions with a pooled odds ratio of 0.33 (95% CI, 0.17–0.66). However, the superiority of CBT was only evident in those clinical trials in which it was compared with usual care or a waiting list condition. No superiority was demonstrated against active comparators. There is a paucity of evidence for the use of CBT in older people with anxiety disorders other than GAD due to a lack of methodologically sound studies. Several authors have recommended modifications to CBT for use in older people (e.g., Laidlaw et al. 2003). These modifications include more sessions, explicit learning aids, and manuals with larger print. CBT is likely to suit well-educated psychologically minded older people.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) was designed to treat depression and employs four models to engage the patient: (1) grief following loss of a loved one, (2) conflict in relationships, (3) change in life circumstances, and (4) social isolation. These models are highly relevant to later life, and there is evidence for the efficacy of IPT in depressed older people, including those with comorbid anxiety. However, there are limited data on the use of IPT in older people with anxiety disorders in the absence of comorbid depression. IPT may be of value in the treatment of older people with social anxiety disorder, but more research is needed.

Problem-Solving Therapy

Anxiety has been linked to an inability to solve everyday problems. Problem-solving therapy involves iterative cycles of problem definition, generation of alternative solutions through brainstorming, and identification of the most effective solution. Clinical trials of problem-solving therapy have been undertaken in older people with anxiety symptoms or anxiety disorders, with mixed results (Seekles et al. 2011; Lam et al. 2010). More research is needed before this approach can be recommended in older people.

Mindfulness Therapy

Various types of mindfulness-based therapies have been tested in clinical trials for depressive and anxiety disorders. Overall, the available evidence in adults is positive, albeit relatively weak, but the evidence for efficacy in older adults is quite limited. Helmes and Ward (2015) reported a study of mindfulness-based cognitive therapy (MBCT) for anxiety symptoms in older adults in residential care. Participants were randomized to either eight sessions of MBCT or to an activity-based control condition. The MBCT condition was superior. More research is needed to confirm the value of this approach in older people.

Pharmacological Treatment

Before commencing new psychotropic medication, the clinician should rationalize prescribed, over-the-counter (OTC), and complementary drugs that might cause or exacerbate anxiety and treat intercurrent general medical problems, particularly those causing pain or discomfort.

The Role of Antidepressants

Antidepressant medications are now considered first-line pharmacological treatments for anxiety disorders. It appears that all antidepressant classes have efficacy in the treatment of anxiety disorders. Their effects come on slowly, and adverse effects are often experienced well before beneficial effects emerge. Some modern antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), may cause an initial increase in tremor, insomnia, and anxiety prior to the onset of their anxiolytic action. Patients must be warned about the potential for this initial increase in anxiety and the likely slow onset of therapeutic effects. It is sometimes necessary to use a low-dose benzodiazepine for a week or two during initiation of SSRI therapy. Antidepressants appear to be of value in older people with GAD, OCD, PTSD, panic, and social phobia. They appear to be of no value in specific phobia.

First-generation antidepressants with strong anticholinergic effects should generally be avoided in older people due to their adverse effects.

The choice between an activating antidepressant (e.g., venlafaxine) and a sedating antidepressant (e.g., mirtazapine) requires clinical judgment and discussion with the patient.

Older people should generally be commenced on a lower dose of antidepressant medication than younger people. The dose titration should proceed slowly, with the prescriber checking frequently for both adverse effects and beneficial effects. Older people often require the same ultimate antidepressant dose that younger people require but should get to this dose more slowly.

The risk of hyponatremia is greater in older people, particularly in those on diuretic therapy or who have cerebrovascular disease. Thus, serum sodium estimations should be undertaken during dose titration or whenever there is an unexplained deterioration in the patient's condition.

In cases of moderate or severe anxiety disorder, antidepressant medication can be combined with CBT (Wetherell et al. 2013).

The Role of Benzodiazepines

Data from both the United States (Olfson et al. 2015) and Australia (Hollingworth and Siskind 2010) show that **benzodiazepine** use increases with advancing age. Some of this benzodiazepine usage is likely to be due to regular prescription of hypnotic medication for older people because of misinterpretation of the normal changes in sleep architecture in later life as abnormal. Such normal aging changes include lighter, more fragmented sleep, with more frequent awakenings.

Although benzodiazepine medications appear to be effective as short-term agents for panic and anxiety, they are now considered to have little or no place in the medium- to long-term treatment of anxiety disorders. The limited clinical trial evidence for

benzodiazepine use in older people is based on very short-term studies (see Gonçalves and Byrne 2013), whereas most anxiety disorders are chronic conditions.

In older people, the use of benzodiazepines can be quite problematic. Not only may benzodiazepines lead to dependence, but they are often associated with amnesia, confusion, ataxia, and falls. At higher doses, or in susceptible individuals, they may be associated with hypopnoea, apnoeic episodes, or respiratory arrest.

Benzodiazepines are routinely used in the prevention and management of withdrawal symptoms in alcohol-dependent older people. In this setting, shorter acting drugs (e.g., oxazepam, lorazepam) that do not undergo oxidative metabolism in the liver are preferred in older people. Diazepam and nitrazepam have age-dependent pharmacokinetics that greatly increase their half-life and should generally be avoided in older people.

Benzodiazepines are sometimes used as adjunctive agents in the management of acute agitation in older people with bipolar disorder or schizophrenia, or in palliative care settings. Care must be taken when using benzodiazepines in older people in the acute context. Benzodiazepines are considered ineffective in OCD and of limited value in PTSD.

One question that often arises is whether to continue benzodiazepines in an older person who has been taking them for many years. In this situation, the clinician should proceed cautiously and negotiate a plan with the patient and, if relevant, their family or supporters. Considerable discussion may be needed to persuade the patient and their family of the wisdom of withdrawal from benzodiazepines. Detailed psychoeducation about the nature of anxiety and the effects of benzodiazepines is likely to be needed before proceeding. Provision of support in relation to feared or actual insomnia may be needed. Cross-tolerance of benzodiazepines with alcohol will be a consideration in some older people. The clinician should endeavor to withdraw the patient from their benzodiazepine medication slowly over several months while providing appropriate alternative treatment with antidepressant medication and psychotherapy. However, sometimes this is not feasible or the patient seeks prescriptions from an alternative source. Voshaar et al. (2006) have discussed this issue in detail.

Modern alternatives to benzodiazepines, such as zopiclone and zolpidem, have similar properties to the benzodiazepines and no clear advantages in older people.

The Role of Antipsychotics

Some prescribers employ sedating, low-potency antipsychotic medication for anxiety or insomnia in older people. They do this presumably because they know that benzodiazepines are often problematic in older people. However, while modern low-potency antipsychotics, such as quetiapine, do have short-term efficacy in generalized anxiety disorder (Gonçalves and Byrne 2013), their long-term risks and benefits in older people are largely unknown. There are no clear benefits to the routine use of antipsychotic medication for anxiety symptoms and disorders.

The Role of Mood Stabilizers

There is no established role for lithium, valproate, or carbamazepine in the routine management of anxiety disorders in older people.

Conclusions

Anxiety is essential for survival but in some individuals may become maladaptive and lead to mental disorder. Once established, anxiety disorders tend to run a chronic course. Anxiety frequently complicates other mental and physical disorders. Anxiety arising for the first time in later life may be a harbinger of cognitive impairment or dementia. Fortunately, effective treatments are available, and non-pharmacological approaches should be given priority over pharmacological approaches. Straightforward approaches using relaxation training, behavioral activation, and exposure are recommended. The use of antidepressants as first-line drug treatment is emphasized.

References

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

Andreas S, Schulz H, Volkert J, Dehoust M, Sehner S, Suling A, Ausin B, Canuto A, Crawford M, Da Ronch C, Grassi L, Hershkovitz Y, Muñoz M, Quirk A, Rotenstein O, Santos-Olmo AB, Shalev A, Strehle J, Weber K, Wegscheider K, Wittchen HU, Härter M. (2016) Prevalence of mental disorders in elderly people: the European MentDis_ICF65+ study. Br J Psychiatry, Sep 8. pii: bjp.bp.115.180463 (Epub ahead of print]

Archer N, Brown RG, Reeves SJ, Boothby H, Nicholas H, Foy C, Williams J, Lovestone S (2007) Premorbid personality and behavioural and psychological symptoms in probable Alzheimer disease. Am J Geriatr Psychiatry 15:202–213

Baxter AJ, Vos T, Scott KM, Norman RE, Flaxman AD, Blore J, Whiteford HA (2014a) The regional distribution of anxiety disorders: implications for the Global Burden of Disease Study, 2010. Int J Methods Psychiatr Res 23(4):422–438

Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA (2014b) The global burden of anxiety disorders in 2010. Psychol Med 44:2363–2374

Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML (2010) High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch Gen Psychiatry 67:489–496

Byrne GJ (2013) Anxiety disorders in older people. Ch 45. In: Dening T, Thomas A (eds) Oxford textbook of old age psychiatry. Oxford University Press, Oxford

Byrne GJ, Pachana NA (2011) Development and validation of a short form of the geriatric anxiety inventory – the GAI-SF. Int Psychogeriatr 23:125–131

Byrne GJ, Raphael B (1997) The psychological symptoms of conjugal bereavement in elderly men over the first 13 months. Int J Geriatr Psychiatry 12:241–251

Byrne GJ, Steele SJ, Pachana NA (2015) Delusion-like experiences in older people with anxiety disorders. Int Psychogeriatr 27:1191–1196

Coelho CM, Goncalves DC, Purkis H, Pocinho M, Pachana NA, Byrne GJ (2010) Specific phobias in older adults: characteristics and differential diagnosis. Int Psychogeriatr 22:702–711

Darwin C (1872) The expression of the emotions in man and animals. John Murray, London

Dissanayaka NN, Sellbach A, Matheson S, O'Sullivan JD, Silburn PA, Byrne GJ, Marsh R, Mellick GD (2010) Anxiety disorders in Parkinson's disease: prevalence and risk factors. Mov Disord 25:838–845

Dissanayaka NN, O'Sullivan JD, Pachana NA, Marsh R, Silburn PA, White EX, Torbey E, Mellick GD, Copland DA, Byrne GJ (2016) Disease-specific anxiety symptomatology in Parkinson's disease. Int Psychogeriatr 28:1153–1163

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Fung AW, Chan WC, Wong CS, Chen EY, Ng RM, Lee EH, Chang WC, Hung SF, Cheung EF, Sham PC, Chiu HF, Lam M, Chiang TP, van Os J, Lau JT, Lewis G, Bebbington P, Lam LC; Hong Kong Mental Morbidity Survey Team. (2016) Prevalence of anxiety disorders in community dwelling older adults in Hong Kong. Int Psychogeriatr Oct 21:1–9. [Epub ahead of print]

Gilbertson MW, Shenton ME, CIszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242–1247

Gillespie NA, Kirk KM, Evans DM, Health AC, Hickie IB, Martin NG (2004) Do the genetic or environmental determinants of anxiety and depression change with age? A longitudinal study of Australian twins. Twin Res 7:39–53

Gonçalves DC, Byrne GJ (2012) Sooner or later: age at onset of generalized anxiety disorder in older adults. Depress Anxiety 29:39–46

Gonçalves DC, Byrne GJ (2013) Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. J Anxiety Disord 26:1–11

Gould CE, Segal DL, Yochim BP, Pachana NA, Byrne GJ, Beaudreau SA (2014) Measuring anxiety in late life: a psychometric examination of the geriatric anxiety inventory and geriatric anxiety scale. J Anxiety Disord 28:804–811

Helmes E, Ward BG (2015) Mindfulness-based cognitive therapy for anxiety symptoms in older adults in residential care. Aging Ment Health 13:1–7. [Epub ahead of print]

Hollingworth SA, Siskind DJ (2010) Anxiolytic, hypnotic and sedative medication use in Australia. Pharmacoepidemiol Drug Saf 19:280–288

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013) Validation of the Addenbrooke's cognitive examination III in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 36:242–250

Laidlaw K, Thompson LW, Dick-Siskin L, Gallagher-Thompson D (2003) Cognitive behaviour therapy with older people. Wiley, Chichester

Lam CL, Fong DY, Chin WY, Lee PW, Lam ET, Lo YY (2010) Brief problem-solving treatment in primary care (PST-PC) was not more effective than placebo for elderly patients screened positive for psychological problems. Int J Geriatr Psychiatry 25:968–980

Liu D, Diorio J, Day JC, Francis DD, Meaney MJ (2000) Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci 3:799–806

Miloyan B, Byrne GJ, Pachana NA (2014) Social phobia symptoms across the adult lifespan. J Affect Disord 168:86–90

Miloyan B, Byrne GJ, Pachana NA (2015) Threshold and subthreshold generalized anxiety disorder in later life. Am J Geriatr Psychiatry 23:633–641

Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699

Nepon J, Belik SL, Bolton J, Sareen J (2010) The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Depress Anxiety 27:791–798

Nilsson J, Ostline S, Waern M, Karlsson B, Sigstrom R, Guo X, Skoog I (2012) The 1-month prevalence of generalized anxiety disorder according to DSM-IV, DSM-V, and ICD-10 among nondemented 75-year-olds in Gothenburg, Sweden. Am J Psychiatr 20(11):963–972

Norrholm SD, Ressler KJ (2009) Genetics of anxiety and trauma-related disorders. Neuroscience 164:272–287

Olfson M, King M, Schoenbaum M (2015) Benzodiazepine use in the United States. JAMA Psychiatry 72:136–142

Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E (2007a) Development and validation of the geriatric anxiety inventory. Int Psychogeriatr 19:103–114

Pachana NA, Woodward RM, Byrne GJ (2007b) Treatment of specific phobia in older adults. J Clin Interv Aging 2:469–476

Prigerson HG, Shear MK, Newsom JT, Frank E, Reynolds CF, Maciejewski PK, Houck PR, Bierhais AJ, Kupfer DJ (1996) Anxiety among widowed elders: is it distinct from depression and grief? Anxiety 2:1–12

Prina AM, Ferri CP, Guerra M, Brayne C, Prince M (2011) Prevalence of anxiety and its correlates among older adults in Latin America, India and China: cross-cultural study. Br J Psychiatry 199:485–491

Robins Wahlin TB, Byrne GJ (2011) Personality changes in Alzheimer's disease: a systematic review. Int J Geriatr Psychiatry 26:1019–1029

Seekles W, van Straten A, Beekman A, van Marwijk H, Cuijpers P (2011) Effectiveness of guided self-help for depression and anxiety disorders in primary care: a pragmatic randomized controlled trial. Psychiatry Res 187:113–120

Shapiro AM, Benedict RH, Schretlen D, Brandt J (1999) Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin Neuropsychol 13:348–358

van der Veen DC, Van Zelst WH, Schoevers RA, Comijs HC, Voshaar RC (2015) Comorbid anxiety disorders in late-life depression: results of a cohort study. Int Psychogeriatr 27:1157–1165

Voshaar RC, Couvee JE, van Balkom AJ, Mulder PG, Zitman FG (2006) Strategies for discontinuing long-term benzodiazepine use: meta-analysis. Br J Psychiatry 189:213–220

Voshaar RC, van der Veen DC, Kapur N, Hunt I, Williams A, Pachana NA (2015) Suicide in patients suffering from late-life anxiety disorders: a comparison with younger patients. Int Psychogeriatr 27:1197–1205

Wetherell JL, Petkus AJ, White KS, Nguyen H, Kornblith S, Andreescu C, Zisook S, Lenze EJ (2013) Antidepressant medication augmented with cognitive-behavioral therapy for generalized anxiety disorder in older adults. Am J Psychiatry 170:782–789

Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, Weiss RD, Farrer L, Gelernter J (2009) Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in two independent populations. Arch Gen Psychiatry 66:1201–1209

Yerkes RM, Dodson JD (1908) The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 18:459–482

Cognition and Bipolar Disorder in Older Adults (Including Question of "Neuroprogression")

11

Sergio A. Strejilevich and Diego J. Martino

Abstract

The rise in life expectancy has in turn led to an increase in the proportion of older adults with bipolar disorder (OABD), with the consequent need to improve understanding of the clinical features of this population. However, only in the last decade has the neurocognitive profile of OABD begun to be described.

Cross-sectional studies in OABD showed impairments in verbal memory, attention, and executive functions with medium to large effect sizes compared to healthy controls, which closely resemble the findings of younger patients. The first longitudinal studies in OABD tend to find that cognitive deficits are static rather than progressive. Therefore, both cross-sectional and longitudinal studies do not appear to support the notion of progressive cognitive impairment over the course of the disease, which is proposed as the hypothesis for neuroprogression and staging models for BD.

On the other hand, preliminary evidence has suggested a possible association between BD and an increased risk of developing dementia, although the underlying causes are still matters of speculation. Some cases of late-onset BD may represent early stages of neurodegenerative or cerebrovascular diseases and contribute in part to this association. In addition, there are multiple factors

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_12

that can affect cognitive function in OABD such as the exposure to psychotropic drugs and different medical and psychiatric comorbidities.

The clinical and theoretical implications of these topics are discussed throughout this chapter.

Keywords

Antipsychotic exposure • Autoimmune thyroiditis • Clock drawing test • Cognitive function • Dementia • Lithium • Cognition • Cognitive heterogeneity • Longitudinal studies • Pharmacological treatment

Contents

Introduction

In recent years, cognitive aspects of bipolar disorders went from being considered as theoretical or research topics to being considered as a mainstream clinical issue that should be incorporated in the management of people affected by bipolar disorders. Today, a consistent body of data has shown that almost two thirds of euthymic bipolar patients of any age suffer persistent impairments in verbal memory, attention, and executive functions, which present a strong correlation with overall functionality. In fact, cognitive dysfunctions in BD are considered one of the main predictors of functional outcome, representing almost 30% of the causes of persistent functional disability of these disorders (Martino et al. 2009; Bonnín et al. 2010).

Cognitive function acquires even more importance in older adults with BD (OABD). The reduction of cognitive reserve due to normal ageing and the exponential increase in the prevalence of neurodegenerative disorders in this stage of life require special attention to cognitive functioning in the management of this group of patients. But, in recent years, a number of important emergent hypotheses that would redefine the entire field of bipolar disorders have found the cognitive aspects of elderly patients, a fertile ground for research. First, a series of proposals aimed at describing and explaining the long-term course of bipolar disorders suggest a model in which cognitive dysfunction would increase along the course of the disorder. The progressive decrement in cognitive function is explained by a series of mechanisms generally called "neuroprogression" which determine a pathological reorganization of the central nervous system is produced by alterations in neurotrophins, inflammation mediators, and oxidative stress that

occurs as a consequence of affective episodes (Fries et al. 2012). Concomitantly, the neuroprogression hypothesis was included as the cornerstone of staging models of BDs proposed in recent years (Berk et al. 2007; Berk 2009; Kapczinski et al. 2009). Staging models suggest that BDs start with no cognitive impairment in the premorbid stage or even in patients with well-defined periods of euthymia without overt psychiatric symptoms, to evolve into a progressive cognitive decline that affects independent function in later stages (Kapczinski et al. 2014).

Although the neuroprogressive hypothesis should determine how clinicians will consider therapeutic interventions, it was at first rather uncritically accepted as the state of the art of BDs (Grande et al. 2016). However, following the impact with which this hypothesis burst on to the field, a significant amount of conflicting data emerged, much of which comes from the specific study of cognition in OABD (Strejilevich et al. 2015).

Older adult patients represent the best population to examine the impact of long-term pharmacological exposure on cognitive function and brain health. As an example, while it was proposed that lithium could produce neuroprotective effects and prevent dementia, other data show that antipsychotic exposure could produce detrimental effects on cognition. Logically, OABD would be the area where these problems could be addressed and the emerging data about these issues could redefine many aspects of pharmacological treatment of BD.

The aim of this chapter is to review data on cognitive functioning in OABD and factors that modulate cognition in order to address the long-term trajectories of cognition in BDs.

Review of Cognition in OABD

Pioneer Studies

In 2007, two independent meta-analyses concluded that euthymic mixed-age patients with bipolar disorder (BD) display cognitive dysfunction in a variety of domains, with medium to large effect sizes of impairment observed for attention/processing speed, verbal memory, and executive functions (Robinson et al. 2006; Torres et al. 2007). These data found a negative correlation between the number of affective episodes and cognitive function (for a review, see Robinson and Ferrier 2006). These findings were usually interpreted as an increase in cognitive deficits associated with successive episodes of BD and became the main argument for the concept of staging and neuroprogression proposed for BD (Berk et al. 2007; Berk 2009; Kapczinski et al. 2009).

A hypothesis that intends to explain the long-term evolution of a disease must have the data for patients who have long been suffering the same. However, the cumulative evidence about neurocognition in mixed-age euthymic patients with BD as well as the hypotheses of staging and neuroprogression were apparently in conflict with the data about OABD in that time. In fact, in 2006 Young and colleagues published a review of cognition in OABD and found only seven studies with

significant methodological limitations that appeared to provide support for the neuroprogressive hypothesis. For example, Broadhead and Jacoby (1990) studied manic patients who recovered prior to discharge and found that 25% of the older group scored in the demented range on the Kendrick Battery subtests. In another study, nearly half of the BD patients showed one or more standard deviations from the mean regarding healthy controls on the Mini-Mental State Examination (MMSE) and Mattis Dementia Rating Scale, and 17% scored between one and two standard deviations below the mean of the comparison subjects on the executive interview (Gildengers et al. 2004). Accordingly, in the first longitudinal study in elderly patients, Dhingra and Rabins (1991) followed a cohort of 25 older patients using the Mini-Mental State Examination (MMSE) for 5–7 years after a hospitalization for a manic episode. At the end of the follow-up, 32% of the sample experienced a decline to a score below 24, an indicator of dementia.

However, these early studies had methodological problems that limited their findings: among the seven studies included in the review, only two had evaluated euthymic patients; almost all of them had used screening tests which do not allow for a characterization of cognitive profile and importantly, none of these early studies discriminated early from late-onset bipolar disorder in their samples (Young et al. 2006).

New Studies

Cross-sectional studies: In the last decade, neurocognitive research in BDs has experienced exponential growth, expanding and improving previous data. More recent meta-analyses confirmed results of the earlier cross-sectional studies regarding the impairments in verbal memory, attention/processing speed, and executive functions in euthymic BD patients (Mann-Wrobel et al. 2011; Bourne et al. 2013). Likewise, the relationship between the number of episodes and cognitive impairment was corroborated in further studies conducted by López-Jaramillo et al. (2010), in which euthymic BD patients with only one episode of mania showed better overall cognitive performance compared to those with more than three manic episodes. Similarly, Torres et al. (2010) reported that patients who recovered from their first manic episode showed less impairment in verbal memory and executive functions than those reported in meta-analyses of euthymic multiple episode BD patients. These findings were taken as further evidence that each recurrence has a cost in terms of cognitive impairment and, therefore, interpreted as evidence of neuroprogression in BDs (Berk et al. 2011; Gama et al. 2013; Kapczinski et al. 2014; Post et al. 2012; Rodrigues et al. 2014; Vieta et al. 2011). However, some issues about cognition in mixed-age euthymic patients with BD were not considered in the interpretation of these findings. First, different authors suggested that cognitive functioning might be heterogeneous and that studies reporting mean values of cognitive functioning in BD might be failing to recognize that a subgroup of bipolar patients demonstrates most of the impairment (Altshuler et al. 2004; Martino et al. 2008a). This was reinforced by recent research that identified subgroups of patients with severe cognitive

impairment while others remain cognitively intact despite their illness (Burdick et al. 2014; Martino et al. 2014; Bora et al. 2016). Second, it is important to emphasize that the data about the relationship between cognition and number of previous episodes are based exclusively on cross-sectional studies and, therefore, the direction of causality of this association cannot be clearly determined (Martino et al. 2013a). Finally, these conclusions ignored the new data that were emerging from elderly patient populations.

New data about cognition in OABD: In the last decade, cross-sectional studies in OABD using a better selection of cases and extensive neuropsychological batteries began to find a different panorama: these new studies tend to show similar results, with as regard to the domains affected and the magnitude of impact compared to those reported in younger patients (results are summarized in Table 1). In 2013 Samamé et al. published the first meta-analysis of neurocognition in OABD, analyzing 11 reports that included 382 BD patients (weighted mean age = 69.2 years) and 363 healthy controls. This review reported moderate to large patients-controls differences in verbal memory, attention/processing speed, and executive functions, mirroring the findings in samples of mixed-age patients with euthymic BD (Fig. 1). In contrast with the original studies, this meta-analysis showed that screening tests, such as the Mini-Mental State Examination and the clock-drawing test, were not useful in differentiating patients from controls. Another study, aimed at testing the neuroprogression hypothesis, directly compared neurocognitive performance of OABD and younger BD patients stratifying by age and level of education (Strejilevich and Martino 2013). In that study, there was no difference between groups in neurocognitive performance despite the fact that OABD had a duration of illness three times longer than in younger patients. So, what are the implications of these new data regarding the neuroprogression hypothesis? If BD presents with progressive cognitive impairment, as suggested by a staging model and the neuroprogression hypothesis, we should expect older patients to exhibit a more pronounced magnitude of cognitive impairment in comparison to younger ones. These new cross-sectional studies in OABD suggest that cognitive impairment tends to be stable rather than progressive along the course of the disorder. Notwithstanding this clinical depiction, it is possible that these cross-sectional studies could be subject to selection bias. That is, patients with greater cognitive impairment including some that could develop dementia may have been excluded from these studies. Therefore, these data need to be supplemented with those derived from longitudinal studies.

Longitudinal studies: Longitudinal studies about neurocognition in euthymic OABD patients were also published in recent years. In a study conducted by Gildengers et al. (2009), 33 euthymic BD patients were assessed with the Dementia Rating Scale. The authors found that OABD exhibited worse cognitive function and more rapid cognitive decline than expected given their age and education. Another study by Depp et al. (2008) assessed 35 middle aged OABD with a battery of neuropsychological tests, repeated once (1–3 years after baseline), and compared their performance with that of demographically matched healthy subjects and patients with schizophrenia. The authors concluded that BD individuals did not differ from healthy controls or patients with schizophrenia in the mean trajectory of

Table 1 Summary of cross-sectional studies assessing neurocognitive functioning older adults with euthymic BD during the last decade

Summary of cross-sectional studies assessing neurocognitive functioning older adults with euthymic BD during the last decade.

Primary study	Sample	Mean Age BD (SD), years	Criteria of Euthymia	Cognitive Measures	Main Results
Gildengers et al., 2007	BD (n=20), HC (n=40)	73.6 (8.4)	No specifically reported. MADRS and YMRS cut-off scores not given	CDT TMT-A/TMT-B Category Fluency Delayed Recall	BD<HC in information / processing speed and executive functioning
Martino et al., 2008b	BD (n=20), HC (n=20)	66.6 (8.2)	HDRS<8 and YMRS<6 for at least 8 weeks.	Tapping Test Serial learning / Delayed recall CPT / WCST	BD<HC in psychomotor performance, delayed recall, and executive functioning
Radanovic et al., 2008	BD (n=33), HC (n=33)	67.0 (4.5)	HDRS<7 and YMRS<4 for at least 4 weeks.	Verbal Memory Category Fluence	BD<HC in verbal related activity
Brooks et al., 2009	BD (n=16), HC (n=11)	58.7 (7.5)	No specifically reported. MADRS and YMRS cut-off scores not given	Verbal Memory	BD<HC in delayed free verbal recall
Delaloye et al., 2009	BD (n=22), HC (n=22)	68.5 (5.5)	DSM-IV (absence of symptoms for at least 2 months) + GDS < 5; YMRS < 5	Simple reaction time Digit span forwards / backwards Color Trail Making Category / Phonemic fluency	BD<HC in processing speed, working memory, verbal fluency, and episodic memory
Schouws et al., 2009	EO-BD (n=59) , LO-BD (n=60), HC (n=78)	70.4 (7.2)	DSM IV + CES-D; YMRS cut off scores not given	MMSE / CDT TMT-A/ TMT-B Category / Phonemic fluency Digit span forwards / backwards Learning / Delayed recall	Both patient groups<HC in all measures. LO-BD<EO-BD in psychomotor performance and executive functioning
Tsai et al., 2009	BD (n=59) , HC (n=59)	71.1 (5.9)	HDRS < 7; YMRS < 5 for 2 months	MMSE	BD>HC in abnormal education-adjusted MMSE scores
Brooks I et al., 2010	BD (n=16), HC (n=11)	58.7 (7.5)	No specifically reported. MADRS and YMRS cut-off scores not given	CPT	BD>HC in omission errors
Ladeira et al, 2010	BD (n=35), HC (n=35)	68.1 (5.8)	No specifically reported.	CDT	BD=HC
Martino et al, 2013	EO-BD (n=20), LO-BD (n=20), HC (n=20)	68.0 (6.6)	HDRS<8 and YMRS<6 for at least 8 weeks.	WAIS vocbulary Digit span forwards / backwards Serial learning / Delayed recall Verbal Fluency / WCST	EO-BD<HC in delayed recall, and executive functioning LO-BD<HC in all measures
Aprahamian et al, 2014	BD (N=79), AD (n=60), HC (n=70)	67.1 (4.0)	Clinical impression + HDRS<7 and YMRS<4 for at least 1 month	MMSE, CDT (3 scores) Category Fluency	BD<HC in MMSE, 1 score of CDT, and category fluency

BD: bipolar disorder; HC: Healthy Controls; EO-BD: Early Onset BD; LO-BD: Late Onset BD; AD: Alzheimer Disease; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; GDS: Geriatric Depression Scale; CDT: Clock Drawing Test; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; MMSE: Mini-Mental State Examination; WCST: Wisconsin Card Sorting Test; CPT: WAIS: Wechsler Adult Intelligence Scale; CPT: Continuous Performance Test

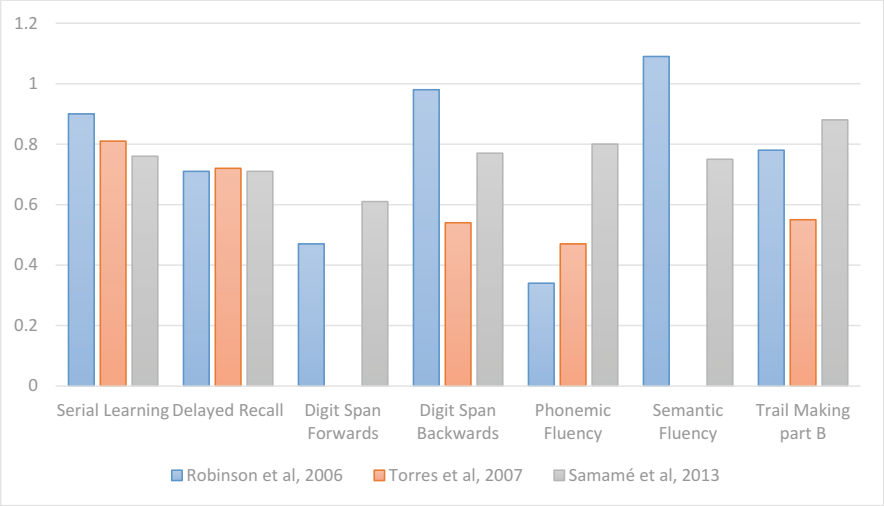

Fig. 1 Mean effect sizes of patient-control differences for neurocognitive domains in mixed age (Robinson et al. 2006; Torres et al. 2007) and older adults with bipolar disorder (Samamé et al. 2013)

change between time points, although BD group displayed more intraindividual variability over time than either comparison group. Moreover, Delaloye et al. (2011) reported that euthymic BD patients did not differ from controls in the mean trajectory of cognitive changes during a 2-year follow-up period. Changes in longitudinal gray matter and white matter did not differentiate between BD patients and normal controls. Similarly, Schouws et al. (2012) reported that, although euthymic OABD patients had worse cognitive function than healthy subjects, there was no significant group-by-time interaction between the patients and the comparison group. Finally, another study by Gildengers et al. (2013) reported that OABD patients did not exhibit accelerated cognitive decline over 2 years. All these findings were included with others conducted in mixed-age patients, in a meta-analysis of longitudinal studies of cognition in bipolar disorder (Samamé et al. 2014). This meta-analysis based on 357 BD patients reported that performance on 14 cognitive measures remained stable after a mean follow-up period of 4.62 years (Samamé et al. 2014). More recently, another study conducted by Schouws et al. (2016) assessed performance of a sample of OABD and age matched healthy controls using a comprehensive neuropsychological test battery at baseline and 5 years later. In that study, although patients performed worse than healthy controls both at baseline and at follow-up, there were no differences between groups in the level of cognitive decline during the period of 5 years. Longitudinal studies in BD suggest that cognitive impairment might be stable rather than progressive, which does not support the hypotheses of staging and neuroprogression. However, the results of longitudinal studies should be considered preliminary as they generally have relatively short follow-up periods, which may be insufficient to detect cognitive decline. Therefore,

further longitudinal studies with longer follow-up periods are needed to clarify if cognitive impairment is static or progressive in BD.

Cognitive Heterogeneity and Age at Onset in Bipolar Disorders

Far from being an homogeneous characteristic of BDs, cognitive dysfunction in mixed-age BD patients presents a heterogeneous distribution in subgroups of patients with severe cognitive impairment and others who are intact or have a minimal degree of cognitive deficits (Martino et al. 2008b, 2014; Burdick et al. 2014; Bora et al. 2016). Therefore, when analyzing the general profile of cognitive deficits in OABD, it is necessary to consider that heterogeneity is even greater in this subpopulation because OABD actually constitute a heterogeneous population composed of both early-onset patients (EO-BD) who develop their illness during early adulthood and late-onset patients (LO-BD) who experienced their first mood episode at an older age. A series of studies that have used admixture analysis have confirmed the existence of a late-onset subgroup of BDs, previously described by Shulman and Post (1980). LO-BD represents around 20% of the total BD population (Kennedy et al. 2005) with a mean age of first manic episode onset around 40 years old (Bellivier et al. 2003). LO-BD patients differ from EO-BD by presenting less frequent family history of affective disorders, a different clinical profile, and a higher frequency of neurological comorbidities, features that have suggested the existence of different etiological factors in these subgroups (Shulman and Post 1980; Schürhoff et al. 2000; Moorhead and Young 2003; Depp and Jeste 2004) (Table 2). New studies have confirmed the differences of LO-BD at a neurocognitive level. Schouws et al. (2009), in a study specifically designed to assess cognitive performance in these populations through an extensive neuropsychological battery, reported that LO-BD patients were more impaired in psychomotor performance and mental flexibility than EO-BD patients. Similarly, in another recent study, EO-BD showed poorer performance than healthy controls in two measures of verbal memory and two measures of executive functions, whereas patients with LO-BD exhibited lower performance scores than healthy controls in almost all of the measures assessed (Martino et al. 2013b). In that study, cognitive impairment in LO-BD affected domains typically preserved in BDs such as naming (Martino et al. 2013b).

The fact that LO-BD patients have more extensive and severe cognitive impairment than EO-BD patients supports the hypothesis that different etiological mechanisms may be involved in the development of the illness in these subgroups. In contrast to genetic factors associated with EO-BD (Schürhoff et al. 2000; Moorhead and Young 2003; Depp and Jeste 2004), different neuropsychiatric conditions have been proposed as possible brain mechanisms that might trigger BDs at an older age. Compared with patients with EO-BD, LO-BD patients showed a greater prevalence of vascular risk factors (Cassidy and Carrol 2002) and silent cerebral infarctions (Fujikawa et al. 1995), and greater deep white matter hyperintensities have been reported in LO-BD. Similarly, late-onset cases of BD have been described as secondary to autosomal dominant cerebral arteriopathy with subcortical infarcts

Table 2 Clinical and demographic differences between Older Adults with Early and Late Onset Bipolar Disorder

Clinical and demographic differences between Older Adults with Early and Late Onset Bipolar Disorder

	Early Onset	Late Onset
Family antecedents	↑↑ (OR=5.24)	↓↓
Manic Load	↑↑	↓↓
Psychotic Symptoms	↑↑ (OR=6)	↓↓
Depressive Load	↓↓	↑↑
Mood Instability	↑	↓
Cognitive Dysfunction	↑	↑↑↑

and leukoencephalopathy (CADASIL) (Park et al. 2014) or due to lacunar infarcts (Antelmi et al. 2014). Other case series were published suggesting that different neurodegenerative diseases, such as frontotemporal dementia and Alzheimer's disease, at early stages could simulate symptoms of BD (Ng et al. 2008; Velakoulis et al. 2009). Therefore, it is possible that in some cases, such as patients with a history of subthreshold manifestations of BD, the beginning of a vascular or neurodegenerative process could manifest as LO-BD in a prodromal stage. If this were the case, while affective symptoms would be the core of the longitudinal course of EO-BD, the outcome of LO-BD would be dominated by the progression of neuropsychiatric illness. However, to date, this perspective remains speculative, and further longitudinal studies comparing changes in brain neuroimaging and neurocognitive performance in EO-BD and LO-BD would be necessary in order to test this hypothesis.

The Relationship Between BDs and Dementia Risk

Findings from epidemiological studies suggest that individuals who suffer from affective disorders, especially BDs, develop dementia at a higher rate than expected among healthy subjects (da Silva et al. 2013). Kessing and colleagues found, in analyses done in the Danish psychiatric case register of admissions, that subjects

previously discharged with the diagnosis of BD had a higher risk of suffering a subsequent diagnosis of dementia compared to the incidence of dementia in the Danish general population and other patients included in this database with previous diagnoses of unipolar depression, schizophrenia, neurosis (1999) (HR: 13.70 [12.1–15.40]), osteoarthritis, and diabetes (2003) (HR: 3.38 [2.39–4.79]). In another analysis, Kessing et al. (2004) explored the impact of the number of psychiatric admissions on the risk of developing dementia and did not find statistically significant results (Kessing and Andersen 2004). More recently, Wu et al. (2013) found similar results analyzing Taiwan's National Health Insurance (NHI) research database. After a proper statistical control for covariates (middle-age diagnosis of cerebrovascular disease, diabetes, dyslipidemia, hypertension, alcohol substance-related disorders, and health service utilization), the diagnosis of BD was significantly associated with an increased risk of dementia [adjusted odds ratio = 4.32, 95% confidence interval (CI): 3.21–5.82].

These data show that the risk of suffering dementia among people affected by BDs is 4–6 times higher than the general population, an argument used to support the neuroprogression hypothesis. However, some methodological issues should be taken into account when examining these data. In the studies done on the Danish data set, only those patients who had at least one psychiatric admission were included, with the consequence of an inclusion bias with overrepresentation of severe cases. The diagnoses were not made systematically for the purpose of these studies, so we cannot rule out possible diagnostic errors, such as confusing bipolar episodes with behavioral symptoms of dementia syndromes, as was discussed above (Velakoulis et al. 2009). In a study by Wu and colleagues which also reported an increased risk of dementia, only 0.25% of patients of the analyzed database had a diagnosis of BD. Although the authors report that this percentage is similar to the prevalence found in the general population, this percentage seems remarkably low. Finally, for the analysis of these studies, the early- and late-onset BD patients were not separated.

Pharmacological Treatment and Other Cognitive Modulators

The study of OABD provides a unique opportunity to examine whether long-term pharmacological exposure is associated with cognitive dysfunction or brain health, as affected subjects are exposed for more than two thirds of their lives to a psychopharmacological treatment. New data have shown that the effects on cognition and brain tissue integrity could be critically different depending on the type of drug used.

On the one hand, antipsychotic exposure has been related to decrements in cognitive function and reduction in brain volume. A series of reports have consistently shown that antipsychotic exposure in mixed-age BD patients is associated with cognitive impairment, especially in executive functions (Frangou et al. 2005; Torrent et al. 2011). This detrimental effect of antipsychotics could be independent of the presence of psychotic symptoms (Donaldson et al. 2003). Although we did

find similar data of this effect in OABD, it is reasonable to assume that this effect should be even greater among these patients. Brain dopamine concentrations show a linear decline later in life, which creates an increased susceptibility to cognitive and motor side effects of drugs that produce a downregulation of dopamine in older adults (Volkow et al. 1998). It should be noted that BD patients would be especially susceptible to acute and late extrapyramidal side effects (Gao et al. 2008; Hamra et al. 1983), and as in younger patients, extrapyramidal symptoms are positively correlated with executive brain function (Martino et al. 2008). Moreover, duration of antipsychotic exposure has been related to a reduction in cerebral volumes both in animal models (Vernon et al. 2011) and people affected by schizophrenia (Ho et al. 2011; Fusar-oli et al. 2013; Vita et al. 2015). Although there has been a dramatic increase in the use of antipsychotics in mood disorders (Mauer et al. 2014a, b), there is still a lack of information about the impact of antipsychotics in BD patients. A recent follow-up study in OABD found that longer exposure to antipsychotic medication was related to lower gray matter volumes (Gildengers et al. 2014).

On the other hand, lithium treatment at appropriate therapeutic serum levels seems to be relatively safe in neurocognitive terms and may be protective of brain tissue integrity. Wingo et al. (2009) did a meta-analysis of 12 studies ($N = 276$ subjects) that assessed cognitive effects of lithium, concluding that lithium had only few and minor negative effects on cognition. Concomitantly, the neuroprotective effects of lithium at a molecular level have led to the proposal that it could be useful in producing a neuroprotective effect in preventing dementia (Chuang and Manji et al. 2007). In a systematic review, Mauer and colleagues (2014a, b) found that current data justify greater efforts to promote the potential preventive effects of lithium on dementia. Five out of seven epidemiological studies found an association between standard-dose lithium and low dementia rates. However, two small prospective trials designed to test lithium effects on cognition failed to find positive results. Macdonald et al. (2008) in an open-label 1-year follow-up study ($N = 22$) found that lithium treatment is relatively safe in Alzheimer's patients but did not find changes in cognition. Hampel et al. (2009) in 10 weeks of follow-up did not find significant effects on cognitive performance and in the cerebrospinal fluid (CSF) concentrations of Alzheimer's disease-related biomarkers. However these studies were done in individuals with an established dementia syndrome. In a related study, Forlenza et al. (2011) conducted a randomized placebo-controlled study in 45 patients with mild cognitive impairment. They found that lithium treatment was associated with a significant decrease in CSF concentrations of P-tau ($P = 0.03$) and better performance on the cognitive subscale of the Alzheimer's disease assessment scale as well as in attention tasks. Moreover, lithium has been associated with potential protection against chronic motor side effects. In a 9-year follow-up study of a cohort of psychiatric patients, lithium exposure showed a significant and independent protective effect against tardive dyskinesia in patients exposed to antipsychotics (Van Harten et al. 2008).

Nonetheless, the biggest effect sizes favoring lithium were found in studies with samples of patients with mood disorders (Mauer et al. 2014a, b). The question remains open whether these studies are detecting a protective effect of lithium or the absence

of a detrimental cognitive effect, direct or indirect, of other drugs, such as antipsychotics. The same question applies in the cross-sectional study recently published by Gildengers et al. (2015). In this study, they examined cognitive and neuroimaging data in 58 individuals with BDs (mean age 64.5 ± 9.8 years; 33 who were treated with long-term lithium and 25 without lithium treatment) compared to 21 controls. Longer duration of lithium treatment was related to higher white matter integrity after controlling for age and vascular disease burden, but not to better cognitive performance. In this study, neither the intensity nor the kind of antipsychotic exposure were assessed.

Cognitive function can be modulated by more than pharmacological treatment. As was observed in other psychiatric (Lindenmayer et al. 2012) and nonpsychiatric illnesses (Farr et al. 2008; Naderali et al. 2009), metabolic, endocrinal, and cardiovascular issues can modulate cognitive function. Recent studies have found a positive correlation between obesity metabolic syndrome (Yim et al. 2012; Depp et al. 2014), general medical morbidity (Tsai et al. 2009), and cognitive impairments in BDs. Such correlation could be even greater than in schizophrenia, and may have an impact similar to that usually found between euthymic bipolar patients and normal controls (Depp et al. 2014). BD patients have close to double the risk of developing obesity, diabetes, hypertension, and vascular disease (Goldstein et al. 2009; McElroy and Keck 2014). The relationship between metabolic syndrome and antipsychotic exposure could reflect a synergistic interaction (antipsychotics produce metabolic syndrome while both produce cognitive detriments) resulting in higher cognitive dysfunction, but is impossible to confirm with the available data. Finally, imbalances in the thyroid axis, even at the subclinical level, could modify cognitive performance (Martino and Strejilevich 2015).

Discussion

During the last decade, evidence about the neurocognitive profile of OABD has begun to appear. Cross-sectional studies show similar cognitive deficits to those reported in younger patients in the affected domains and magnitude of effects. Longitudinal studies show a rate of cognitive decline similar to that of the general population. Therefore, from our perspective, current data do not support the hypotheses of neuroprogression and staging in which cognitive deficits should increase throughout the course of the disorder. Future studies should include longer follow-up periods in order to prove or disprove these hypotheses.

On the other hand, preliminary data show that people suffering from BD have a higher risk of developing dementia although little is known about the mechanism underlying this association. Some authors suggest that this relationship supports the hypothesis of neuroprogression, as evidence of the end stage that can be reached with progressive cognitive decline. However, this view contrasts sharply with the results of cross-sectional and longitudinal studies. Alternatively, some subjects could co-inherit risk factors for BD and dementia, similarly to what has been described for autoimmune thyroiditis and BD (Vonk et al. 2007). Likewise,

several other factors overrepresented in people with BD, such as vascular risk factors, alcohol and drugs abuse, unhealthy life habits, or chronic exposure to antipsychotics, could contribute to the high risk of dementia in this population. Conversely, some psychotropic medications such as lithium and antipsychotics could mitigate the risk of developing dementia. Therefore, further studies should clarify the association between dementia and BD as well as the potential underlying pathophysiological mechanisms.

From a clinical point of view, available data strongly suggest the need to include neurocognitive assessment as one of the tools in the routine assessment of OABD. Since both clinical and subsyndromal symptoms have a negative influence on cognitive performance, in order to assess the core deficits of BD, neurocognitive assessments should be conducted only when patients reach euthymia. The identification of cognitive deficits or decline in neurocognitive performance should always lead to ruling out treatable conditions before considering them clinical features of BD. Subclinical symptoms of BD and psychiatric comorbidity such as anxiety disorders or substance abuse, medical comorbidity such as hypothyroidism, or medications with potential cognitive side effects must all be considered as potentially treatable causes of cognitive impairment in BD. After controlling for treatable causes of cognitive impairment, one might consider the remaining cognitive deficits as part of the core of BD. Only those patients with such remaining deficits should be included in a program of cognitive/functional remediation.

The possibility that neuropsychiatric conditions such as cerebrovascular or neurodegenerative diseases are presenting as late onset-BDs highlights the need for rigorous medical evaluation. Therefore, the examination of these patients should include psychiatric and neurological evaluation, as well as neurocognitive, laboratory, and neuroimaging investigations. Obviously, the detection of these underlying neuropsychiatric conditions has clinical implications, such as the control of vascular risk factors or delay the progression of neurodegenerative diseases.

Perhaps the best way to summarize the current state of knowledge on cognitive functioning of OABD is by saying that it carries good news for people affected by BD. Though it is clear that better data are necessary, the current findings show that OABD should not necessarily expect progressive decline of their cognitive functioning. Although there is a higher chance of suffering from dementia for people affected by BDs, in individual terms this statistic is not clinically significant and this minimal risk could be reduced by the same preventive actions that apply for general health. Moreover, people who have been treated for long periods with lithium should not fear brain damage or cognitive decrement but can actually have hope they will be protected from some of the cerebral insults that all people are exposed to.

The totality of data clearly questions the neuroprogression hypothesis and the current proposal for a staging system of BDs (Cardoso et al. 2015; Passos et al. 2016). This could be perceived as a disappointment among clinicians and researchers because neuroprogression and staging models provided an initial way to uncover pathophysiology, but also a justification for many therapeutic actions (e.g., polypharmacy) that although commonly used are still awaiting a better rationale. While current data on cognition in OABD do not support neuroprogression and

staging proposals, they provide useful tools for treatment and new insights for future research. Although currently available data do not support the hypothesis of a progressive course of cognitive deficits in BD, this does not imply that the question about cognitive evolution in BD has been resolved. For example, present data do not preclude the existence of other trajectories or heterogeneity in the clinical course of cognitive functioning. An exploration of cognitive subtypes should be a priority (Martino et al. 2014). In the same way, the confirmation of late-onset BD as a discrete subgroup will create more homogeneous samples to explore the pathogenesis and etiology of these disorders. The fact that the cognitive profile is not significantly different between older and younger adults with BDs suggests that the mechanisms are related to the early stages of the disorder (Strejilevich et al. 2015). Findings from cognitive research in OABD will have even more value for clinicians. First, they justify a more optimistic prognosis for the long-term course of people affected by BDs. At the same time, we need to stress the necessity of incorporating preventative steps in the cognitive care of these patients. Moreover, the possibility that antipsychotic use, cerebrovascular or metabolic illnesses may affect cognitive function in some patients, highlights the need for a holistic approach to clinical care. For example, the limited use of drugs that have a negative metabolic and cognitive impact should be a primary concern if cognitive functioning and thus overall functionality are among the main objectives of treatment. However, these emerging issues are not being adequately considered. Efficacy trials usually do not incorporate cognitive function among their safety parameters at the same time that the use of antipsychotics in BD treatment has increased in recent years. These data should not only influence clinical decisions about treatment but also the research methodology used to prove their effectiveness. After all, it should be obvious that the treatment of a chronic disease that begins in youth must be based on the data emerging from those who have experienced a lifetime with the effects of the disease and its treatment.

References

Altshuler L, Ventura J, van Gorp W, Green M, Theberge D, Mintz J (2004) Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol Psychiatry 56(8):560–569

Antelmi E, Fabbri M, Cretella L, Guarino M, Stracciari A (2014) Late onset bipolar disorder due to a Lacunar State. Behav Neurol 2014:780742

Bellivier F, Golmard JL, Rietschel M, Schulze TG, Malafosse A, Preisig M, McKeon P, Mynett-Johnson L, Henry C, Leboyer M (2003) Age at onset in bipolar I affective disorder: further evidence for three subgroups. Am J Psychiatry 160(5):999–1001

Berk M (2009) Neuroprogression: pathways to progressive brain changes in bipolar disorder. Int J Neuropsychopharmacol 12:441–445

Berk M, Conus P, Lucas N, Hallam K, Malhi GS, Dodd S et al (2007) Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord 9(7):671–678

Berk M, Brnabic A, Dodd S, Kelin K, Tohen M, Malhi GS, Berk L, Conus P, McGorry PD (2011) Does stage of illness impact treatment response in bipolar disorder? Empirical treatment

data and their implication for the staging model and early intervention. Bipolar Disord 13(1):87–98

Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, Murru A, Sanchez-Moreno J, Vieta E (2010) Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J Affect Disord 121(1–2):156–160

Bora E, Hıdıroğlu C, Özerdem A, Kaçar ÖF, Sarısoy G, Civil Arslan F, Aydemir Ö, CubukcuogluTas Z, Vahip S, Atalay A, Atasoy N, Ateşci F, Tümkaya S (2016) Executive dysfunction and cognitive subgroups in a large sample of euthymic patients with bipolar disorder. Eur Neuropsychopharmacol 26(8):1338–1347. doi:10.1016/j.euroneuro.2016.04.002. 29. pii: S0924-977X (16) 30027-X

Bourne C, Aydemir Ö, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JT, Clark L, Cubukcuoglu Z, Dias VV, Dittmann S, Ferrier IN, Fleck DE, Frangou S, Gallagher P, Jones L, Kieseppä T, Martínez-Aran A, Melle I, Moore PB, Mur M, Pfennig A, Raust A, Senturk V, Simonsen C, Smith DJ, Bio DS, Soeiro-de-Souza MG, Stoddart SD, Sundet K, Szöke A, Thompson JM, Torrent C, Zalla T, Craddock N, Andreassen OA, Leboyer M, Vieta E, Bauer M, Worhunsky PD, Tzagarakis C, Rogers RD, Geddes JR, Goodwin GM (2013) Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr Scand 128(3):149–162

Broadhead J, Jacoby R (1990) Mania in old age: a first prospective study. Int J Geriatr Psychiatry 5:515–522

Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, Malhotra AK (2014) Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med 44(14):3083–3096

Cardoso T, Bauer IE, Meyer TD, Kapczinski F, Soares JC (2015) Neuroprogression and cognitive functioning in bipolar disorder: a systematic review. Curr Psychiatry Rep 17(9):75

Cassidy F, Carrol BJ (2002) Vascular risk factors in late onset mania. Psychol Med 32:359–362

Chuang DM, Manji HK (2007) In search of the holy grail for the treatment of neurodegenerative disorders: has a simple cation been overlooked? Biol Psychiatry 62(1):4–6

da Silva J, Gonçalves-Pereira M, Xavier M, Mukaetova-Ladinska EB (2013) Affective disorders and risk of developing dementia: systematic review. Br J Psychiatry 202(3):177–186

Delaloye C, Moy G, Baudois S, de Bilbao F, Remund CD, Hofer F, RagnoPaquier C, Campos L, Weber K, Gold G, Moussa A, Meiler CC, Giannakopoulos P (2009) Cognitive features in euthymic bipolar patients in old age. Bipolar Disord 11(7):735–743

Delaloye C, Moy G, de Bilbao F (2011) Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. Int J Geriatr Psychiatry 26:1309–1318

Depp CA, Jeste DV (2004) Bipolar disorder in older adults: a critical review. Bipolar Disord 6:343–367

Depp CA, Jin H, Mohamed S et al (2004) Bipolar disorder in middle-aged and elderly adults: is age of onset important? J NervMent Dis 192(11):796–799

Depp CA, Savla GN, Moore DJ, Palmer BW, Stricker JL, Lebowitz BD, Jeste DV (2008) Short-term course of neuropsychological abilities in middle-aged and older adults with bipolar disorder. Bipolar Disord 10(6):684–690

Depp CA, Strassnig M, Mausbach BT, Bowie CR, Wolyniec P, Thornquist MH, Luke JR, McGrath JA, Pulver AE, Patterson TL, Harvey PD (2014) Association of obesity and treated hypertension and diabetes with cognitive ability in bipolar disorder and schizophrenia. Bipolar Disord 16:422–431

Dhingra U, Rabins PV (1991) Mania in the elderly: a 5–7 year follow-up. J Am Geriatr Soc 39:581–583

Donaldson S, Goldstein LH, Landau S, Raymont V, Frangou S (2003) The maudsley bipolar disorder project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. J ClinPsychiatry 64(1):86–93

Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, Banks WA, Morley JE (2008) Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology 149:2628–2636

Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF (2011) Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry 198:351–356

Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH (2005) The maudsley bipolar disorder project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry 58:859–864

Fries G, Pfaffenseller B, Stertz L, Paz AV, Dargél A, Kunz M, Kapczinski F (2012) Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep 14(6):667–675

Fujikawa T, Yamawaki S, Touhouda Y (1995) Silent cerebral infarctions in patients with late-onset mania. Stroke 26:946–949

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013) Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 37(8):1680–1691

Gama CS, Kunz M, Magalhães PV, Kapczinski F (2013) Staging and neuroprogression in bipolar disorder: a systematic review of the literature. Rev Bras Psiquiatr 35:70–74

Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR (2008) Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. J Clin Psychopharmacol 28(2):203–209

Gildengers AG, Butters MA, Seligman K, McShea M, Miller MD, Mulsant BH, Kupfer DJ, Reynolds CF 3rd (2004) Cognitive functioning in late-life bipolar disorder. Am J Psychiatry 161(4):736–738

Gildengers AG, Mulsant BH, Begley A, Mazumdar S, Hyams AV, Reynolds Iii CF, Kupfer DJ, Butters MA (2009) The longitudinal course of cognition in older adults with bipolar disorder. Bipolar Disord 11(7):744–752

Gildengers AG, Chisholm D, Butters MA, Anderson SJ, Begley A, Holm M, Rogers JC, Reynolds CF, Mulsant BH (2013) Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychol Med 30:1–11

Gildengers A, Chung K, Huang SH, Begley A, Aizenstein HJ, Tsai SY (2014) Neuroprogressive effects of lifetime illness duration in older adults with bipolar disorder. Bipolar Disord 16 (6):617–623

Gildengers AG, Butters MA, Aizenstein HJ, Marron MM, Emanuel J, Anderson SJ, Weissfeld LA, Becker JT, Lopez OL, Mulsant BH, Reynolds CF 3rd (2015) Longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder. Bipolar Disord 17(3):248–256

Goldstein BI, Fagiolini A, Houck P, Kupfer D (2009) Cardiovascular disease and hypertension among adults with bipolar disorder I in the United States. Bipolar Disord 11:657–662

Grande I, Berk M, Birmaher B, Vieta E (2016) Bipolar disorder. Lancet 387(1027):1561–1572

Hampel H, Ewers M, Bürger K, Annas P, Mörtberg A, Bogstedt A, Frölich L, Schröder J, Schönknecht P, Riepe MW, Kraft I, Gasser T, Leyhe T, Möller HJ, Kurz A, Basun H (2009) Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicentre 10-week study. J Clin Psychiatry 70:922–931

Hamra BJ, Nasrallah HA, Clancy J, Finn R (1983) Psychiatric diagnosis and risk for tardive dyskinesia. Arch Gen Psychiatry 40(3):346–347

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch of Gen Psychiatr 68:128–137

Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, Berk M (2009) Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother 9(7):957–966

Kapczinski F, Magalhães PV, Balanzá-Martinez V, Dias VV, Frangou S, Gama CS, Gonzalez-Pinto A, Grande I, Ha K, Kauer-Sant'Anna M, Kunz M, Kupka R, Leboyer M, Lopez-Jaramillo-C, Post RM, Rybakowski JK, Scott J, Strejilevich S, Tohen M, Vazquez G, Yatham L, Vieta E,

Berk M (2014) Staging systems in bipolar disorder: an International Society for Bipolar Disorders task force report. Acta Psychiatr Scand 130(5):354–363
Kennedy N, Everitt B, Boydell J, Van Os J, Jones PB, Murray RM (2005) Incidence and distribution of first-episode mania by age: results from a 35-year study. Psychol Med 35(6):855–863
Kessing LV, Andersen PK (2004) Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 75(12):1662–1666
Kessing L, Nilsson F (2003) Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord 73(3):261–269
Kessing L, Olsen E, Mortensen P, Andersen P (1999) Dementia in affective disorder: a case-register study. Acta Psychiatr Scand 100(3):176–185
Lindenmayer JP, Khan A, Kaushik S, Thanju A, Praveen R, Hoffman L, Cherath L, Valdez G, Wance D (2012) Relationship between metabolic syndrome and cognition in patients with schizophrenia. Schizophr Res 142:171–176
López-Jaramillo C, Lopera-Vásquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, Martínez-Arán A, Vieta E (2010) Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 12(5):557–567
Macdonald A, Briggs K, Poppe M, Higgins A, Velayudhan L, Lovestone (2008) A feasibility and tolerability study of lithium in alzheimer's disease. Int J Geriatr Psychiatry 23(7):704–711
Mann-Wrobel MC, Carreno JT, Dickinson D (2011) Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord 13:334–342
Martino DJ, Strejilevich SA (2015) Subclinical hypothyroidism and neurocognitive functioning in bipolar disorder. J Psychiatr Res 61:166–167
Martino DJ, Igoa A, Marengo E, Scápola M, Ais ED, Strejilevich SA (2008a) Cognitive and motor features in elderly people with bipolar disorder. J Affect Disord 105:291–295
Martino DJ, Strejilevich SA, Scápola M, Igoa A, Marengo E, Ais E, Perinot L (2008b) Heterogeneity in cognitive functioning among patients with bipolar disorder. J Affect Disord 109 (1–2):149–156
Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, Strejilevich SA (2009) Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. J Affect Disord 116(1–2):37–42
Martino DJ, Strejilevich SA, Manes F (2013a) Neurocognitive functioning in early-onset and late-onset older patients with euthymic bipolar disorder. Int J Geriatr Psychiatry 28:142–148
Martino DJ, Strejilevich SA, Marengo E, Igoa A, Fassi G, Teitelbaum J, Caravotta P (2013b) Relationship between neurocognitive functioning and episode recurrences in bipolar disorder. J Affect Disord 147(1–3):345–351
Martino DJ, Strejilevich SA, Marengo E, Ibañez A, Scápola M, Igoa A (2014) Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder. J Affect Disord 167:118–124
Mauer S, Alahmari R, Vöhringer PA, Vergne DE, Lövdahl H, Correa E, Patkar A, Pae C, Strejilevich S, Dalley S, Ghaemi SN (2014a) International prescribing patterns for mood illness: the International Mood Network (IMN). J Affect Disord 167:136–139
Mauer S, Vergne D, Ghaemi SN (2014b) Standard and trace-dose lithium: a systematic review of dementia prevention and other behavioral benefits. Aust N Z J Psychiatry 48(9):809–818
McElroy SL, Keck PE Jr (2014) Metabolic syndrome in bipolar disorder: a review with a focus on bipolar depression. J Clin Psychiatry 75:46–61
Meng X, D'Arcy C (2012) Common and unique risk factors and comorbidity for 12-month mood and anxiety disorders among Canadians. Can J Psychiatr 57:479–487
Moorhead SRJ, Young AH (2003) Evidence for a late onset bipolar-I disorder sub-group after 50 years. J Affect Disord 73:271–273

Naderali EK, Ratcliffe SH, Dale MC (2009) Obesity and alzheimer's disease: a link between body weight and cognitive function in old age. Am J Alzheimers Dis Other Dement 24:445–449

Ng B, Camacho A, Lara DR, Brunstein MG, Pinto OC, Akiskal HS (2008) A case series hypothesized connection between dementia and bipolar spectrum disorders: bipolar type VI? J Affect Disord 107:307–315

Park S, Park B, Kyung Koh M, HoJoo Y (2014) Case report: bipolar disorder as the first manifestation of CADASIL. BMC Psychiatry 14:175

Passos I, Mwangi B, Vieta E, Berk M, Kapczinski F (2016) Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand 134(2):91–103. doi:10.1111/acps.12581

Post RM, Fleming J, Kapczinski F (2012) Neurobiological correlates of illness progression in the recurrent affective disorders. J Psychiatr Res 46:561–573

Robinson L, Ferrier N (2006) Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 8:103–116

Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB (2006) A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 93:105–115

Rodrigues AA, Rosa AR, Kunz M, Bruna A, Kapczinski F (2014) Bipolar disorder: staging and neuroprogression. Psychiatr Pol 48(2):231–243

Samamé C, Martino DJ, Strejilevich SA (2013) A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disord 15(6):633–644

Samamé C, Martino DJ, Strejilevich SA (2014) Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J Affect Disord 164:130–138

Schouws SN, Comijs HC, Stek ML, Dekker J, Oostervink F, Naarding P, van der Velde I, Beekman AT (2009) Cognitive impairment in early and late bipolar disorder. Am J Geriatr Psychiatry 17 (6):508–515

Schouws SN, Stek ML, Comijs HC, Dols A, Beekman AT (2012) Cognitive decline in elderly bipolar disorder patients: a follow-up study. Bipolar Disord 14:749–755

Schouws SN, Comijs HC, Dols A, Beekman AT, Stek ML (2016) Five-year follow-up of cognitive impairment in older adults with bipolar disorder. Bipolar Disord 18(2):148–154

Schürhoff F, Bellivier F, Jouvent R, Mouren-Siméoni MC, Bouvard M, Allilaire JF, Leboyer M (2000) Early and late onset bipolar disorders: two different forms of manic-depressive illness? J Affect Disord 58(3):215–221

Shulman K, Post F (1980) Bipolar affective disorder in old age. Early and late onset bipolar disorders: two different forms of manic-depressive illness? Br J Psychiatry 136:26–32

Strejilevich SA, Martino DJ (2013) Cognitive function in adulthood and elderly euthymic bipolar patients: a comparison to test models of cognitive evolution. J Affect Disord 150:1188–1191

Strejilevich SA, Samamé C, Martino DJ (2015) The trajectory of neuropsychological dysfunctions in bipolar disorders: a critical examination of a hypothesis. J Affect Disord 175:396–402

Torrent C, Martinez-Arán A, Daban C, Amann B, Balanzá-Martínez V, del Mar BC, Cruz N, Franco C, Tabarés-Seisdedos R, Vieta E (2011) Effects of atypical antipsychotics on neurocognition in euthymic bipolar patients. Compr Psychiatry 52(6):613–622

Torres IJ, Boudreau VG, Yatham LN (2007) Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand 116:17–26

Torres IJ, DeFreitas VG, DeFreitas CM, Kauer-Sant'Anna M, Bond DJ, Honer WG, Lam RW, Yatham LN (2010) Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first manic episode. J Clin Psychiatry 71(9):1234–1242

Tsai SY, Kuo CJ, Chung KH, Huang YL, Lee HC, Chen CC (2009) Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. Am J Geriatr Psychiatry 17:1004–1011

vanHarten PN, Hoek HW, Matroos GE, van Os J (2008) Evidence that lithium protects against tardive dyskinesia: the curaçao extrapyramidal syndromes study VI. Eur Neuropsychopharmacol 18(2):152–155

Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C (2009) Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: clinic-pathological series and review of cases. Br J Psychiatry 194(4):298–305

Vernon A, Natesan S, Modo M, Kapur S (2011) Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. Biol Psychiatry 69:936–944

Vieta E, Reinares M, Rosa AR (2011) Staging bipolar disorder. Neurotox Res 19:279–285

Vita A, De Peri L, Deste G, Barlati S, Sacchetti E (2015) The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. Biol Psychiatry 78(6):403–412

Volkow N, Gur R, Wang G, Fowler J, Moberg P, Ding Y, Hitzemann R, Smith G, Logan J (1998) Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 155(3):344–349

Vonk R, van der Schot AC, Kahn RS, Nolen WA, Drexhage HA (2007) Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder? Biol Psychiatry 62:135–140

Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ (2009) Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry 70(11):1588–1597

Wu KY, Chang CM, Liang HY, Wu CS, Chia-Hsuan Wu E, Chen CH, Chau YL, Tsai HJ (2013) Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. Bipolar Disord 15:787–794

Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS (2012) The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. Eur Psychiatry 27:223–228

Young R, Murphy C, Heo M, Schulberg H, Alexopoulos G (2006) Cognitive impairments in bipolar disorder in old age: literature review and findings in manic patients. J Affect Disord 92:125–131

Schizophrenia and Cognition in Late Life 12

Tarek K. Rajji

Abstract

The number of older patients with schizophrenia is increasing as the general population continues to grow old. Patients with schizophrenia arrive to old age with well-characterized cognitive and functional deficits. These deficits are likely to interact with aging-related factors that affect cognition and function, potentially increasing the risk of developing dementias as it has been demonstrated in epidemiological studies. In this chapter, we review the nature of cognitive impairments in older patients with schizophrenia, their trajectories based on longitudinal studies, and their relationship to changes in functional abilities. Finally, we review the evidence to date behind interventions that aims at enhancing cognition and function in this population. Notwithstanding the limited literature on older patients with schizophrenia, current knowledge suggests that most patients are relatively stable with respect to cognition and that they are likely to benefit from cognitive and functional enhancing interventions.

Keywords

Cognition • Function • Late life • Schizophrenia

Contents

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_11

Introduction

Almost 1% of older adults are living with schizophrenia. This rate is comparable to the rate among the general population (Gurland and Cross 1982; Cohen 1990, 2000). As the general population continues to age, the number of older patients with schizophrenia is expected to increase. The burden of schizophrenia in late life is particularly high on the personal and economic level (Cuffel et al. 1996; Karim et al. 2005). This burden is to a large extent attributed to the function impairments that patients with schizophrenia experience. Cognitive deficits associated with schizophrenia are among the strongest predictors of these function impairments across the adult life span in this population (Green et al. 2000). These deficits are accompanied and potentially exacerbated by aging-related cognitive and function impairments (Rajji and Mulsant 2008). This chapter describes the nature, determinants, and course of cognitive deficits in older patients with schizophrenia and their relationships to their function abilities and then summarizes the intervention studies that aimed at enhancing cognition or function in this population.

Cross-Sectional Studies

Studies that assessed cognition and its trajectory in older adults with schizophrenia focused on either community-dwelling patients or chronically institutionalized ones. In turn, their findings depended on their settings. Community-dwelling patients were relatively younger (mean age in the 50s) and less cognitively impaired than institutionalized patients, allowing a more detailed cognitive assessment. In contrast, chronically institutionalized patients, some of them were institutionalized for decades, tended to be severely impaired, lending itself to the assessment of global cognition.

Global Cognition

Global cognition has been assessed using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), the Dementia Rating Scale (DRS) (Mattis 1973), or

the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al. 1998). Both community-dwelling and chronically institutionalized patients were found to be impaired on these measures compared to age-matched healthy individuals, i.e., on the MMSE (Miller et al. 1991; Almeida et al. 1995; Jeste et al. 1995; Davidson et al. 1996; Patterson et al. 1998; Sachdev et al. 1999; Harvey et al. 2000; Sachdev et al. 2000; McBride et al. 2002; Moore et al. 2004; Rajji et al. 2013), the DRS (Cohen et al. 1988; Jeste et al. 1995; Patterson et al. 1998; Evans et al. 1999; Zorrilla et al. 2000; Palmer et al. 2004; Bankole et al. 2007), and the RBANS (Jeste et al. 2007).

Executive Function

Similar to adult patients, community-dwelling older patients with schizophrenia have been consistently shown to be impaired on executive function whether it was assessed globally as a domain (Miller et al. 1991; Jeste et al. 1995; Fucetola et al. 2000; Sachdev et al. 2000; Evans et al. 2003; Rajji et al. 2013) or using individual tests of executive function, e.g., Wisconsin Card Sorting Test, letter fluency, and Tower of London (Almeida et al. 1995; Sachdev et al. 1999; Depp et al. 2007). These impairments did not differ in severity whether patients had an early-onset or late-onset (i.e., after the age of 40) schizophrenia (Heaton et al. 1994; Jeste et al. 1995; Sachdev et al. 1999).

Visuospatial Ability

Impairments in visuospatial ability have also been consistently observed among community-dwelling and institutionalized patients whether it was assessed as a domain (Fucetola et al. 2000) or using individual tests (Davidson et al. 1996; Evans et al. 1999; Sachdev et al. 1999; Harvey et al. 2000; McBride et al. 2002; Depp et al. 2007). Further, when community-dwelling patients were compared to age-matched institutionalized ones, there was no difference in the degree of impairment (Evans et al. 1999).

Verbal Fluency

Similar to executive function and visuospatial ability, deficits in verbal fluency have been consistently reported and in both patient types, institutionalized (Harvey et al. 2000; Kosmidis et al. 2005) and community-dwelling patients (Moore et al. 2006; Rajji et al. 2013). Further, these deficits were not different when patients with early- and late-onset schizophrenia were compared (Heaton et al. 1994; Jeste et al. 1995; Sachdev et al. 1999).

Psychomotor Function

Older patients with schizophrenia, particularly community-dwelling patients, have been shown to be impaired on psychomotor information processing speed compared

to healthy individuals (Evans et al. 2003; Heaton et al. 1994; Jeste et al. 1995). Furthermore, older patients with early-onset did not differ from those with late-onset schizophrenia (Heaton et al. 1994; Jeste et al. 1995).

Memory

Deficits in memory functions, including both encoding and recall, have been consistently impaired among institutionalized and community-dwelling patients (Cohen et al. 1988; Davidson et al. 1996; Depp et al. 2007; Evans et al. 1999, 2003; Fucetola et al. 2000; Harvey et al. 2000; Jeste et al. 1995; Miller et al. 1991; Sachdev et al. 1999; Sachdev et al. 2000), with the former group being more impaired than the latter (Evans et al. 1999). Compared to patients with Alzheimer's dementia, older patients with schizophrenia have been shown to be equally impaired on learning but less so on recall, especially of the information that has been learned (Heaton et al. 1994; Davidson et al. 1996; McBride et al. 2002; Ting et al. 2010). These findings support the model that memory deficits in older patients with schizophrenia who do not have dementia are driven by frontal lobe deficits rather than temporal lobe dysfunction which results in rapid forgetting as in Alzheimer's dementia. Finally, patients with early onset did not differ from those with late-onset schizophrenia on memory deficits (Heaton et al. 1994; Jeste et al. 1995; Sachdev et al. 1999).

Attention and Working Memory

Working memory requires functional attentional networks but also depends on intact executive functions (Baddeley 1996). Studies that assessed working memory found consistently that older patients with schizophrenia were impaired (see above Executive Function section). In contrast, studies that assessed only attention or that separated attention from working memory found variable results with some studies reporting no deficits in attention (Almeida et al. 1995; Miller et al. 1991; Cohen et al. 1988) while others reporting impairments (Evans et al. 2003; Fucetola et al. 2000; Heaton et al. 1994; Jeste et al. 1995; Sachdev et al. 1999; Rajji et al. 2013). Again, older patients with early or late onset did not differ (Heaton et al. 1994; Jeste et al. 1995; Sachdev et al. 1999).

Longitudinal Studies

Several studies aimed at identifying whether older patients with schizophrenia, with or without a late onset, are at a higher risk of developing cognitive decline or dementia. A large epidemiological study demonstrates that patients with schizophrenia are at double the risk of developing dementia (Ribe et al. 2015). The best

evidence comes from longitudinal studies which, like cross-sectional studies, have been focused on either institutionalized or community-dwelling patients. One of the first studies was published in 1955 by Roth who reported on 46 patients, aged 60 or above, with an age at onset of paraphrenia after age 45 (except one), and who were followed up for 3–4.5 years (Roth 1955). Over this period of follow-up, only one of those patients (2%) was ascertained to have developed dementia. Using similar diagnostic criteria, Holden (1987) reported on 37 patients with paraphrenia and an onset after age 50 whom he followed up for up to 3 years and noted that 13 (35%) of them developed dementia (Holden 1987). More recent studies on older patients with an early- or late-onset schizophrenia and that used DMS-III criteria or later followed up on patients from 1 to 10 years with a sample size ranging from 19 to 424. Most of the publications are based on institutionalized patients due the convenience of studying and following up these patients compared to community-dwelling ones.

Community-Dwelling Patients with Schizophrenia

In general, studies of community-dwelling patients with schizophrenia found that cognition is relatively stable compared with the course of cognition in age-matched healthy individuals. This relative stability of cognition did not depend on whether patients had an early or late onset, i.e., the age of 45 (e.g., Heaton et al. 2001; Palmer et al. 2003; Savla et al. 2006). However, these studies tended to be relatively short in their follow-up, with a maximum follow-up period of 3 years. Further, these studies tended to focus on mid- to late-life patients with schizophrenia, with a mean age in the mid-50s. Longer follow-up studies with older samples of patients did observe an accelerated cognitive decline; however, these studies are small in size (Brodaty et al. 2003; Laks et al. 2006). Adequately powered studies with long-term follow-up are yet to be reported on among community-dwelling older patients with schizophrenia.

Institutionalized Patients with Schizophrenia

More is known about older institutionalized patients with schizophrenia than community-dwelling ones. Older institutionalized patients with schizophrenia are typically more cognitively impaired at baseline than community-dwelling ones. They are also older, in their 60s or older. Taking these differences into account, older institutionalized patients with schizophrenia do experience an accelerated cognitive decline, though a slower decline than older patients with Alzheimer's dementia. This decline is also typically observed after more than 2 years of follow-up (Harvey et al. 1995, 1996a, b, 1999; Waddington and Youssef 1996; McGurk et al. 2000; Friedman et al. 2001; Barch et al. 2004).

Relationship Between Cognition and Function

The relationship between cognition and real-world function is complex. Real-world function and abilities of older patients with schizophrenia are determined by their cognitive abilities (Green 1996). The strength of the association between cognition and functional capacity remains as strong late in life as earlier in life, despite aging-related factors that could confound this association (Kalache et al. 2015; Tsoutsoulas et al. 2016). Still, real-world abilities are affected by the environment they live in, by the resources and social supports available to them, and by their mood and motivation states (Granholm et al. 2009). Few studies assessed the specific relationship between cognition and function in a longitudinal design in patients with schizophrenia. Among these studies, a handful focused on patients who are in mid to late life and in the chronic phase of the illness.

In one study, baseline visual memory, information processing speed, and executive function predicted functional abilities among midlife patients with schizophrenia at 6 months from baseline (Lewandowski et al. 2013). Similarly, in another study with a 1 year follow-up, baseline verbal memory and psychomotor speed predicted function 1 year later among another sample of chronic patients with schizophrenia (Tabares-Seisdedos et al. 2008). This ability of baseline cognition, especially on verbal learning and memory and sustained attention, to predict functional abilities persists even at 2 years of follow-up among chronic patients with schizoaffective disorders (Arts et al. 2011).

In contrast, there seems to be a weaker association between baseline cognition and future functional abilities among chronically and institutionalized patients with schizophrenia who tend to be more symptomatic than the samples described above. In a relatively large sample of chronically institutionalized patients with schizophrenia who were in their mid-50s and followed up for 5 years, baseline verbal fluency predicted social function at follow-up (Nemoto et al. 2014). However, when baseline clinical symptoms were accounted for, the association between baseline cognition and follow-up function did not persist. Further, clinical and functional symptoms consistently improved over the 5 years of follow-up (Nemoto et al. 2014).

Intervention Studies

Over the past three to four decades, there has been an exponential growth in the literature on interventions that aim at improving cognition and consequently function in patients with schizophrenia. However, despite this strong interest in the field, few studies have focused on older patients with schizophrenia.

Pharmacological Interventions

In an 8-week randomized controlled trial (Harvey et al. 2003; Jeste et al. 2003; Kennedy et al. 2003), 176 patients with schizophrenia aged 60 or older were tapered

off their antipsychotic medication and randomized to receive olanzapine (5–20 mg/day) or risperidone (1–3 mg/day). The two groups did not differ in their clinical or cognitive outcomes, and both experienced improvements in attention and memory from baseline.

In a 12-week randomized controlled trial (Kasckow et al. 2010), 198 patients with schizophrenia aged 41–75 years old and experiencing subsyndromal depression were randomized to receive citalopram or placebo. In addition to improvement in depressive symptoms, patients randomized to citalopram improved on social function.

In a cross-sectional study of patients with schizophrenia aged 60 or above, 17 patients receiving trihexyphenidyl were compared on cognition to 14 patients who were not receiving it and who were on comparable antipsychotic doses (Heinik 1998). Patients receiving trihexyphenidyl were highly impaired on measures of global cognition and memory compared to those who were not receiving it. This negative impact on cognition was thought to be due to the anticholinergic property of trihexyphenidyl.

In an antipsychotic dose-reduction study that reduced the antipsychotic dose by up to 40% among 37 chronically stable patients aged 50 or above, the reduction resulted in an increase in dopaminergic receptor availability in the whole striatum and an association between this availability and overall cognition. This association did not exist before the dose reduction. However, there was also no improvement in cognition after the dose reduction (Rajji et al. 2016). These findings suggest that reducing antipsychotics while maintaining clinical stability could allow these older patients to benefit from cognitive enhancing interventions.

Cognitive Remediation (CR) Interventions

CR comprises several forms of cognitive training interventions that aim at reducing the cognitive deficits observed in patients with schizophrenia using drill and practice or strategic-based approaches (Eack 2012). Few studies focused on older patients with schizophrenia, although even patients aged 60 or older are adherent to CR-based interventions (Golas et al. 2015).

In a sub-analysis from two randomized controlled trials in adult patients with depression, bipolar disorder, or schizophrenia that assessed the addition of CR to vocational rehabilitation, 34 patients aged 45 or older were compared to 42 patients aged 44 or younger (McGurk and Mueser 2008). Among the older patients, 18 received CR vs. 19 among the older group. In the younger group, there was significant improvement on several cognitive measures in response to CR but none in the older group.

In a randomized controlled trial of patients with schizophrenia aged less than 40 ($N = 55$) or 40 and above ($N = 30$), CR was delivered at least 3 days per week until 40 sessions were completed (Wykes et al. 2009). CR benefited younger participants in cognitive flexibility, memory, and planning. In contrast, it only benefited older participants in memory.

In a small randomized controlled trial of patients with schizophrenia aged 60 or above, 14 patients received virtual reality CR, and 15 patients received treatment as usual (TAU). CR consisted of ten sessions. Patients randomized to CR experienced better overall cognition (Chan et al. 2010).

In a sub-analysis from a randomized controlled trial and an observational study of a CR intervention among patients with schizophrenia (Kontis et al. 2013), 77 patients aged less than 40 were compared to 57 aged 40 or above. Patients received either CR for at least 20 sessions (49 among the younger and 37 among the older group) or a control condition (TAU or CR less than 20 sessions) (28 among the younger and 20 among the older group). In contrast to the younger patients who experienced improvements in working memory if they received CR compared to control condition, older patients did not experience any benefits from CR.

In a pilot study among 22 patients aged 60 or above, CR was delivered once a week for 8 weeks. There was no control intervention. While CR was well tolerated and adherent to, patients did not experience improvement in cognition (Golas et al. 2015).

Psychosocial Interventions

In one small randomized controlled trial (Barak et al. 2001), animal-assisted therapy was shown to improve social skills among patients with schizophrenia, aged 65 or older, at 6 and 12 months.

In a 24-week randomized controlled trial of patients with schizophrenia aged 42–74 years (Granholm et al. 2005), 37 patients received Cognitive Behavioral Social Skills Training (CBSST), and 39 received TAU. CBSST consisted of weekly groups that addressed cognitive and behavioral symptoms, communication deficits, and problem-solving skills. CBSST resulted in improvement of independent living skills, and these improvements persisted for 1 year even in the absence of any booster intervention (Granholm et al. 2007). Further, baseline cognition predicted response in both intervention arms without a moderating effect of CBSST effects in particular (Granholm et al. 2008).

In a 24-week randomized controlled trial of patients with schizophrenia with a mean age of about 50 years (Patterson et al. 2006), 124 patients received Functional Adaptation Skills Training (FAST), and 116 patients received TAU. FAST consisted of a manualized group intervention that was delivered once for 120 min each and that addressed six areas of everyday functioning: medication management, social skills, communication skills, organization and planning, transportation, and financial management. At the end of the trial, FAST resulted in improvement on performance-based abilities in the above areas of functioning.

In the Helping Older People Experience Success (HOPES) trial (Mueser et al. 2010; Bartels et al. 2014), 90 older patients, mean age 60 years, with depression, bipolar disorder, schizoaffective disorder, or schizophrenia were randomized to receive HOPES and 93 TAU. Mean age of patients with schizophrenia or schizoaffective disorder was 59 years. HOPES included a manualized psychosocial

intervention that was delivered weekly for 1 year followed by monthly booster sessions for another year. The intervention covered seven modules: Communicating Effectively, Making and Keeping Friends, Making the Most of Leisure Time, Healthy Living, Using Medications Effectively, and Making the Most of a Health Care Visit. In addition to the psychosocial intervention, HOPES included preventative health care which consisted of monthly meetings with a nurse embedded in a mental health setting. At the 1- and 2-year mark, HOPES resulted in significant improvement on performance-based functional abilities, psychosocial functioning, and leisure and recreation activities. Further, patients who received HOPES were able to maintain some of these improvements 1 year after the end of the booster sessions.

Conclusion

Older patients with schizophrenia are growing in numbers. As patients with schizophrenia grow old, their cognitive and functional impairments interact with aging-related processes that also impair cognition and function. Despite the aging-related processes and the comorbidities that older patients with schizophrenia experience, the cognitive abilities of those living in the community are relatively stable, while the abilities of those chronically institutionalized decline more rapidly. The current literature also demonstrates that older patients with schizophrenia benefit from psychosocial interventions. They also tolerate cognitive remediation interventions which still need to be better tailored to improve cognition in older patients as they do in younger adult patients. Finally, these cognitive abilities are likely to benefit from optimizing the pharmacological treatments that they receive to minimize the negative cognitive impact of these treatments, i.e., due to their anticholinergic effects.

References

Almeida OP, Howard RJ, Levy R, David AS, Morris RG, Sahakian BJ (1995) Cognitive features of psychotic states arising in late-life (late paraphrenia). Psychol Med 25(4):685–698

Arts B, Jabben N, Krabbendam L, van Os J (2011) A 2-year naturalistic study on cognitive functioning in bipolar disorder. Acta Psychiatr Scand 123(3):190–205

Baddeley A (1996) The fractionation of working memory. Proceedings of the National Academy of Sciences of the United States of America 93(24):13468–13472

Bankole AO, Cohen CI, Vahia I, Diwan S, Kehn M, Ramirez PM (2007) Factors affecting quality of life in a multiracial sample of older persons with schizophrenia. Am J Geriatr Psychiatr 15 (12):1015–1023

Barak Y, Savorai O, Mavashev S, Beni A (2001) Animal-assisted therapy for elderly schizophrenic patients: a one-year controlled trial. Am J Geriatr Psychiatry 9(4):439–442

Barch DM, Mitropoulou V, Harvey PD, New AS, Silverman JM, Siever LJ (2004) Context-processing deficits in schizotypal personality disorder. J Abnorm Psychol 113(4):556–568

Bartels SJ, Pratt SI, Mueser KT, Forester BP, Wolfe R, Cather C, Xie H, McHugo GJ, Bird B, Aschbrenner KA, Naslund JA, Feldman J (2014) Long-term outcomes of a randomized trial of

integrated skills training and preventive healthcare for older adults with serious mental illness. Am J Geriatr Psychiatr 22(11):1251–1261
Brodaty H, Sachdev P, Koschera A, Monk D, Cullen B (2003) Long-term outcome of late-onset schizophrenia: 5-year follow-up study. Br J Psychiatry 183:213–219
Chan CL, Ngai EK, Leung PK, Wong S (2010) Effect of the adapted virtual reality cognitive training program among Chinese older adults with chronic schizophrenia: a pilot study. Int J Geriatr Psychiatry 25(6):643–649
Cohen CI (1990) Outcome of schizophrenia into later life – an overview. Gerontologist 30(6):790–797
Cohen CI (2000) Directions for research and policy on schizophrenia and older adults: summary of the GAP committee report. Psychiatr Serv 51(3):299–302
Cohen CI, Stastny P, Perlick D, Samuelly I, Horn L (1988) Cognitive deficits among aging schizophrenic-patients residing in the community. Hosp Community Psychiatry 39(5):557–559
Cuffel BJ, Jeste DV, Halpain M, Pratt C, Tarke H, Patterson TL (1996) Treatment costs and use of community mental health services for schizophrenia by age cohorts. Am J Psychiatr 153(7):870–876
Davidson M, Harvey P, Welsh KA, Powchik P, Putnam KM, Mohs RC (1996) Cognitive functioning in late-life schizophrenia: a comparison of elderly schizophrenic patients and patients with Alzheimer's disease. Am J Psychiatr 153(10):1274–1279
Depp CA, Moore DJ, Sitzer D, Palmer BW, Eyler LT, Roesch S, Lebowitz BD, Jeste DV (2007) Neurocognitive impairment in middle-aged and older adults with bipolar disorder: comparison to schizophrenia and normal comparison subjects. J Affect Disord 101 (1–3):201–209
Eack SM (2012) Cognitive remediation: a new generation of psychosocial interventions for people with schizophrenia. Soc Work 57(3):235–246
Evans JD, Negron AE, Palmer BW, Paulsen JS, Heaton RK, Jeste DV (1999) Cognitive deficits and psychopathology in institutionalized versus community-dwelling elderly schizophrenia patients. J Geriatr Psychiatry Neurol 12(1):11–15
Evans JD, Heaton RK, Paulsen JS, Palmer BW, Patterson T, Jeste DV (2003) The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. Biol Psychiatry 53(5):422–430
Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state – practical method for grading cognitive state of patients for clinician. J Psychiatr Res 12(3):189–198
Friedman JI, Harvey PD, Coleman T, Moriarty PJ, Bowie C, Parrella M, White L, Adler D, Davis KL (2001) Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. Am J Psychiatr 158(9):1441–1448
Fucetola R, Seidman LJ, Kremen WS, Faraone SV, Goldstein JM, Tsuang MT (2000) Age and neuropsychologic function in schizophrenia: a decline in executive abilities beyond that observed in healthy volunteers. Biol Psychiatry 48(2):137–146
Golas AC, Kalache SM, Tsoutsoulas C, Mulsant BH, Bowie CR, Rajji TK (2015) Cognitive remediation for older community-dwelling individuals with schizophrenia: a pilot and feasibility study. Int J Geriatr Psychiatry 30(11):1129–1134
Granholm E, McQuaid JR, McClure FS, Auslander LA, Perivoliotis D, Pedrelli P, Patterson T, Jeste DV (2005) A randomized, controlled trial of cognitive behavioral social skills training for middle-aged and older outpatients with chronic schizophrenia. Am J Psychiatry 162(3):520–529
Granholm E, McQuaid JR, McClure FS, Link PC, Perivoliotis D, Gottlieb JD, Patterson TL, Jeste DV (2007) Randomized controlled trial of cognitive behavioral social skills training for older people with schizophrenia: 12-month follow-up. J Clin Psychiatry 68(5):730–737
Granholm E, McQuaid JR, Link PC, Fish S, Patterson T, Jeste DV (2008) Neuropsychological predictors of functional outcome in cognitive behavioral social skills training for older people with schizophrenia. Schizophr Res 100(1–3):133–143

Granholm E, Ben-Zeev D, Link PC (2009) Social disinterest attitudes and group cognitive-behavioral social skills training for functional disability in schizophrenia. Schizophr Bull 35(5):874–883

Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatr 153(3):321–330

Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 26(1):119–136

Gurland BJ, Cross PS (1982) Epidemiology of psycho-pathology in old-age – some implications for clinical services. Psychiatr Clin N Am 5(1):11–82

Harvey PD, White L, Parrella M, Putnam KM, Kincaid MM, Powchik P, Mohs RC, Davidson M (1995) The longitudinal stability of cognitive impairment in schizophrenia – mini-mental state scores at one-year and 2-year follow-ups in geriatric inpatients. Br J Psychiatry 166:630–633

Harvey PD, Lombardi J, Leibman M, White L, Parrella M, Powchik P, Davidson M (1996a) Cognitive impairment and negative symptoms in geriatric chronic schizophrenic patients: a follow-up study. Schizophr Res 22(3):223–231

Harvey PD, Lombardi J, Leibman M, White L, Parrella M, Powchik P, Mohs RC, Davidson M (1996b) Performance of chronic schizophrenic patients on cognitive neuropsychological measures sensitive to dementia. Int J Geriatr Psychiatry 11(7):621–627

Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, Davidson M, Davis KL (1999) Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. Biol Psychiatry 45(1):32–40

Harvey PD, Jacobsen H, Mancini D, Parrella M, White L, Haroutunian V, Davis KL (2000) Clinical, cognitive and functional characteristics of long-stay patients with schizophrenia: a comparison of VA and state hospital patients. Schizophr Res 43(1):3–9

Harvey PD, Napolitano JA, Mao L, Gharabawi G (2003) Comparative effects of risperidone and olanzapine on cognition in elderly patients with schizophrenia or schizoaffective disorder. Int J Geriatr Psychiatry 18(9):820–828

Heaton R, Paulsen JS, McAdams LA, Kuck J, Zisook S, Braff D, Harris MJ, Jeste DV (1994) Neuropsychological deficits in schizophrenics – relationship to age, chronicity, and dementia. Arch Gen Psychiatry 51(6):469–476

Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV (2001) Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiatry 58(1):24–32

Heinik J (1998) Effects of trihexyphenidyl on MMSE and CAMCOG scores of medicated elderly patients with schizophrenia. Int Psychogeriatr 10(1):103–108

Holden NL (1987) Late paraphrenia or the paraphrenias – a descriptive study with a 10-year follow-up. Br J Psychiatry 150:635–639

Jeste DV, Harris MJ, Krull A, Kuck J, McAdams LA, Heaton R (1995) Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. Am J Psychiatr 152(5):722–730

Jeste DV, 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. [Erratum appears in Am J Geriatr Psychiatry. 2004 Jan-Feb;12(1):49] Am J Geriatr Psychiatr 11(6):638–647

Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, Kim K, Meeks T, Kraemer HC (2007) A new brief instrument for assessing decisional capacity for clinical research. Arch Gen Psychiatry 64(8):966–974

Kalache SM, Mulsant BH, Davies SJC, Liu AY, Voineskos AN, Butters MA, Miranda D, Menon M, Kern RS, Rajji TK (2015) The impact of aging, cognition, and symptoms on functional competence in individuals with schizophrenia across the lifespan. Schizophr Bull 41(2):374–381

Karim S, Overshott R, Burns A (2005) Older people with chronic schizophrenia. Aging Ment Health 9(4):315–324

Kasckow J, Lanouette N, Patterson T, Fellows I, Golshan S, Solorzano E, Zisook S (2010) Treatment of subsyndromal depressive symptoms in middle-aged and older adults with schizophrenia: effect on functioning. Int J Geriatr Psychiatry 25(2):183–190

Kennedy J, Jeste D, Kaiser C, Golshan S, Maguire G, Tollefson G, Sanger T, Bymaster F, Kinon B, Dossenbach M, Gilmore J, Breier A (2003) Olanzapine vs haloperidol in geriatric schizophrenia: analysis of data from a double-blind controlled trial. Int J Geriatr Psychiatry 18(11):1013–1020

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. Am J Geriatr Psychiatr 21(3):218–230

Kosmidis MH, Bozikas VP, Vlahou CH, Kiosseoglou G, Giaglis G, Karavatos A (2005) Verbal fluency in institutionalized patients with schizophrenia: age-related performance decline. Psychiatry Res 134(3):233–240

Laks J, Fontenelle LF, Chalita A, Mendlowicz MV (2006) Absence of dementia in late-onset schizophrenia – a one year follow-up of a Brazilian case series. Arq Neuropsiquiatr 64(4):946–949

Lewandowski KE, Cohen BM, Keshavan MS, Sperry SH, Ongur D (2013) Neuropsychological functioning predicts community outcomes in affective and non-affective psychoses: a 6-month follow-up. Schizophr Res 148(1–3):34–37

Mattis S (1973) Dementia rating scale. Psychological Assessment Resources, Inc., Odessa

McBride T, Moberg PJ, Arnold SE, Mozley LH, Mahr RN, Gibney M, Kumar A, Gur RE (2002) Neuropsychological functioning in elderly patients with schizophrenia and Alzheimer's disease. Schizophr Res 55(3):217–227

McGurk SR, Mueser KT (2008) Response to cognitive rehabilitation in older versus younger persons with severe mental illness. Am J Psychiatr Rehabil 11:90–105

McGurk SR, Moriarty PJ, Harvey PD, Parrella M, White L, Davis KL (2000) The longitudinal relationship of clinical symptoms, cognitive functioning, and adaptive life in geriatric schizophrenia. Schizophr Res 42(1):47–55

Miller BL, Lesser IM, Boone KB, Hill E, Mehringer CM, Wong K (1991) Brain-lesions and cognitive function in late-life psychosis. Br J Psychiatry 158:76–82

Moore DJ, Palmer BW, Jeste DV (2004) Use of the mini-mental state exam in middle-aged and older outpatients with schizophrenia: cognitive impairment and its associations. Am J Geriatr Psychiatr 12(4):412–419

Moore R, Blackwood N, Corcoran R, Rowse G, Kinderman P, Bentall R, Howard R (2006) Misunderstanding the intentions of others: an exploratory study of the cognitive etiology of persecutory delusions in very late-onset schizophrenia-like psychosis. Am J Geriatr Psychiatr 14(5):410–418

Mueser KT, Pratt SI, Bartels SJ, 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. J Consult Clin Psychol 78(4):561–573

Nemoto T, Niimura H, Ryu Y, Sakuma K, Mizuno M (2014) Long-term course of cognitive function in chronically hospitalized patients with schizophrenia transitioning to community-based living. Schizophr Res 155(1–3):90–95

Palmer BW, Bondi MW, Twamley EW, Thal L, Golshan S, Jeste DV (2003) Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. J Neuropsychiatry Clin Neurosci 15(1):45–52

Palmer BW, Dunn LB, Appelbaum PS, Jeste DV (2004) Correlates of treatment-related decision-making capacity among middle-aged and older patients with schizophrenia. Arch Gen Psychiatry 61(3):230–236

Patterson TL, Klapow JC, Eastham JH, Heaton RK, Evans JD, Koch WL, Jeste DV (1998) Correlates of functional status in older patients with schizophrenia. Psychiatry Res 80(1):41–52

Patterson TL, Mausbach BT, McKibbin C, Goldman S, Bucardo J, Jeste DV (2006) Functional adaptation skills training (FAST): a randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. Schizophr Res 86(1–3):291–299

Rajji TK, Mulsant BH (2008) Nature and course of cognitive function in late-life schizophrenia: a systematic review. Schizophr Res 102(1–3):122–140

Rajji TK, Voineskos AN, Butters MA, Miranda D, Arenovich T, Menon M, Ismail Z, Kern RS, Mulsant BH (2013) Cognitive performance of individuals with schizophrenia across seven decades: a study using the MATRICS consensus cognitive battery. Am J Geriatr Psychiatr 21(2):108–118

Rajji, T. K., B. H. Mulsant, S. Nakajima, F. Caravaggio, T. Suzuki, H. Uchida, P. Gerretsen, W. Mar, B. G. Pollock, D. C. Mamo and A. Graff-Guerrero (2016). Cognition and dopamine D2 receptor availability in the striatum in older patients with schizophrenia. In Press.

Randolph C, Tierney MC, Mohr E, Chase TN (1998) The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 20 (3):310–319

Ribe, A. R., T. M. Laursen, M. Charles, W. Katon, M. Fenger-Grøn, D. Davydow, L. Chwastiak, J. M. Cerimele and M. Vestergaard (2015). Long-term risk of dementia in persons with schizophrenia. JAMA Psychiatry In Press.

Roth M (1955) The natural history of mental disorder in old age. J Ment Sci 101(423):281–301

Sachdev P, Brodaty H, Rose N, Cathcart S (1999) Schizophrenia with onset after age 50 years 2: neurological, neuropsychological and MRI investigation. Br J Psychiatry 175:416–421

Sachdev P, Brodaty H, Cheang D, Cathcart S (2000) Hippocampus and amygdala volumes in elderly schizophrenic patients as assessed by magnetic resonance imaging. Psychiatry Clin Neurosci 54(1):105–112

Savla GN, Moore DJ, Roesch SC, Heaton RK, Jeste DV, Palmer BW (2006) An evaluation of longitudinal neurocognitive performance among middle-aged and older schizophrenia patients: use of mixed-model analyses. Schizophr Res 83(2–3):215–223

Tabares-Seisdedos R, Balanza-Martinez V, Sanchez-Moreno J, Martinez-Aran A, Salazar-Fraile J, Selva-Vera G, Rubio C, Mata I, Gomez-Beneyto M, Vieta E (2008) Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. J Affect Disord 109(3):286–299

Ting C, Rajji TK, Ismail Z, Tang-Wai DF, Apanasiewicz N, Miranda D, Mamo D, Mulsant BH (2010) Differentiating the cognitive profile of schizophrenia from that of Alzheimer disease and depression in late life. PLoS One 5(4)

Tsoutsoulas C, Mulsant BH, Kalache SM, Kumar S, Ghazala Z, Voineskos AN, Butters MA, Menon M, Rajji TK (2016) The influence of medical burden severity and cognition on functional competence in older community-dwelling individuals with schizophrenia. Schizophr Res 170 (2–3):330–335

Waddington JL, Youssef HA (1996) Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. Psychol Med 26(4):681–688

Wykes T, Reeder C, Landau S, Matthiasson P, Haworth E, Hutchinson C (2009) Does age matter? Effects of cognitive rehabilitation across the age span. Schizophr Res 113(2–3):252–258

Zorrilla LTE, Heaton RK, McAdams LA, Zisook S, Harris MJ, Jeste DV (2000) Cross-sectional study of older outpatients with schizophrenia and healthy comparison subjects: no differences in age-related cognitive decline. Am J Psychiatr 157(8):1324–1326

Physical Comorbidities Associated with Late-Life Dementia

13

Susan Kurrle, Roseanne Hogarth, and Henry Brodaty

Abstract

There are a number of physical health conditions (physical comorbidities) that occur more commonly in people with late-life dementia than in the general population of the same age. This chapter provides an overview of these physical conditions which accompany and complicate dementia. These include delirium, epilepsy, falls, weight loss and nutritional disorders, incontinence, sleep disturbance, visual disturbance, oral disease, and frailty. The chapter describes how these conditions may present, what the underlying pathology is likely to be, and gives detailed information and evidence-based recommendations on how to recognize and manage these conditions. It aims to provide practical explanations and suggestions on improving care for people with late-life dementia.

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_14

Keywords
Dementia • Physical comorbidity • Delirium • Epilepsy • Falls • Weight loss • Incontinence • Sleep disturbance • Visual disturbance • Oral disease • Frailty

Contents

Introduction

Dementia is an increasing problem across the world as the population of older people grows in numbers. There is a lack of knowledge about the health conditions, such as epilepsy and delirium that occur more commonly in people with dementia than in the older population generally. While there has been a great deal of focus on the cognitive and behavioral symptoms of dementia and their management, the physical comorbidities of dementia have been neglected. This chapter provides information about these conditions which are common and impact greatly on the care and quality of life of the person with dementia, their caregivers, and family members. As many of these physical conditions are treatable, appropriate recognition and treatment are likely to reduce disability and improve quality of life.

Delirium

Key Points

- Dementia is the strongest risk factor for the occurrence of delirium, and people with dementia have a fivefold increased risk of developing delirium compared to people without dementia.
- Two-thirds of cases of delirium occur in people with dementia, but many cases go unrecognized as dementia is blamed for the symptoms.
- Lower educational level and greater severity of dementia predict greater severity of delirium.
- There are likely to be similar underlying mechanisms for dementia and delirium including decreased cerebral metabolism, cholinergic deficits, and inflammation.

Introduction

Delirium is a common syndrome of acute confusion, which presents with a rapid onset, an altered level of consciousness; disturbances in attention, orientation, memory, thinking, perception, and behavior; and a fluctuating course. Signs of delirium include being easily distracted, exhibiting disorganized speech; experiencing periods of altered perception, restlessness, and agitation alternating with lethargy; and showing a clear variability in cognitive function over the course of a day. Delirium may manifest itself in the patient as hyperactivity, as hypoactivity, or as a mixed form of delirium (NICE 2014).

A person with dementia has a fivefold increased risk of developing delirium, and approximately three-quarters of patients who develop delirium have already been diagnosed with dementia. Dementia is the major risk factor for the development of delirium in hospitalized older patients. While delirium is often viewed as a transient state, it can in fact persist for many months and can result in permanent cognitive and functional changes in those who experience it (Marcantonio et al. 2003). Developing delirium increases the risk for older people of poor functional status, dementia, institutionalization, and death.

Epidemiology of Delirium in Dementia

Delirium occurring in a patient with dementia is a common problem. A systematic review of delirium superimposed on dementia in patients across a range of accommodation options found that delirium occurs in between 22% and 89% of people aged 65 and over with dementia (Fick et al. 2002). Lower rates were more likely to be seen in community-dwelling older people, with higher rates observed in residential care.

Etiology of Delirium in Dementia

It is suggested that people with dementia are more likely to develop delirium due to an underlying vulnerability in the brain resulting from changes occurring through disease processes such as AD. This predisposes these patients to developing delirium when they undergo surgery, or an acute medical illness occurs, or a medication with anticholinergic effects is prescribed. There is ongoing debate about the cause and effect relationship between the two conditions, with evidence that delirium may initiate or accelerate an underlying previously undiagnosed dementia (Inouye 2014). An episode of delirium occurring in a patient with no previous history of dementia, particularly if it occurs after surgery, should always alert clinicians to the possibility of an underlying dementia.

Risk Factors for Delirium in Dementia

Dementia is the strongest predisposing factor for the occurrence of delirium, but other factors include age, acute medical illness, the presence of chronic disease, the patient's level of functional autonomy, pain, depression, behavioral disturbances, the number and type of medications taken, dehydration, fever, malnutrition, and anemia.

Precipitating factors for the development of delirium in hospitalized older people include the use of physical restraints, malnutrition, addition of more than three medications during hospitalization, the use of an indwelling bladder catheter, and the occurrence of an iatrogenic event. When looking specifically at people with dementia who develop delirium, precipitating factors have been found to include the use of physical restraints, a low level of sensory stimulation, an inappropriate physical environment, and the use of narcotic medications.

The Impact of Delirium on Dementia

The presence of delirium is associated with an increased length of hospital stay, increased health service costs, increased mortality, increased rates of admission to residential care facilities, and increased functional disability. Symptoms of delirium may persist for up to 6 months following discharge from hospital, and persistent delirium is a significant predictor of 1-year mortality.

It may be difficult for clinicians to distinguish the onset of a delirium in a person with dementia, but the consequences of missing the diagnosis of delirium are significant and include a longer hospital stay, worsening incontinence and decreased function, and early readmission (Fick 2002). The distinguishing features of delirium include a rapid onset and fluctuating symptoms, compared to a more gradual onset and slowly progressive deterioration of cognition in dementia. However, the significant overlap of symptoms and signs is illustrated in cases of diffuse Lewy body

disease (DLBD), where the signs of fluctuating levels of cognition and visual hallucinations are common to both delirium and dementia (Inouye 2014).

Assessment and Management of Delirium in Dementia

Assessment

Delirium is not well recognized and up to two-thirds of cases of delirium remain undiagnosed (Mittal et al. 2011). In practice it may be very difficult to distinguish delirium from dementia in a patient, so delirium can be missed and symptoms attributed to dementia, particularly in the hypoactive form of delirium. There is also an overlap of cognitive and behavioral symptoms in delirium and dementia, with both associated with agitation, aggression, hallucinations, and delusions.

A diagnosis of delirium is made using multiple sources of information, including the patient's medical history, physical examination, and behavioral observations, including the use of standardized assessment instruments and gathering information from family and professional carers as to the person's prior level of cognition. The Confusion Assessment Method (CAM) is a widely used and well-validated instrument for the detection of delirium (Inouye 2014), and more recently, the 4AT (Belelli 2014) has been validated as a useful screening tool for delirium and can be administered in a few minutes. An acute decline in the cognitive function of a person with dementia should suggest the presence of a superimposed episode of delirium.

Management

While there are no specific guidelines for the management of delirium in dementia, there are a number of guidelines available with comprehensive evidence-based information to guide the prevention, diagnosis, and management of people with delirium generally (BGS and RCP 2006; National Institute for Health and Clinical Excellence 2014), and it is recommended that guidelines be used as a basis for management.

It is essential to treat the underlying cause of the delirium such as infection, hypoxia, medication adverse events, fluid and electrolyte imbalance, and hypoxia. Management of delirium also includes the use of a specialized ward environment with staff knowledgeable in the management of delirium.

The pharmacological management of delirium should be targeted toward the underlying causes, such as treating with antibiotics for infection and with analgesics for pain relief. If the patient is experiencing behavioral or psychological symptoms which are causing distress such as agitation, aggression, hallucinations, or delusions, then antipsychotic medication may be appropriate. The Cochrane systematic review on the use of antipsychotics in delirium concludes that there is evidence for the use of haloperidol, risperidone, and olanzapine (Lonergan et al. 2007). The Cochrane review of the use of benzodiazepines in delirium concluded that there is no evidence for their use except in alcohol withdrawal-related delirium (Lonergan et al. 2009).

Recommendations

1. Expect delirium in unwell and hospitalized older patients with dementia and use a simple screening test such as the 4AT or CAM regularly to detect delirium. Look for a patient who is easily distracted, has periods of altered perception, exhibits disorganized speech, has periods of both restlessness with agitation and lethargy, and who has a clear variation in cognitive function over the course of a day.
2. Find the cause of the delirium and treat symptomatically. This includes correcting fluid and electrolyte imbalances, treating infection, ceasing inappropriate medication (particularly medications with anticholinergic effects), considering alcohol or benzodiazepine withdrawal, and managing hypoxia.
3. Nurse in an appropriately specialized ward environment (e.g., delirium room) and ensure that spectacles and hearing aids are available, and the patient has a clock or watch available and a view of daylight to assist in orientation. The patient should be kept as mobile as possible.
4. Avoid the use of restraints and keep use of sedative or antipsychotic medications to a minimum. If constant supervision is required, consider encouraging family members to be present or arrange the use of one-to-one nursing.
5. Discourage patient bed moves and changes in location.

Epilepsy

Key Points

- People with dementia have a sixfold increased risk of having a seizure compared to the normal population.
- Between 5% and 10% of people with dementia are likely to have a seizure.
- Seizures are more likely to occur in younger people with Alzheimer's disease than in older people, and seizure incidence is higher in patients with vascular dementia than Alzheimer's disease.

Introduction

Epileptic seizures are defined as brief, unprovoked disturbances of consciousness, behavior, motor function, or sensation and are known to occur more frequently in older people. However, the likelihood of seizures in people with dementia is further increased compared to an age-matched population (Amatniek 2006), and it has been suggested that many of these, particularly partial seizures, are not detected and remain undiagnosed (Mendez 2003).

Epidemiology and Prevalence of Seizures in Dementia

A large number of studies have confirmed that people with dementia have a significantly higher chance of developing new-onset seizures during the course of their disease than those without dementia. Many of these studies have looked specifically at people with AD and have reported results indicating that seizures may occur in up to 23% of people with the disease (Mendez 2003).

Hesdorffer et al. (1996) found that the presence of diagnosed AD increased the risk of developing new onset seizures sixfold, and the presence of other types of dementia (particularly vascular dementia) increased the risk by a factor of eight. In a cohort study of patients recruited following a diagnosis of AD, 7% of these patients developed seizures during the follow-up period (Amatniek 2006). The authors noted that the diagnosis of AD increased the risk of having seizures in patients aged 50–59 years by a factor of 87, compared to the non-AD population.

While many studies have examined seizures in people with AD, other dementias are also recognized as a cause of seizures. The presence of vascular disease in the brain increases the chance of seizures occurring, and a prospective study of 202 stroke patients showed that those with preexisting dementia had a fourfold increased chance of developing seizures following a stroke, compared to patients without a known dementia (Cordonnier et al. 2005). Seizures are also known to occur in dementia with Lewy bodies, Huntington's disease, and people with Down syndrome who develop Alzheimer's disease.

Etiology of Seizures

The pathogenesis of seizures in dementia remains unclear, and a number of theories have been proposed. One possible cause is thought to be the development of epileptogenic lesions associated with the selective loss of neurons and glial cells in the parietal, neocortical, and hippocampal areas (Mendez 2003). Occult vascular lesions have been suggested as another possible source of seizures, as have alterations in neurotransmitters, particularly acetylcholine and dopamine. Although stroke and cerebrovascular disease are known causes of seizures, the presence of other diseases in the brain does not appear to increase the chance of seizures occurring.

Where comparisons have been made between AD patients with and without seizures, no apparent distinction can be made between these groups with respect to the presence of hypertension, diabetes, or other medical illnesses, the use of psychotropic drugs or other medication, or alcohol use (Mendez 2003). There are a number of medications used in the treatment of dementia that may potentially lower the seizure threshold. These include the antipsychotics and the cholinesterase inhibitors (Mendez 2003). Though this possibility should be considered, there is currently little evidence that these medications do increase the occurrence of seizures in people with dementia.

Features of Seizures in Dementia

Seizures may occur at any stage in the course of dementia, although these are more likely to occur later in the disease process. The risk for developing seizures appears to be much higher in younger dementia patients (those under the age of 65 years) than in older patients, with studies reporting up to an 87-fold increase in the risk of seizures among the younger age group (Amatniek 2006).

Seizures in dementia are usually partial in nature, although generalized onset seizures are also seen (Hesdorffer 1996). Complex partial seizures were the seizure type experienced most commonly, as shown in a retrospective review of 63 patients with dementia and epilepsy (Rao 2009).

Management of Seizures in Dementia

Diagnoses of seizures in people with dementia can be problematic due to difficulties associated with history taking and examination and the concurrent presence of other conditions such as syncope or transient ischemic attacks. In addition to taking a thorough clinical history with confirmatory information from family or carers as an essential first step, a detailed physical and neurological examination should also be performed. Symptoms and signs of seizures may be subtle, and complex partial seizures may go unrecognized given that their characteristics may mimic dementia symptoms, such as transient amnesia or wandering. Seizures may also present as a fall or syncope with consequences such as a head injury, a subdural hematoma, or a hip or other fractures.

It is important to exclude other potential causes of seizures such as traumatic brain injury, tumor, stroke, metabolic disturbance, or infection, and routine laboratory investigations and neuroimaging may be appropriate in these patients to exclude other potentially treatable seizure causes. Unless taken during a seizure, an electroencephalogram is rarely diagnostic and may just show a general slowing (Mendez 2003).

Treatment of seizures is important in patients with AD, and it is recommended that therapy be instituted after two seizures given the high risk of recurrence. There have been no specific trials addressing drug treatment of seizures in dementia, so information from drug trials in epilepsy in the general population has been extrapolated for these patients. In a retrospective study by Rao et al. (2009) of patients with dementia and epilepsy, the authors noted that the majority of patients had a very good response to antiepileptic therapy. However, about one-third of patients experienced adverse events, which included confusion, mental slowing, drowsiness, ataxia, and visual disturbances. The possible interaction with concurrent medications such as the antipsychotics, antidepressants, and cholinesterase inhibitors also need to be considered.

Mendez (2003) suggests starting with low doses of carbamazepine (100 mg/day), valproic acid (125 mg/day), gabapentin (300 mg/day), or lamotrigine (25 mg/day) as first-line monotherapy for seizures in older patients with dementia. These dosages can be gradually titrated upward.

Recommendations

1. Consider the possibility of seizures if people with dementia or their carers report the occurrence of falls, syncope or faints, altered mental status, or acute confusional episodes.
2. Be aware that seizures may be atypical and the EEG may be inconclusive.
3. If seizures are suspected, exclude other possible causes for new onset seizures.
4. If two or more seizures have occurred, consider treatment with anticonvulsants such as carbamazepine, valproate, gabapentin, or lamotrigine.

Falls

Key Points

- Falls occur in people with dementia at twice the rate of the normal population, and 70–80% of people with dementia will fall at least once a year.
- Fractures are three times more common in people with dementia than in the normal population, and hip fracture is also three times more common.
- The increased rate of falls may be due to the presence of gait abnormalities, orthostatic hypotension, postural instability, impaired executive function, and impaired visuospatial skills.
- No interventions have been shown to prevent falls specifically in people with dementia.

Introduction

Falls are a major health issue in older people. A fall is defined as an event reported by the faller or a witness, resulting in a person inadvertently coming to rest on the ground or another lower level (Shaw 2003). A fall can precipitate a downward spiral of immobility, reduced confidence, and incapacity which may result in early institutionalization and death (AGS 2011). Studies have consistently shown that dementia is associated with an increased risk of falls which is twice that of cognitively intact older people. The annual incidence of falls in older people with dementia is 70–80%, and this high rate of falling is also seen in younger people with dementia. Dementia is also associated with a three- to fourfold increase in risk of hip fracture and a threefold increase in 6-month post-fracture mortality rate compared to older people without dementia.

Etiology of Falls in Dementia

In the general population, the risk of falling is determined by numerous factors. These include a previous history of falls; impairments of balance, muscle strength,

coordination, and gait; impaired vision, the use of bi- or multifocal glasses, functional impairment, medical conditions of the heart or brain causing fainting or low blood pressure, medication use, impaired cognition and mood, environmental hazards, and inappropriate footwear (AGS 2011). These factors are all relevant to patients with dementia. In addition, there are many other possible reasons why people with cognitive impairment or dementia have an increased risk of falls.

Gait abnormalities are seen commonly in dementia, particularly in people with vascular dementia, dementia with Lewy bodies, Huntington's disease, and Parkinson's disease with dementia. In a study of 210 older people with dementia who had presented to the emergency department with a fall, 99% were found to have an impairment of gait or balance (Shaw 2003). Postural hypotension is commonly seen in dementia with Lewy bodies and Parkinson's disease with dementia, and decreased postural instability is common to all dementias.

Normal walking has been shown to require not only intact motor and sensory systems but also intact executive control and navigational and visuospatial abilities and attention, in order to choose an appropriate path while recognizing and avoiding hazards. People with dementia, particularly Alzheimer's disease and dementia with Lewy bodies, have impaired visual and visuospatial skills which increase the risk of falling. Good postural stability is also important for normal walking; thus, poor control of postural sway, inadequate vision, and increased reaction times can all contribute to an increased risk of falling (Lord 1996). Dementia can affect all of these abilities, leading to an increased risk of falling when these functions are affected. Impaired motor planning skills and reduced attention span contribute to the risk of falling, and agitation, restlessness, and wandering also increase the risk of falls. People with dementia may also have an unrealistic perception of their own motor abilities resulting in impulsivity and risk-taking behavior which also contribute to the risk of falling.

Centrally active medications such as antipsychotics and antidepressants are well known to increase the risk of falls, and these are commonly prescribed in people with dementia. Cholinesterase inhibitors are used as symptomatic treatment in AD and other dementias, and some studies have shown them to increase the risk of syncope and hip fracture in some older people. However, a meta-analysis of randomized trials of the cholinesterase inhibitors and memantine, also used as a symptomatic treatment in AD, showed that while the cholinesterase inhibitors may increase the chance of syncope in patients, they were not directly associated with an increased risk for falls or fractures (Kim 2011).

Management

There is strong evidence for interventions to prevent falls in the general older population, but no studies have been successful in showing that falls can be prevented specifically in people with dementia living in the community (Booth 2015). Studies in residential care facilities have indicated that multifactorial

interventions may be effective in preventing or reducing falls in a population of frail older people, some of whom have dementia. There is no evidence that screening for fall risk in people with dementia reduces falls; however, it seems reasonable to intervene opportunistically and offer assessment and interventions as appropriate.

A multifactorial assessment for fall risk is recommended for all older people who have had a fall or have gait or balance problems (AGS 2011). Thus, an assessment of risk factors for each individual may reveal areas where risk is heightened and where modifications can be made to mitigate this risk. This assessment should include the circumstances surrounding falls that have occurred, current medications, focusing particularly on those known to increase falls risk (including psychotropics and antihypertensives); an evaluation of gait and balance, muscle strength, heart rate and rhythm, blood pressure, and presence of postural hypotension; and a review of footwear and environmental hazards. The presence of urinary incontinence has also been shown to be a risk factor for falls.

Medication management, strength and balance training, treatment of postural hypotension, treatment of osteoporosis, treatment of cataracts, occupational therapy home hazard assessment, and the use of hip protectors and helmets and falls alarms are some of the interventions that have been shown to reduce falls or fall-related injuries in the older population generally and should be considered in the older person with dementia. The use of physical restraints to prevent falls is not recommended, as there is no evidence for their use, and they may in fact increase the risk of falls.

Recommendations

1. While there is no evidence that screening people with dementia for fall risk is effective in reducing falls, consider opportunistic screening for risk modification.
2. Do not use physical restraints as their use is likely to worsen fall risk.
3. While there are no interventions proven to prevent falls specifically in people with dementia, consider the following:
   (a) Review medications particularly psychotropic medication.
   (b) Assess and treat postural hypotension.
   (c) Assess and treat visual impairment due to cataracts or refraction errors.
   (d) Treat osteoporosis and vitamin D deficiency.
4. Consider the use of:
   (a) Exercise, particularly strength and balance training
   (b) Occupational therapy home hazard assessment and environmental modification
   (c) Hip protectors
   (d) Fall alarms
5. Assess and treat orthostatic hypotension.

Weight Loss and Nutritional Disorders

Key Points

- People with Alzheimer's disease may lose up to 10% of body weight during the course of the disease. People with vascular dementia and frontotemporal dementia are also likely to lose weight.
- Weight loss may occur up to 20 years before the appearance of cognitive symptoms.
- Dementia patients at risk of weight loss and malnutrition should be identified and treated to prevent loss of muscle mass and strength, pressure ulcers, and loss of immunity with subsequently increased rate of infection.

Introduction

Weight loss accompanied by malnutrition is one of the major manifestations of Alzheimer's disease (AD) and is also seen in other types of dementia. Alois Alzheimer mentioned this particular manifestation of the disease in the case report of his second patient, "Johann F." Alzheimer noted "his body-weight falls slowly and steadily" (1911), and this weight loss as a symptom is consistent with the diagnosis of AD according to the criteria defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) work group.

Over the past 30 years, weight loss has been recognized as a significant comorbidity with dementia, and research has shown that malnutrition increases morbidity and mortality, as a loss of muscle mass leads to reduced overall function, resulting in an increase in falls, fractures, decubitus ulcers, and infections (Gillette-Guyonnet 2007).

The Impact of Dementia on Body Weight and Nutrition

Many studies have identified low body weight, thinness, and weight loss as clinical characteristics of patients with dementia and in particular those with AD, especially in the later stages of the disease process, and weight loss is considered by many to be one of the principal manifestations of AD (Gillette-Guyonnet 2007). Patients with AD can lose up to 5% of their body weight annually, and weight loss is also seen in patients with vascular dementia and frontotemporal dementia.

Even at an early stage in the disease process, weight changes may become apparent, and weight loss may even precede the diagnosis of dementia. While some explanations have been offered for the occurrence of weight loss and malnourishment, sometimes in the presence of adequate food intake, the mechanisms still remain unclear. Alterations in eating patterns may contribute to weight loss and may vary with the type of dementia.

Causes of Weight Loss and Malnutrition in Dementia

While it is well established that weight loss accompanies dementia, there is still a lack of understanding about the mechanism of this weight loss. It is important to understand the reasons behind this weight loss, as some of these factors may be amenable to treatment, and those factors that are reversible should be identified and addressed.

Some of the weight and nutritional changes of dementia may be attributable to changes in eating patterns. This may occur early in the development of the disease, particularly in people who live alone. Difficulties with shopping and cooking due to declining abilities in daily living activities may result in a decreased dietary intake. Factors such as apathy and a loss of initiative, or a loss of olfactory function, might be reasons for the occurrence of weight loss due to inadequate dietary intake.

Behavioral symptoms appear to have some effect on weight loss and nutrition. Depression and apathy are implicated as causes of decreased food intake in patients with dementia, and other symptoms such as an increased tendency for distraction, anxiety, and agitation, especially with constant pacing, are also significant (Gillette-Guyonnet 2007).

A number of changes in feeding behavior occur later in the disease process and can be divided into four areas (Gillette-Guyonnet 2007). These include food selection behaviors where there is preference for one type of food over another and a refusal to eat certain foods, an active resistance to feeding and the spitting out of food, feeding dyspraxia where there is an inability to use implements or to know how to put food into the mouth, and dysphagia where there is a change or loss of the ability to chew and swallow food.

Dysphagia (difficulty with swallowing) may be a factor in some cases of malnutrition in dementia, particularly in the later stages of the disease, and is seen in frontotemporal dementia, vascular dementia, and Parkinson's disease with dementia, as well as Alzheimer's disease.

Concomitant medications used by people with dementia, particularly cholinesterase inhibitors, may lead to changes in food intake due to various side effects which can include decreased appetite and anorexia, nausea and vomiting, and dry mouth.

Intervention and Management for Weight Loss and Malnutrition

It is important to consider active intervention to prevent and treat malnutrition in patients with dementia in order to prevent the consequences of poor nutrition. These consequences include reduced muscle strength, an increased risk of falls, loss of independence, an increased risk of decubitus ulceration, impaired immunity and an increased chance of infection, and greater risk of death.

Assessment

The accurate detection of malnourished patients or those at risk of malnutrition is important. Clinicians may not properly identify potentially malnourished patients on the basis of BMI alone, and weight change as measured by regular weight measurement is recommended as the optimal way to detect patients at risk of malnutrition (Belmin and Expert Panel and Organisation Committee 2007). Those patients at greater risk of weight loss require closer monitoring of their food intake and weight and secondary conditions that may affect the ability to eat need to be addressed, such as the dentition of the patient, and the use of regular oral fluids or artificial saliva may assist in the management of a dry mouth and improve food intake.

Management of Nutrition

Targeted nutritional interventions are generally effective in addressing poor nutrition and weight loss, particularly when combined with staff education and education of carers. The use of oral supplements between meals and availability of finger foods are important in ensuring adequate nutrition.

The environment in which eating occurs has also been shown to have an effect on nutritional status. It is important to preserve a homelike environment in residential care situations, with smaller tables, the use of tablecloths, and perhaps background music.

It is important to ensure that the person with dementia has adequate sensory input in order to participate in the meal. Wearing spectacles and a hearing aid will allow for greater levels of social interaction and ensure that the person with dementia is able to see their food.

The timing of meals and supplements is also important as the highest energy intake occurs in the morning, so meals should be of high nutrient density early in the day when cognition is usually better in people with dementia, and there should be plenty of time allocated for the meal.

The use of enteral nutrition in late-stage dementia remains controversial. Naso-gastric feeding tubes and percutaneous endoscopic gastrostomy (PEG) tubes have been used with the aim of improving nutrition and preventing aspiration in patients with severe dysphagia. However, a number of studies have shown decreased survival in patients with dementia and feeding tubes, and the use of feeding tubes has not been shown to reduce the risk of aspiration pneumonia, malnutrition, or decubitus ulceration. Careful hand-feeding of patients with severe dementia with appropriate food may be more effective than enteral feeding, and the most recent Cochrane systematic review on the subject of enteral feeding in patients with advanced dementia concluded that there is insufficient evidence to show that enteral feeding is beneficial in patients with dementia (Sampson 2009).

Overfeeding

The obverse pattern of excessive eating can occur in dementia which in association with reduced initiative and less physical activity can lead to obesity and its complications. Frontotemporal dementia is often characterized by stereotyped eating patterns, usually for sweets, and sometimes hyperphagia even to the extent of choking to death.

Recommendations for the Diagnosis and Management of Weight Loss in Dementia

Belmin and colleagues (2007) have developed a comprehensive set of consensus guidelines for the diagnosis and management of weight loss in Alzheimer's disease based on a literature review and consensus development approach. The following recommendations are extracted from those guidelines:

1. In patients with dementia, nutritional status should be assessed at the time of diagnosis and/or the start of treatment. This should include measurement of body weight and the Mini Nutritional Assessment (MNA) carried out with the help of a family caregiver.
2. Body weight should be measured and recorded monthly and on visits to the treating physician.
3. Initiation of a nutritional intervention should occur if two or more of the following are present:
   (a) MNA score < 17
   (b) Plasma albumin <35 g/L
   (c) A decrease in food intake assessed over 3 days
   (d) Loss of more than 5% of body weight over 6 months
4. A nutritional intervention should include:
   (a) A search for reversible medical or socio-environmental causes for intake reduction
   (b) Increased calorie/protein intake (oral supplementation by food and/or by dietary supplements)
   (c) Daily physical activity monitoring
   (d) Evidence of malabsorption or persistent diarrhea
5. If situations involving medical stress occur, such as surgery or severe infection, nutritional support should be provided.
6. To improve food intake, consider the use of finger foods, favorite foods, homelike environment (e.g., tablecloths), contrast colors of food and plate, and background music, and give oral supplements 2 h before meals rather than with meals.

7. Education of family and professional caregivers in the management of weight loss and the use of nutritional interventions may be beneficial.
8. Enteral feeding in late-stage dementia is unlikely to be effective.

Incontinence

Key Points

- In dementia there is a loss of cognitive ability to interpret the sensation of a full bladder, loss of motivation to inhibit the passage of urine, and an inability to plan how to self-toilet. Together with dressing dyspraxia and visuospatial deficits, this leads to incontinence.
- Urinary incontinence occurs earlier in the course of vascular dementia, dementia with Lewy bodies, and frontotemporal dementia, than in Alzheimer's disease.

Introduction

Urinary incontinence (UI) or feces in older age can cause great distress and lead to social isolation. Age-related changes in bladder and bowel function are common in the older population and are due to a combination of comorbidities, medication, functional decline, and age-related changes (Orme et al. 2015). Incontinence in the person with dementia is a combination of normal ageing changes and the inability to employ compensatory measures to avoid incontinence due to cognitive impairment and executive dysfunction. Dementia is associated with a threefold increase in UI in the older population (Orme 2015). The frequency of UI increases with age and lower cognition. The cholinergic actions of the cholinesterase inhibitors stimulate bladder and bowel contractions and cause feelings of desire to micturate and/or to defecate.

The Impact of Dementia on Continence

Urinary incontinence in dementia occurs at different times in the course of the disease process, depending on the type of dementia. UI is seen more frequently in late-stage Alzheimer's disease and early-stage frontotemporal dementia and dementia with Lewy bodies (Diehl-Schmid et al. 2007). Incontinence in people with dementia (when not linked to infection) is the result of a progressive dysfunction directly linked to a lack of concentration, insight, judgment, and motivation, in addition to disorientation and general lethargy. Visuospatial difficulties, apraxia, and procedural memory loss can also interfere with the ability to maintain continence, leading to difficulties in performing self-toileting. Loss of prefrontal control over voiding reflexes and a loss of sphincter control also contribute to UI (Diehl-Schmid 2007).

Assessment of Urinary Incontinence

Given that the etiology of incontinence in the person with dementia can be multifactorial, a comprehensive assessment is required to rule out reversible causes of incontinence. A number of causes of incontinence have been identified in the literature as avoidable and reversible. These include delirium, infection, atrophic urethritis and vaginitis, prostatic hypertrophy, medication side effects, excessive urinary output, fecal impaction, restricted mobility, and the use of physical restraints (Sakakibara et al. 2008; Specht 2011).

It is also recommended that a thorough medical assessment be completed covering the following areas (Hägglund 2010):

- *Medical history*: including the most relevant medical background (diabetes, heart failure, other neurological disorders) and relevant surgical history (urological, gynecological, pelvic surgery).
- *Cognitive assessment*: including the severity and type of dementia.
- *Physical examination*: including rectal examination and pelvic examination.
- *Medication review*: prescription and over-the-counter medications (diuretics, laxatives, sedatives-hypnotics, antipsychotics, antidepressants, analgesics) and the use of cholinesterase inhibitors.
- *Functional assessment*: of mobility and transfer ability. Consider environmental factors limiting access to the toilet.
- *History of incontinence*: recency of onset, frequency, history of urinary tract infections, nocturia, urge, stress, retention, overflow, and diarrhea.
- *Laboratory assessments*: including urinalysis, blood count, and biochemistry.
- *Urodynamic studies*: bladder ultrasound to measure post-void residual volume and consider urodynamic studies if the cause of incontinence is unclear.

Intervention and Management for Urinary Incontinence in Dementia

Medication Use

Some medications may theoretically cause or worsen UI. Several case studies of medication usage were found in the literature linking incontinence to the use of cholinesterase inhibitors. Hashimoto et al. (2000) reported on 94 observed cases of donepezil use with a 7.4% incidence of incontinence in the first 2–14 days of treatment. However, this has not been supported by findings from randomized controlled trials for donepezil or other cholinesterase inhibitors.

Detrusor hyperactivity or overactive bladder is seen as the major cause of UI in persons with dementia and can be treated with antimuscarinic medication. Caution is advised when using medications to treat urinary incontinence in this patient group due to their anticholinergic effects, which can increase the risk of confusion, delirium, falls, disorientation, and memory impairment and decreased levels of consciousness. Thus, careful patient selection and monitoring are required if these

drugs are concomitantly used in older patients, particularly in those older patients with dementia (Specht 2011; Orme et al. 2015).

Prompted Voiding Programs

Prompted voiding (PV) programs dominate the literature as a management tool for older adults, both for those with and without dementia residing in the community or residential care. The design of PV programs varies slightly depending on the environment. The timing of prompts ranges from every 2 to 3 h during waking hours. The main goals of a PV program are to reduce the incidence of incontinent events, increase bladder awareness, and promote self-initiated toileting (Specht 2011).

There was no evidence that the effects of the program are sustained over time or persist after stopping the program. PV programs were labor intensive for caregivers and residential aged care staff.

Fecal Incontinence

It is estimated that the prevalence of fecal incontinence within the normal older population is between 2% and 5% and may be considerably higher in the population of older people with dementia. Management of the problem relies on treating the cause of the fecal incontinence. Constipation with overflow is routinely treated with laxatives and enemas in the first instance, followed by dietary modification such as increasing fluid and fiber intake and increasing exercise and physical activity.

Recommendations

1. Undertake a comprehensive assessment to identify reversible and treatable causes of incontinence. Look particularly for urinary tract infection, constipation, and prostatic hypertrophy with secondary bladder hyperactivity.
2. Conduct a full review of current medication use, including over-the-counter laxative use, antipsychotics, and antidepressants.
3. Acknowledge caregiver stress and provide support and education on noninvasive cost-effective measures for managing incontinence, e.g., using protective sheeting on beds, sourcing a linen service, etc.
4. Implement individual incontinence management programs. Suggested components include the following:
   - Allow adequate fluids during the day and avoid fluids in the evening.
   - Ensure easy toilet access with grab rails, a toilet surround frame or raised toilet seat, and use contrasting paint on the toilet door and adequate lighting.
   - Ensure appropriate clothing with ease of access, e.g., using elasticized waistbands and Velcro closures rather than buttons or zips.
   - If pads are used, ensure that they are easy to pull down so that toileting can be encouraged.
   - Follow a prompted toileting program with a fixed timing schedule.

- Look for clues of a full bladder – including restlessness, pacing, and pulling at pants.
- Ensure appropriate mobility aids such as walking stick or frame that are available to encourage independent mobility and access to toilet.
- Consider medication or catheterization as a last resort.

Sleep Disturbance

Key Points

- Changes in sleep occur in many older people, but are more prominent in people with dementia, particularly Alzheimer's disease, with up to 50% reporting significant sleep disturbance.
- The circadian rhythm is disrupted in Alzheimer's disease, with delays and fragmentation of the sleep-wake cycle and increased nighttime wakenings and increased daytime sleeping.
- The severity of sleep disturbance increases with the severity of the dementia.

Introduction

Age-related changes in sleep patterns are well documented in the older adult population. Changes occur in several areas, with increased time taken to fall asleep, more awakenings, and more time spent in the lighter stages of sleep. In addition, total sleep time, sleep efficiency, and rapid eye movement (REM)/non-rapid eye movement (NREM) cycles are reduced (Cole and Richards 2006).

In dementia, and particularly in Alzheimer's disease (AD), there is reduced sleep efficiency, increased amounts of NREM sleep, and an increase in the number of awakenings when compared with age-matched controls. There is equally a comparative decrease in the amount of REM sleep, a reduction in total sleep length, and more sleep-wake rhythm disturbance (Tractenberg 2005). The severity of these changes in sleep appears to increase concurrently with increasing dementia severity. Disrupted sleep patterns have a significant impact on patient's and carer's quality of life, with chronic sleep deprivation playing a key role in the decision to institutionalize the patient.

Pathology of Sleep Disturbance

It is thought that changes that occur in circadian rhythm with advancing age are related to age-associated degenerative changes in the suprachiasmatic nucleus (SCN) of the hypothalamus. Dementia can further change and disrupt the sleep-wake

rhythm of the older person, as damage to the neural pathways interferes with the body's ability to initiate and maintain sleep. The pathology behind the marked changes in sleep patterns of AD sufferers is thought to be related to the presence of neurofibrillary tangles (but not amyloid plaques) within the SCN and the subsequent loss of neurons (Ancoli-Israel 2006). This can explain the inversion of sleep rhythm and the day-night reversal that are seen in AD patients. It is probable that a combination of neuroanatomical and neurochemical changes associated with Alzheimer's disease (AD) and other dementias all contribute to the disruption of the sleep-wake cycle.

Rapid eye movement (REM) sleep disorder is one of the earliest symptoms of Lewy body dementia. Partners may complain of the person with Lewy body dementia exhibiting excessive or violent movements, gesturing, or speaking during their sleep.

The Epidemiology of Sleep Disorders in Dementia

The association between dementia and sleep disorders is well documented in the literature, with between 25% and 50% of dementia sufferers reporting some sleep disturbance. The studies have assessed patients from the community and supported accommodation and nursing home care. In the community, studies have found that sleep problems were reported in those people with dementia who had a significantly longer duration of disease and significantly lower scoring on function in activities of daily living. The studies have identified a range of sleep disturbances in both groups, with increased daytime sleep the most distinctive feature in the dementia group (Tractenberg 2005).

Studies have consistently shown that those dementia patients who resided in nursing homes with the lowest MMSE scores recorded the highest level of sleep disturbance. These results were attributed to the severity of dementia in the nursing home population, environmental factors including poor lighting and institutional routines, and lower levels of daytime activity including exposure to sunlight (Cole and Richards 2006).

Intervention and Treatment for Sleep Disturbance in Dementia

It is important to ensure that the person with dementia does not have underlying physical or medical problems exacerbating their sleep problems. A full physical examination excluding causes of discomfort or pain should be carried out. Arthritic pain, shortness of breath, muscle cramps, and constipation are all causes of sleep interruption. Sleep hygiene measures should be instituted including a darkened room at a comfortable temperature, avoidance of caffeine-containing beverages, a regular routine and time for retiring, and avoidance of daytime napping.

Exposure of the eyes to adequate light during the day is important for the quality, duration, and timing of sleep. However, there is little evidence of benefit for the effects of bright light therapy on sleep, behavior, and mood disturbances associated with dementia.

The use of sedating medication to improve sleep in patients with dementia should be considered with care as the side effects and risks associated with sedative-hypnotic medication may increase confusion or increase the risk of injury in people with dementia. Alternatives such as melatonin, a pineal hormone involved in the physiological regulation of sleep, have some evidence for their use (de Jonghe 2010).

Activity programs in residential care also appear to have some benefit on promoting healthy sleep patterns in people with dementia and in community-dwelling older people with dementia; daily walking, increased light exposure, and improved sleep hygiene measures were effective in improving sleep (Cole and Richards 2006).

Carer Burden and Sleep Disturbance

Carer stress is reported as a key factor in the decision to institutionalize a care recipient. Sleep deprivation and frequent nocturnal awakenings add to the burden of caring for a person with dementia.

The provision of residential respite care to reduce carer burden is often central to the support of AD patients and carers in the community. There is higher quality of sleep reported by carers during periods of residential respite, but studies have shown that there is worsening sleep quality in the person with dementia during this time, and on return home (Lee 2007).

Recommendations

1. Inquire about sleep disturbances for all patients presenting with cognitive impairment and dementia, including reviewing patient sleep habits with the caregiver, to ensure the recognition and management of sleep disorders in this population.
2. Conduct a full physical review of the patient, including the assessment and treatment of any pain.
3. Ensure that factors that may disturb sleep have been assessed and managed, e.g., current medication, pain, heat, cold, and infection.
4. Encourage good sleep hygiene measures by keeping noise to a minimum, keeping the room dark, and maintaining a comfortable temperature. Discourage daytime napping and engage the person with dementia in regular physical activities. Maintain regular sleep-wake routines and meal schedules and limit caffeine intake, restricting this after 2:30 pm.
5. Consider implementing a scheduled routine of daily physical exercise and increase the amount of exposure to daylight.

6. Choose non-pharmaceutical treatment options over pharmaceutical interventions before considering the use of sedative medication to manage sleep disturbance, and then only use melatonin and sedating medications with caution in this patient group.

Visual Disturbance

Key Points

- Symptoms of visual dysfunction may occur before cognitive symptoms in Alzheimer's disease and other dementias.
- Symptoms include blurred and distorted vision, difficulty recognizing familiar objects or faces, difficulty locating familiar objects, difficulty reading or writing, and hallucinations.
- Symptoms may be due to changes in visual acuity and contrast sensitivity, deficits in visuospatial function and color vision, and visual field defects.
- Visual dysfunction is likely to be due to dementia-associated changes in both the cerebral cortex and the retina and optic nerve.

Introduction

Visual dysfunction refers to restrictions in visual function, and there is a substantial body of research that identifies that visual dysfunction occurs in Alzheimer's disease (AD) and many of the other dementias. Patients may present with complaints of visual problems quite early in the disease process, well before problems with memory are identified. Altered contrast sensitivity and visual acuity, particularly in conditions of low light, as well as changes in the patient's color vision can impact upon activities of daily living for individuals with dementia. Impaired visual acuity may also be linked to increased occurrence of visual hallucinations. Visual field defects resulting in the loss of part of the field of vision and problems with visuospatial perception leading to difficulty with depth perception are also known to occur. Visuospatial deficits are key symptom of Lewy body dementia.

Visual dysfunction in dementia may underlie many of the difficulties experienced by patients in undertaking their activities of daily living. Some of the common visual symptoms identified by patients and carers for which an ophthalmologist consultation is sought included blurred and distorted vision, difficulty in reading and writing, problems with depth perception and bumping into objects; difficulty in identifying or locating familiar objects or people, driving a car, walking outdoors, manipulating objects, dressing, or judging distances; and visual agnosia (Lee and Martin 2004). No studies have identified the prevalence of visual dysfunction in dementia, and most information is from case reports, case control studies, and cohort studies, and these most commonly relate to Alzheimer's disease.

Pathology of Visual Dysfunction in Dementia

The underlying pathophysiology of visual dysfunction in AD and other dementias remains unclear with studies suggesting a number of different causes. There is a substantial body of research that ties visual impairment to underlying cortical damage. It is suggested that the visual defects in dementia are likely to be related to pathological changes in the primary visual and association cortices in dementia rather than to changes in the retina or optic nerve (Mendez 1990). However, neurodegenerative changes have been identified in the optic nerve in Alzheimer's disease and other dementias, with reduction in retinal nerve fiber layer thickness also being noted.

The Impact of Visual Dysfunction in People with Dementia

The impact of dementia-associated visual dysfunction on the person with dementia can be considerable. Patients may present with visual symptoms before the development of other signs of dementia. These include blurred or distorted vision, difficulties with reading, loss of part of the field of vision, prominent visuospatial problems, inability to recognize faces or familiar objects, and environmental disorientation. These symptoms are sometimes considered to be part of the visual variant of AD (VVAD) which has gained recognition in the past 10 years (Lee and Martin 2004; Cronin-Golomb 1995).

Other dementias may also present with visual problems. Posterior cortical atrophy is associated with prominent visual deficits, and visual hallucinations are a hallmark feature of dementia with Lewy bodies, and visuospatial impairments may also be present early in the disease.

Features of Visual Dysfunction in Dementia

Contrast sensitivity refers to the ability to distinguish objects from their background. Contrast sensitivity measures are highly sensitive to alterations in the visual system, and there is strong evidence that dementia, particularly AD, affects contrast sensitivity (Cronin-Golomb et al. 2007). This can have a significant impact on activities of daily living (ADL) and navigational ability, which may also affect the risk of falls.

Visual acuity refers to the ability to clearly and accurately see objects both near and in the distance. Most eye test charts are designed as a measure of visual acuity. Visual acuity has been strongly associated with cognitive impairment even after adjusting for factors such as age and education and may be a strong factor for the occurrence of hallucinations in people with dementia (Tay 2006).

Visual field refers to the amount of the environment seen by each eye, when both eyes that are looking forward. A number of studies have found that dementia may be

associated with visual field defects such as a homonymous hemianopia (loss of half the field of vision in each eye) without any corresponding deficits on neuroimaging (Lee and Martin 2004).

Visuospatial function refers to the ability to visually perceive the spatial relationships between objects and remain visually orientated in space. This function allows the individual to navigate through the physical environment, locate and manipulate objects, and carry out basic and instrumental activities of daily living. There is a considerable body of evidence indicating that dementia is associated with visuospatial dysfunction, and it is likely that visuospatial difficulties may underlie a number of problems with activities of daily living for patients with dementia, including difficulty dressing, misreaching for objects, bumping into objects, misjudging steps or uneven surfaces, losing one's way in a familiar environment, and falling.

Other Visual Symptoms

Other visual symptoms include problems with spatial localization, difficulty recognizing simple objects or pictures, and hemispatial neglect. Impairments in color vision have also been noted in people with Alzheimer's disease compared with controls (Pache 2003).

Assessment of Vision in People with Dementia

There are some simple screening tests which can be used to detect visual dysfunction in patients with dementia:

1. Ask the patient to read a paragraph from a newspaper or magazine.
2. Ask the patient to copy a line drawing.
3. Show the patient a picture and ask them to describe what they see.
4. Ask the patient to identify photographs of famous people.
5. Ask the patient to reach for objects held up in front and to the side of them.
6. Ask the patient to look at and name colors.

In order to test specific areas of visual loss or dysfunction, contrast sensitivity should be tested, as well as visual acuity and visual fields, and the optic disc should be visualized.

Interventions for Visual Dysfunction in Dementia

Interventions to improve vision include correction of refractive errors and cataract surgery, both of which should occur as early as possible in the course of the

dementia. Improved lighting and appropriate use of spectacles may also lead to an improvement in vision.

Recommendations

1. Be aware that visual dysfunction may be a presenting symptom of dementia, particularly AD. Older adults with persistent visual complaints not attributable to structural eye problems may benefit from referral to a neurologist or geriatrician.
2. Be aware that during the course of dementia, visual problems may arise which can have a significant impact on the performance of assessment tasks and on function in activities of daily living. Ask the patient with dementia about visual symptoms.
3. A review by optometrist or ophthalmologist should be undertaken early in the disease process, to address refractive errors, check intraocular pressures, and assess for the presence of cataracts.
4. Visual acuity and contrast sensitivity may be improved by the correction of conditions such as cataracts and making environmental changes such as improved lighting and the use of high contrast markers.
5. People with the later stages of dementia should be encouraged to continue using their spectacles which should be clearly labelled for identification.

Oral Disease

Key Points

- Poor oral health is more common in people with dementia than in people without dementia.
- Changes may occur before the diagnosis of dementia is made.
- Oral disease occurring in dementia includes increased plaque accumulation and caries, fewer retained natural teeth, dry mouth, and less use of dentures.
- Oral disease in dementia is due to many factors including lack of dental monitoring, poor self-care, inability to follow instructions, decreased executive function, increasing dyspraxia and agnosia, and behavioral problems.

Introduction

Recent advances in preventive dentistry and the retention of natural teeth into older age mean that more people will require dental attention as they age. As a large proportion of these older people will have dementia, it is important that there be an integration of oral hygiene and dental care into healthcare planning for people with dementia.

Worldwide studies report an increased incidence of poor oral hygiene and increased tooth caries in the dementia population compared to those individuals without dementia, in both community dwellings and residential care (Chalmers 2005). In addition to generally poor oral hygiene, dementia patients have been found to have fewer natural teeth, with the incidence of denture use lower in edentulous individuals with dementia than in those without dementia. Dementia sufferers are also seen with higher levels of plaque and calculus load compared to older people with no dementia, and the prevalence of xerostomia (dry mouth) has also been reported to be higher in the dementia population, due to a combination of physiological changes in saliva production and medication use (Ship 2004).

The benefits of good oral health should be emphasized for its positive effects on general health, self-esteem and dignity, and nutrition. It is also important for social interaction, as the negative effects of missing or decaying teeth, gingivitis, and halitosis are significant. Undiagnosed and untreated dental disease can significantly affect an individual's quality of life and behavior. Poor oral health greatly impacts on an individual's general health with the potential development of a number of conditions including poor nutrition, dehydration, oral and systemic infections, and aspiration pneumonia, which may all in turn impact negatively on cognition.

Epidemiology of Oral Disease in Dementia

Older people in residential aged care facilities appear to be particularly at risk of oral disease with many studies showing that up to half of the residents had poor dental health, with high levels of dental caries and plaque accumulation. There was a significantly higher incidence of caries in those older residents with dementia than in those without dementia (Chalmers 2002). This higher incidence of oral disease has also been found in people with dementia living in the community when compared to controls. There was a significant correlation between increasing caries and decreasing cognition (Ship 1992). Though a relationship has been established between dementia and poor oral health, it remains unclear as to whether the link is casual or causal.

The Impact of Dementia on Oral Health

The effects on oral health of the increasing cognitive impairment and decreasing function that occur in dementia are multifactorial. Disturbance in executive functioning is associated with impaired planning and organization and the ability to initiate tasks. There is also deterioration in the older person's ability to self-care, along with an impaired ability to learn new information or to adapt to changes such as dental prostheses. Apraxia and agnosia result in difficulty using a toothbrush or recognizing what it is for.

Changes in behavior also impact upon oral health. There may be an increase in combative behaviors such as aggression and agitation, with subsequent resistance to personal care, including oral care. Apathy may also impact on care with the requirement for full assistance with dental hygiene. The emergence of sucking reflexes and involuntary tongue movements later in the progress of dementia may hinder the delivery of oral care (Nordenram 1997).

The Impact of Medication on Oral Health in Dementia

Medications used by people with dementia can significantly influence their oral health, and it is important that dentists are aware of the drugs their patients are taking. Prescription drugs may have specific side effects such as xerostomia, stomatitis, or tardive dyskinesia or specific adverse effects such as osteonecrosis of the jaw.

Antipsychotic and anticonvulsant medications together with other anticholinergic medications have been linked to the dysfunction of the salivary glands, leading to xerostomia (dry mouth). Other medications that can also potentially cause xerostomia include diuretics such as frusemide, lithium, ACE inhibitors, antihistamines, antidepressants such as citalopram, and tricyclic antidepressants such as amitriptyline. Without the antibacterial and lubricating, remineralizing, and buffering effects of saliva, the risk of plaque accumulation increases, resulting in problems with dentures and an increased likelihood of tooth caries and periodontal disease, the results of which can then compromise the nutritional intake of dementia patients (Fiske 2006).

Other medication-related problems include gingival hyperplasia and possibly oral ulceration that can occur with anticonvulsants such as phenytoin, and oral candidiasis may occur with antibiotics, particularly in the presence of poor oral hygiene.

Symptoms and Signs of Oral Disease in Dementia

Patients in the early stages of dementia are usually able to describe their symptoms and express their needs. However, as the disease progresses, this can become difficult, and patients may be unable to interpret their own discomfort or pain. For these patients, it is important that the family or professional carer is able to recognize changes in behavior or recognize other signs that may indicate the presence of dental problems (Fiske 2006).

Common symptoms and signs of oral disease may include:

- Refusing to eat or drink
- Refusing to open their mouth
- Moaning or shouting
- Restlessness and agitation
- Halitosis
- Holding or pulling at their face

- Drooling and spitting
- Bleeding from the gums, tongue, or cheeks
- Refusing to wear previously worn full or partial dentures
- Disturbed sleep
- Refusing to allow tooth brushing or mouthwashes
- Aggressive behavior

The appearance of any of these symptoms or signs should alert carers to the possibility of active oral disease.

Management of Oral Disease in Dementia

Assessment and planning for oral care should begin at the time dementia is diagnosed, before the disease progresses and the patient becomes less able to cooperate (Fiske 2006).

Goals of Oral Health Care

Good oral care should ensure that daily mouth care is as much part of personal care as hair brushing, with subsequent low risk of mouth infections or discomfort from loose teeth or sore gums. Being able to taste food, chew and enjoy eating, being able to speak normally, having a normal facial appearance, and having fresh breath to allow social behavior such as kissing to occur have also been included as goals of treatment (Nordenram 1997).

Assessment and Treatment

Patients with early dementia should have a full assessment from their own dentist, as cooperation with treatment is not usually a problem at this stage of the disease. The development of a flexible and individualized oral healthcare plan early in the disease process which focuses on prevention and retention of natural teeth is likely to reduce patient stress and the need for emergency treatment later in the disease (Fiske 2006).

It is important that the dentist is aware of the diagnosis of dementia so that treatment can be planned accordingly. The goals for dental treatment in people with dementia will depend on the stage of the patient's dementia. In the early stages of dementia, treatment should focus on active management of any oral disease and restoration of good oral health. As dementia progresses, the treatment focus should shift toward maintenance of oral health and dentition and the prevention of disease. In nursing homes, care plans should include an oral healthcare. Nurses can be trained to examine mouths for lack of saliva and excess acidity and to encourage remedial action such as the use of preventive products from a range of commercially available products such as high-fluoride toothpastes and remineralizing agents, chewing gum,

sodium bicarbonate toothpastes, high-pH oral moisturizing agent to neutralize mouth acids, and an antibacterial toothpaste.

In the later stages of dementia, the patient may not be able to describe symptoms of oral disease, so it is important that conditions such as gingivitis, mouth ulceration, glossitis, oral candidiasis, and angular stomatitis be looked for, recognized, and treated to relieve mouth discomfort. Sedation has been recommended as appropriate management for people in the later stages of dementia who require dental procedures, so as to reduce distress and the likelihood of resistive behavior (Chalmers 2005).

Recommendations

1. Patients with cognitive impairment or early dementia should be referred for a dental consultation and review with the aim of maintaining good oral health or restoring good oral health.
2. A regime of twice-daily teeth and gum brushing should be instituted. A soft toothbrush with high-fluoride toothpaste is recommended. Spitting rather than rinsing the mouth after brushing allows optimal action of the fluoride.
3. Dentures should be cleaned twice daily (out of the mouth) to remove plaque. The gums should be gently cleaned with a soft brush, and dentures should stay soaking in cold water overnight. Dentures should be disinfected weekly.
4. Avoid the complications of a dry mouth by encouraging regular sips or drinks of water and the use of saliva stimulators such as lemon-flavored tooth-friendly sweets or saliva substitutes such as mouth gel or spray.
5. If patients resist oral hygiene measures, consider using a mouthwash or gel containing chlorhexidine to help reduce caries.
6. Consider the effect of medication on oral health, particularly antipsychotics, anticonvulsants, and anticholinergic medications.
7. Consider the use of adequate sedation for dental work, particularly in the later stages of dementia.
8. Provide education to family and professional carers on an appropriate oral hygiene routine for the person for whom they care. Care should be tailored to the patient's stage of dementia.

Frailty

Key Points

- There is evidence that weight loss, decreased muscle strength, and slow walking speed (all features of frailty) antedate the onset of cognitive changes in Alzheimer's disease by many years.
- In large cohort studies with many years of follow-up, more cases of Alzheimer's disease occur in frail older people than in non-frail older people.

- Frailty and dementia may share common underlying mechanisms including raised levels of pro-inflammatory cytokines indicating low-grade chronic inflammation, mitochondrial malfunction, and oxidative stress.

Introduction

Frailty is a state of reduced physiological reserves in the domains of physical ability, cognition, and health. This diminishment increases an individual's vulnerability to adverse outcomes including functional dependence, institutionalization, and death. No single process has been identified to explain frailty, but it is known that frailty increases with age, is more common in women, and is multifactorial in origin, with an interplay of biological, medical, social, and psychological factors (Rockwood et al. 2004). It has been operationalized as a combination of unexplained weight loss, low grip strength, self-reported exhaustion, slow walking speed, and low physical activity (Fried et al. 2001).

Many studies have reported an association between frailty and cognitive impairment, with a higher degree of physical frailty correlating with more severe cognitive impairment, and there is evidence from a number of cohort studies that decreases in muscle strength and walking speed ("frailty") may precede the onset of dementia by many years. As a consequence, it has been suggested that frailty and cognitive impairment may share a common underlying pathogenesis (Buchman et al. 2007).

Epidemiology of Frailty in Dementia

Several of the core components of frailty, including low gait speed, low muscle strength, and weight loss, have been shown to be individually associated with the development of impaired cognitive function. Waite et al. (2005) identified gait slowing as a predictor of dementia in a 6-year prospective cohort study of 630 older people, with those individuals who had both cognitive impairment and gait and motor slowing being five times more likely to develop dementia than those without this combination.

Etiology of Frailty in Dementia

There appear to be a number of different pathways involved in the development of frailty, and these include the effects of chronic disease, alterations in inflammatory processes, and neuroendocrine and metabolic system changes. Similar pathways have been implicated in the development of dementia and AD in particular.

The presence of AD pathology (evidenced by amyloid plaques and neurofibrillary tangles) in the brain has been suggested as a possible contributor to the development

of frailty. Buchman et al. (2007) found a strong association between the presence of frailty before death and the level of AD pathology at autopsy, and they felt that frailty may be a noncognitive manifestation of AD and may be evident before the cognitive symptoms of AD appear.

Management of Frailty in Dementia

There is some evidence for treatment of frailty using exercise, but little for the treatment of frailty in dementia. Venturelli et al. (2011) have shown that regular walking in a group of people with moderately severe dementia can improve walking speed and function in activities of daily living, as well as stabilizing cognitive performance in this group, compared to controls.

If frailty can be seen as a vulnerable health state consisting of accumulated deficits (Rockwood 2004), then ameliorating these deficits should also be considered in the management of frailty in dementia. Improving an individual's general health by optimally managing chronic diseases such as diabetes, cardiac failure, or chronic airflow limitation, as well as the detection and management of depressive symptoms, is likely to improve an individual's general health status. If concomitant weight loss has occurred, dietary modification or nutritional supplementation should be considered.

Recommendations

1. Consider regular exercise that includes both aerobic exercises such as walking, some resistance/strength training, and balance.
2. Ensure that comorbid medical conditions are recognized and managed optimally.
3. If weight loss and poor appetite are factors in the development of frailty, then the nutritional requirements of the person with dementia should be addressed. Nutritional supplementation may be appropriate.

Conclusion

In clinical practice there are many conditions associated with dementia that are often unrecognised. It is important that these conditions are identified and managed appropriately to improve the care of people with dementia.

References

Alzheimer A (1911) Uber eingenartige Krankeitsfalle des spateren Alters (on certain peculiar diseases of old age). Zeitsschrift fur die gesamte Neurologie und Psychiatrie 4:356–385

Amatniek J, Hauser W, Delcastillo-Castaneda C et al (2006) Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia 47:867–872

American Geriatrics Society and British Geriatric Society Panel on Prevention of Falls in Older Persons. (2011) J Am Geriatr Soc 59(1):148–157

Ancoli-Israel S, Vittiello M (2006) Sleep in dementia. Am J Geriatr Psychiatr 14:91–94

Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, Ryan T, Cash H, Guerini F, Torpilliesi T, Del Santo F, Trabucchi M, Annoni G, Maclullich AM (2014) Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 43:496–502

Belmin J, Expert Panel and Organisation Committee (2007) Practical guidelines for the diagnosis and management of weight loss in Alzheimer's disease: a consensus from appropriateness ratings of a large expert panel. J Nutr Health Aging 11:33–37

Booth V, Logan P, Harwood R, Hood V (2015) Falls prevention interventions in people with cognitive impairment: a systematic review of reviews. Int J Ther Rehabil 22(6):289–296

British Geriatrics Society and Royal College of Physicians (2006) Guidelines for the prevention, diagnosis and management of delirium in older people, Concise guidance to good clinical practice series, vol 6. RCP, London

Buchman A, Boyle P, Wilson R et al (2007) Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 69:483–489

Chalmers J, Pearson A (2005) Oral hygiene care for residents with dementia: a literature review. J Adv Nurs 52(4):410–419

Chalmers JM, Carter KD, Spencer AJ (2002) Caries incidence and increments in community-living older adults with and without dementia. Gerodontology 19:80–94

Cole C, Richards K (2006) Sleep in persons with dementia: Increasing quality of life by managing sleep disorders. J Gerontol Nurs 32:48–53

Cordonnier C, Henon H, Derambure P et al (2005) Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. J Neurol Neurosurg Psychiatry 76:1649–1653

Cronin-Golomb A (1995) Vision in Alzheimer's disease. Gerontologist 35:370–376

Cronin-Golomb A, Gilmore GC et al (2007) Enhanced stimulus strength improves visual cognition in aging and Alzheimer's disease. Cortex 43:952–966

De Jonghe A, Korevaar J, Van Muster B et al (2010) Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. Int J Geriatr Psychopharmacol 25:1201–1208

Diehl-Schmid J, Schulte-Overberg J, Hartman J et al (2007) Extrapyramidal signs, primitive reflexes and incontinence in fronto-temporal dementia. Eur J Neurol 2007(14):860–864

Fick D, Agostini J, Inouye S (2002) Delirium superimposed on dementia: a systematic review. J Am Geriatr Soc 50:1723–1732

Fiske J (2006) Guidelines for the development of local standards of oral health care for people with dementia. Gerodontology 23:5–32

Fried L, Tangen C, Walston J, for the Cardiovascular Health Study Collaborative Research Group et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci 56A: 146–156

Gillette Guyonnet S, Abellan Van Kan G et al (2007) IANA (International Academy on Nutrition and Aging) Expert Group: weight loss and Alzheimer's disease. J Nutr Health Aging 11:38–48

Hägglund D (2010) A systematic literature review of incontinence care for persons with dementia: the research evidence. J Clin Nurs 19:303–312

Hashimoto M, Imamura T, Tanimukai S et al (2000) Urinary incontinence: an unrecognized adverse effect with Donepezil. Lancet 356:568

Hesdorffer D, Hauser W, Annegers J et al (1996) Dementia and adult-onset unprovoked seizures. Neurology 46:727–730

Inouye SK, Westendorp RGJ, Saczynski JS (2014) Delirium in elderly people. Lancet 383 (9920):911–922. doi:10.1016/S0140-6736(13)60688-1

Kim DH, Brown RT, Ding EL et al (2011) Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc 59:1019–1031

Lee AG, Martin CO (2004) Neuro-ophthalmic findings in the visual variant of Alzheimer's disease. Ophthalmology 111:376–380; discussion 380–381
Lee D, Morgan K, Lindesay J (2007) Effect of institutional respite care on the sleep of people with dementia and their primary caregiver. J Am Geriatr Soc 55:252–258
Lonergan E, Britton A, Luxenberg J (2007) Antipsychotics for delirium. Cochrane Database Syst Rev 2:CD 005594
Lonergan E, Luxenberg J, Areosa Sastre A (2009) Benzodiazepines for delirium. Cochrane Database Syst Rev 4:CD006379
Lord SR, Lloyd DG, Keung LS (1996) Sensori-motor function, gait patterns and falls in community-dwelling women. Age Ageing 25:292–299
Marcantonio E, Simon S, Bergmann M et al (2003) Delirium symptoms in post-acute care: prevalent, persistent, and associated with poor functional recovery. J Am Geriatr Soc 51:4–9
Mendez MF, Lim GT (2003) Seizures in elderly patients with dementia: epidemiology and management. Drugs Aging 20:791–803
Mendez MF, Mendez MA et al (1990) Complex visual disturbances in Alzheimer's disease. Neurology 40:439–443
Mittal V, Muralee S, Williamson D et al (2011) Delirium in the elderly: a comprehensive review. Am J Alzheimer's Dis Other Demen 26:97–109
National Institute for Health and Clinical Excellence (2014) Delirium in adults (Quality Standard QS63). Available at: http://www.nice.org.uk/QS63. Accessed 5 Aug 2016
Nordenram G, Ryd-Kejellen E, Ericsson K et al (1997) Alzheimer's disease, oral function and nutritional status. Gerodontology 13:9–16
Orme S, Morris V, Gibson W, Wagg A (2015) Managing urinary incontinence in patients with dementia: pharmacological treatment options and considerations. Drugs Aging 32:559–567
Pache M, Smeets CH et al (2003) Colour vision deficiencies in Alzheimer's disease. Age Ageing 32:422–426
Rao SC, Dove GD, Cascino GD et al (2009) Recurrent seizures in patients with dementia: frequency, seizure types and treatment outcome. Epilepsy Behav 14:118–120
Rockwood K, Howlett S, MacKnight C et al (2004) Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. J Gerontol Med Sci 59A:1310–1317
Sakakibara R, Uchiyama T, Yamanishi T et al (2008) Dementia and lower urinary dysfunction: with a reference to anticholinergic use in elderly population. Int J Urol 15:778–788
Sampson EL, Candy B, Jones L (2009) Enteral tube feeding for older people with advanced Dementia. Cochrane Database Syst Rev 2:CD007209
Shaw FE, Bond J, Richardson DA et al (2003) Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. Br Med J 326:73
Ship JA, Puckett SA (2004) Longitudinal study on oral health in subjects with Alzheimer's disease. J Am Geriatr Soc 42:57–63
Ship JA (1992) Oral health of patients with Alzheimer's disease. J Am Dent Assoc 123:53–58
Specht J (2011) Promoting continence in individuals with dementia. J Gerontol Nurs 37(2):17–21
Tay T, Wang JJ et al (2006) Sensory and cognitive association in older persons: findings from an older Australian population. Gerontology 52:386–394
Tractenberg R, Singer C, Kaye J (2005) Characterizing sleep problems in persons with Alzheimer's disease and normal elderly. J Sleep Res 15:97–103
Venturelli M, Scarsini R, Schena F (2011) Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimer's Dis Other Demen 26:381–388
Waite L, Grayson D, Piguet O et al (2005) Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. J Neurol Sci 229–230:89–93

Physical Comorbidities and Mood Disorders in Older Adults

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Abstract

Physical health and mood disorders are intertwined in many ways, and several somatic diseases are directly related to mood disorders. Physical disease may present with depressive symptoms, and several physical symptoms are part of depression. Physical problems may lead to or cause depressive disorder and vice versa. Medication prescribed to treat mood symptoms may have side effects resulting in somatic comorbidity, and somatic medication may provoke mood-related side effects.

In older adults with mood disorders, physical comorbidity is the norm rather than the exception, and over time the mood disorder might act in concert with physical comorbidities to accelerate aging and cognitive deterioration.

Side effects are among the most important reasons for patients to stop taking their medication. Polypharmacy, age, and somatic comorbidities are key factors known to increase side effects. Medical conditions coexisting with a mood disorder may be truly comorbid, related to the treatment of the mood disorder, or a combination of both. For directions on treatment of these somatic comorbidities, the differentiation is important.

Physicians treating older adults with mood disorders should be aware that the physical health of these patients is an important aspect of their lives as it may influence their need for care and quality of life and complicate treatment and the course of the psychiatric disease. Comorbid conditions should be carefully assessed, and treatment options should be chosen taking into account these comorbid states, minimizing side effects and treatment burden.

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_15

Keywords

Physical comorbidity • Somatic • Side effects • Mood disorder • Bipolar • Depression • Medical • Antidepressant • Mood stabilizer

Contents

General Physical Health and Comorbidity in Late-Life Depression

In epidemiological studies, an increased physical morbidity and mortality are shown in depressed older people, not only in severely depressed patients fulfilling the criteria of major depressive disorder (MDD) (Association 2013) but also in those with a so-called mild or minor depression, also referred to as "clinically relevant depressive syndrome" (Lyness et al. 2006; Penninx et al. 1999; Beekman et al. 1997). A variety of factors and mechanisms play a role in these associations.

Here, we will discuss a variety of these factors, the consequences for physical and mental well-being, and the recommendations for the clinician. We use the term "depression," including MDD as well as clinically significant depressive syndrome.

Depression itself is characterized by a broad spectrum of symptoms in the physical, psychological, and social functioning domains. This may cause difficulty in diagnosing the depression as well as comorbid physical disorders that may coexist independently but often are associated with the depression. Particularly in older depressed people, somatic problems tend to get more attention than psychiatric problems, as well from the doctor as the patient himself, which may lead to underestimating the severity and hampering the treatment of the depression (Mitchell et al. 2010). But also vice versa, the existence of depression may lead to underdiagnosis and undertreatment of somatic conditions, due to diminished seeking for medical help and motivational problems in medical treatment in depressed patients (Braam et al. 2005).

As stated in the introduction, somatic comorbidity is the rule in older adults with mood disorders, and therefore it is important to apply a broad perspective in diagnostic evaluation directed toward both psychological problems and physical complaints and diseases.

Physical Diseases with Symptoms of Depression

Symptoms of depression and medical conditions may overlap. Fatigue and loss of energy, often prominent features in depression, are seen in many physical disorders in late life, e.g., chronic infections, cardiovascular and neurological diseases, and cancer. Decreased appetite and weight loss may occur in gastrointestinal problems, chronic infections, or cancer. Sleep disturbances may be due to pain or Parkinson's disease. The latter can be confusing in many ways with a lot of overlapping symptoms, such as motor slowing, starting problems, diminished facial expression, and emotional lability. Concentration and memory problems can be rather severe in depression but may also be a sign of a developing dementia. Psychomotor slowing, weight gain, and increased need of sleep are also found in hypothyroidism, whereas agitation, nervousness, weight loss, and sleep problems may be symptoms of hyperthyroidism. Thyroid dysfunction is rather common in women over 50 and often starts with psychological changes as mentioned above or may be very similar to the normal aging process instead of the well-known symptoms of hair loss, myxoedema, and changes of voice and pitch (Bensenor et al. 2012). There is discussion about the clinical significance of subclinical hypothyroidism (described as no clinical symptoms but abnormal laboratory findings) as a cause of depression and the necessity of treatment; this will be addressed for in more detail later on in this paragraph. Also other hormonal disturbances such as Cushing's syndrome, Addison disease, hyperparathyroidism, pheochromocytoma, or tumors with endocrine activity may mimic depression by altering mood, sleep, appetite, psychomotor function, and energy level.

Physical Problems Due to Depression

Depression may lead to physical problems. Depressed patients often have a less-healthy lifestyle, with decreased food intake, less balanced diet, higher use of tobacco and alcohol, and diminished physical exercise (DiMatteo et al. 2000; Kroenke 2003). This may lead to nutritional deficiencies, weight loss or weight gain, and diminished physical condition, which in turn may lead to new physical problems such as balance problems, falls and fractures, and decreased ability to recover from trivial health problems such as influenza. Due to delay in the search for medical help in case of physical problems in depressed patients, treatment of preexisting or newly emerging physical diseases is hampered (DiMatteo et al. 2000). This may lead to undertreatment of all kinds of common medical conditions such as hypertension, diabetes, pain, and cardiovascular and pulmonary problems (Wahlbeck et al. 2011). Thus, depressed patients tend to spiral down in this reinforcing loop of "depression lifestyle" and physical deterioration, leading to the abovementioned elevated morbidity and mortality.

But unhealthy lifestyle and diminished motivation for seeking medical treatment are not the only mechanisms leading to physical problems. In the Longitudinal Aging Study Amsterdam (LASA), a large population-based study in older Dutch people, a higher cardiac mortality rate was found in the depressed subsample, even in the absence of preexisting cardiovascular disease, and independent of the abovementioned lifestyle differences (Penninx et al. 1999). The finding that depression is an independent risk factor for cardiovascular morbidity and mortality was found in other studies as well (Anda et al. 1993; Regulies 2002; Wassertheil-Smollers et al. 2004; Kamphuis et al. 2006; van der Kooy et al. 2007; Kendler et al. 2008; van Marwijk et al. 2015). In congestive heart failure, depression showed a 2.5-fold risk for severe cardiac complications and death (Lett et al. 2007). In a review on heart failure followed by depression, MDD was a predictor for subsequent all-cause mortality (Fan et al. 2014). In the oldest old (age over 85), depression was found to be related to all-cause mortality as well as cardiovascular mortality (Vinkers et al. 2004). In the Epidemiologic Catchment Area (ECA) study, a large epidemiologic study in the United States, depression at baseline was found to be a risk factor for myocardial infarct (OR 4.5), CVA (OR 2.7), DM type II (OR 2.2), and arthritis (OR 1.3) in the 13-year follow-up (Eaton et al. 2006).

In depressed patients, several changes in the cardiovascular system are found that may contribute to the increased cardiovascular morbidity and mortality. An important finding is a diminished heart rate variability in depression, which may be a sign of diminished flexibility and responsiveness of the cardiac function and thereby lead to coronary heart disease (Rottenberg 2007).

Another finding is an elevated level of platelet adhesion and aggregation in depressed patients, which may increase the risk for cardiovascular events (Laghrissi-Thode et al. 1997). Interesting and promising is that SSRIs have an effect on platelet function and seem to protect against the development of atherosclerotic plaques and arterial thrombosis (Pollock et al. 2000).

Changes in the diurnal cortisol variation and in the responsiveness and feedback system in the HPA axis found in depression may lead to hypertension, which is in turn a risk factor for cardiovascular damage throughout the body.

Physical Problems Leading to Depression

In general, people with physical illness are found to be more vulnerable to depression, which in turn leads to prolonged stay in the hospital, worse functional recovery of the illness, and a higher morbidity and mortality (Creed and Dickens 2007; Mavrides and Nemeroff 2013). High prevalence for depression in adults of all ages is found for cardiovascular disease (17–47%), CVA (14–27%), Alzheimer's disease(11–50%), Parkinson's disease (29–52%), diabetes (9–26%), cancer (22–38%), chronic pain (21–32%), epilepsy (6–80%), migraine, multiple sclerosis, and HIV/AIDS (5–30%) (Evans et al. 2005; Miller et al. 2008; Patten et al. 2003; Torelli et al. 2006; Rouchell 1996; Mavrides and Nemeroff 2013). In heart disease, high percentages of depression were found for coronary problems (20%), congestive heart failure (30–40%), and after bypass operation (50%) (Whooley 2006). Risk for depression after a myocardial infarct is related to the degree of dysfunction of the left ventricle (Melle et al. 2005). Depression after CVA is associated with the intracerebral localization of the ischemic lesion with a greater risk in right-sided lesions (Shimoda and Robinson 1999; Robinson and Starkstein 1990).

Except for HIV/AIDS, all physical diseases mentioned above are rather common in older age. Together with other conditions often found in older persons, such as chronic infections, malnutrition, anemia, rheumatoid arthritis, and chronic pulmonary disease, these physical conditions are considered to be important predictors of depression in late life (Cole and Dendukuri 2003; Djernes 2006). It is not clear how often the presence of (new) physical illness is the main cause of depression, and in most cases the increased prevalence of depression is considered to be the result of more common, not disease-specific, factors. Particularly the functional consequences of physical disease, such as pain, mobility problems, worsening of daily functioning, feelings of loss of control, and changes in roles, are considered to be important in the association with depression (Beekman et al. 1997; Rodin et al. 2005).

In neurological diseases, and in particular in Parkinson's disease and dementia, a high prevalence of depression is found, and psychological as well as more neurobiological factors are supposed to play a role. Scientific background of this phenomenon will be addressed for later on in this chapter.

General Physical Health and Comorbidity in Late-Life Bipolar Disorder

Bipolar disorder has been conceptualized as multisystem disease, rather than brain specific as comorbid medical illnesses in bipolar disorder might be viewed not only as the consequence of health behaviors and of psychotropic medications but rather as

an early manifestation of a multisystemic disorder (Leboyer and Kupfer 2010; Leboyer et al. 2012). Physical comorbidity complicates outcome in late-life bipolar disorder (Lala and Sajatovic 2012). Only a few studies have studied physical comorbidities in bipolar older patients (Lala and Sajatovic 2012); therefore, knowledge on physical comorbidities in bipolar disorder is mainly derived from studies in younger or mixed-aged samples. There are no longitudinal studies, and only five studies of somatic comorbidity have included 50 or more bipolar older patients. A review of comorbidity in late-life bipolar disorder found an average of 3–4 medical comorbidities (Lala and Sajatovic 2012), including metabolic syndrome (up to 50%), hypertension (45–69%), diabetes mellitus (18–31%), cardiovascular disease (9–49%), respiratory illness (4–15%), arthritis (16–21%), endocrine abnormalities (17–22%) (Lala and Sajatovic 2012), as well as atopic diseases such as allergic rhinitis and asthma (6–20%), which can greatly impact quality of life (Tsai et al. 2009; Lala and Sajatovic 2012). With each decade of life, the number of physical comorbidities is reported to increase to 11 comorbid somatic conditions in those older than 70 years (Fenn et al. 2005).

Older bipolar patients have a greater burden of physical comorbidity than age-matched unipolar depressed peers (Gildengers et al. 2008); however, the overall prevalence of physical illnesses in older patients with bipolar disorder is reported to be comparable to rates in community-based geriatric samples (Lala and Sajatovic 2012). Nevertheless, older bipolar patients have much higher mortality rates, and due to cardiovascular and other physical illnesses, they die on average 10 years earlier than the general population (Westman et al. 2013). Therefore, patients with bipolar disorder who survive into old age likely represent a healthy "survivor" subpopulation. This was also illustrated by a report on metabolic syndrome in older bipolar and schizophrenia patients with rates comparable with healthy elderly (Konz et al. 2014).

Physical comorbidity will limit treatment options for bipolar disorder by drug interactions and altered drug metabolisms. Polypharmacy is also frequent, with 31.7% of patients reported to be on six or more medications (Dols et al. 2014b). As some psychiatric patients have a limited access to physical health care, screening, and prevention (De Hert et al. 2009), their physical health should have the attention of mental health professionals. The recommendations for physical work-up have been summarized by the International Society for Bipolar Disorders (Ng et al. 2009). For older patients with bipolar disorder, screening for side effects and/or complications of medication and evaluating their general physical health is recommended more frequently (two to four times a year) (Ng et al. 2009). In patients using antipsychotics, screening for metabolic syndrome is advised (fasting lipid profile, fasting blood glucose, blood pressure, and waist circumference). Prescriptions of other doctors should be double checked at the pharmacist, and inquiries about over-the-counter medication use are no luxury. Clinicians providing care for bipolar elderly patients should carefully assess for comorbid conditions, choose treatment options that take into account these comorbid states, and minimize side effects and treatment burden. Close collaboration between mental health, primary care, and medical speciality clinicians is strongly recommended.

Physical Comorbidity as a Side Effect of Medication

In this paragraph, an overview is given of the most frequent and most important side effects of antidepressants and mood stabilizers commonly used in late-life depression and bipolar disorder. For more detailed information, particularly on pharmacodynamics and pharmacokinetics, we refer to guidelines and textbooks on psychopharmacology.

Cardiovascular Side Effects

Orthostatic and general hypotension, hypertension, heart conducting problems, and heart frequency changes are often found in antidepressant use. For an extensive overview, we refer to the chapter on "▶ Pharmacotherapy for Mood and Anxiety Disorders" for depression and anxiety disorders in the elderly.

Sedation

Sedation and drowsiness are often seen in antidepressants with strong anti-histaminergic or anti-norepinephrinic effect but may be due to alpha-1-receptor blocking and 5-HT2 receptor antagonism as well. Also anticholinergic or hypotensive effects may play a role, particularly in older patients. Strong sedative effects are found for mirtazapine, trazodone, mianserin, doxepin, and amitriptyline and also to a lesser extent in SSRIs in higher doses. The sedative effect may be enhanced by interaction with alcohol or other sedating drugs. Temporarily lowering of the dose may diminish sedation because tolerance for this effect is developed in the first weeks of treatment. Other solutions are administration of the antidepressant in the evening instead of during the day, or changing to a less sedating antidepressant.

Cognitive Impairment

Cognitive impairment can be distressing for patients and may hamper their compliance to treatment. Several studies have demonstrated that patients with bipolar disorder have impaired functioning across a range of cognitive domains, even after resolution of mood symptoms and independent of pharmacological treatment (Young et al. 2006; Martinez-Aran et al. 2005).

Pharmacotherapy, especially lithium, has been associated with poorer cognitive performance. In a recent review, almost 600 studies were identified concerning the effect of lithium on cognitive performance (Wingo et al. 2009), concluding that lithium appears to have only few and minor negative effects on cognition.

The cognitive effects of valproate and carbamazepine have been scarcely evaluated in bipolar patients. Valproate and carbamazepine seem to have roughly the same effect on cognition as lithium (Senturk et al. 2007; Joffe et al. 1988). Lamotrigine

might have a better impact on memory than other anticonvulsants (Daban et al. 2006).

The management of cognitive complaints in bipolar patients is challenging; treatable causes such as clinical or subclinical hypothyroidism should be addressed first. The slowing of cognitive performance ("cognitive dulling") can respond well to dose reduction and/or enhancing thyroid function (Goodwin et al. 2007). Patients may benefit from cognitive remediation therapies combined with lifestyle changes.

In depression, cognitive impairment is found as well. In many patients (reversible), attention and concentration problems are found, sometimes leading to memory problems or mental slowing. Antidepressants may enhance these problems, particularly in the case of anticholinergic or anti-histaminergic side effects.

Neurological Side Effects

(a) SSRIs may cause *extrapyramidal side effects*. Bradykinesia, rigidity, and tremor, and sometimes also acute dystonia and akathisia, have been described for fluoxetine, fluvoxamine, and sertraline. The incidence is low in monotherapy; in most cases SSRIs were combined with antipsychotics, lithium, or TCAs (Jacobson et al. 2007; Carvalho et al. 2016). The advice is to change the antidepressant.

(b) *Tremor* is found in SSRIs, TCAs, trazodone, lithium, valproate, and lamotrigine. The incidence differs in the several studies on antidepressants from almost placebo – level to an elevated risk of 10–20%. Serotonergic stimulation is thought to be the cause. In most cases, habituation is found after 2–3 weeks, and the tremor disappears when the antidepressant is discontinued. Tremor has been reported in up to 65% of patients using lithium (Gelenberg and Jefferson 1995) and in 1–6% of patients using VPA. Management of a medication-induced tremor starts with objective observation of the tremor and an open dialogue to challenge any catastrophic beliefs about perceived impairments (Hallam 2010). Extended-release preparations can reduce tremor. Reducing the use of caffeine and nicotine can have a positive effect. Beta-adrenergic blockers (e.g., propranolol) and vitamin B6 are effective in reducing tremor (Miodownik et al. 2002).

(c) *Myoclonus* is frequently found in TCAs and SSRIs and may lead to speaking problems (myoclonus of the jaw) or sleep problems (myoclonus of arms or legs during the night). Dose reduction sometimes leads to diminishing of these symptoms.

(d) Most antidepressants lower the threshold for *seizures*. For grand mal seizures, an incidence of 0.1–0.6% has been found, and the risk is higher for patients with a history or family history of epilepsy. Particularly TCAs and maprotiline are found to elevate the risk of seizures, with risks up to 15% in higher doses (maprotiline >300/day).

Gastrointestinal Side Effects

(a) With a prevalence up to 80% is a *dry mouth*, one of the most frequent side effects of TCAs and lithium, and it may lead to caries and infections of the mouth and to poorer adherence to treatment (Jacobson et al. 2007; Kennedy et al. 2001). The anticholinergic properties (of the TCAs) are thought to be the cause, although a dry mouth is also reported in SSRIs and trazodone use (Carvalho et al. 2016). This symptom should decrease after a couple of weeks using the antidepressant, but it often persists and may be the reason for patients to stop their medication.
(b) *Constipation* is often caused by the depression itself but may be aggravated by antidepressants with anticholinergic properties.
(c) *Nausea and vomiting* together with *intestinal cramps and diarrhea* are a result of anti-5-HT2 effects and are typically found in serotonergic antidepressants (SSRIs, trazodone, and moclobemide), lithium, and valproate with an incidence ranging from 10% to 60%. Diminished appetite is found in fluoxetine and fluvoxamine; it is dose related and presents particularly in the first weeks of treatment. These complaints are not found in TCAs. Coated or slow-release tablets appear to be better tolerated. To prevent initial nausea, it is best to slowly increase the dose. A temporary reduction is the best management option if nausea occurs, followed by a more gradual increase. Persistent nausea can be treated with the histamine-2 (H2) antagonist famotidine or cimetidine (Stoll AL 1991).

Urinary and Genital Tract

TCAs often cause problems in emptying the bladder, due to a heightened sphincter tonus, an anticholinergic effect. This may lead to urinary retention, in particular in older men with prostate hypertrophy and of course when a combination of anticholinergic drugs is used. It is not dose related and often a change of antidepressant is necessary.

Sexual side effects of medication can be either primary (specific sexual effects) or secondary (e.g., caused by weight gain, hypothyroidism) (Demyttenaere et al. 1998). Sexual dysfunction is found in 30% of patients that use TCAs, consisting of decrease of libido, prolonged time to orgasm, and erectile problems. SSRIs have a high prevalence (50%) of sexual dysfunction with the same problems as the TCAs, and also ejaculatory problems. Mirtazapine and moclobemide show less sexual adverse effects.

Lithium appears to have minor effects on sexual function (Ghadirian et al. 1992). The literature on sexual side effects of anticonvulsants is almost entirely restricted to their use in epilepsy and thus confounded by the fact that epilepsy itself is associated with sexual dysfunction (Harden 2008; Smaldone et al. 2004). Specific recommendations to manage medication-induced sexual dysfunctions are lacking. A correlation between sexual side effects and serum level of lithium could not be

demonstrated (Ghadirian et al. 1992), but thriving for the lowest effective level is always advisable (Sienaert and De Fruyt 2001). A number of pharmacological agents (cyproheptadine, yohimbine, amantadine, bethanechol, neostigmine, PDE5 blockers [sildenafil, tadalafil, vardenafil]) have been proposed in the treatment of specific dysfunctions, but apart from the PDE5-blockers, the clinical experience with these drugs in these indications is limited. Physicians and patients should be encouraged to discuss sexual side effects, in order to increase compliance and quality of life.

Weight Gain and Metabolic Syndrome

Weight gain is a frequent and significant problem in psychiatric patients even without prescription of agents associated with metabolic syndrome. TCAs, mianserin, and mirtazapine often (up to 50%) lead to weight gain, due to the antihistaminergic properties of these antidepressants (Kennedy et al. 2001). It may be a reason for discontinuation of the treatment. Some patients experience an increased appetite, but the weight gain is also contributed to a slowing of the basal metabolism. Nonselective or irreversible MAO inhibitors show weight gain as well, due to the same mechanism.

Weight loss and loss of appetite are found in fluoxetine and fluvoxamine and are probably due to an increased basal metabolism (Carvalho et al. 2016).

Clinically significant weight gain (i.e., >7%) is more frequent in patients on olanzapine than on lithium (McKnight et al. 2012). However, a 5–10% weight gain is reported by 25–50% of patients using lithium (Keck and McElroy 2003; Goodwin et al. 2007). Two to 3 lbs weight gain can be expected as a result of temporary fluid retention. Weight gain may be caused by increased appetite, lithium-related subclinical hypothyroidism, lower metabolic rate, increased food intake secondary to improved mood, and polydipsia resulting in drinking large amounts of high-caloric drinks (Torrent et al. 2008). As for all lithium-induced side effects, weight gain is dose dependent and less likely at plasma levels below 0.8 mmol/l (Sachs and Guille 1999). After 7-year of follow-up, it was reported that weight occurred during the first 1–2 years of prophylactic lithium treatment and then remained constant (Vestergaard et al. 1988). A 1-year follow-up study found that 155 obese patients with bipolar I disorder lost weight (−4.2 kg) while taking lamotrigine and gained weight (6.1 kg) while taking lithium (Bowden et al. 2006), while there was no significant weight change in 399 non-obese patients. The prevalence of weight gain with valproate treatment is estimated to occur in 3–20% of patients and ranges between 3 and 10 kg over a period of 3–12 months (Pijl and Meinders 1996; Bowden 2003). Studies on weight gain in carbamazepine-treated patients show controversial results, and with the paucity of long-term follow-up data in bipolar patients, weight gain due to carbamazepine seems unlikely (Torrent et al. 2008).

Therapeutic options to reduce weight include dietary counseling, and exercise programs should be available for all bipolar patients (Nemeroff 2003), even prior to starting mood stabilizer therapy. Antipsychotic use in older patients is associated

with higher rates of hyperglycemia (Lipscombe et al. 2009) as well as increased mortality and risk for cerebrovascular accidents (Setoguchi et al. 2008; Wang et al. 2005).

In a recent meta-analysis, the rate for metabolic syndrome in patients with schizophrenia, bipolar disorder, and major depressive disorder of all ages was reported to be 32.6% (Vancampfort et al. 2015). Compared with matched general population controls, there was an increased risk for metabolic syndrome in psychiatric patients. The relative risk was not different between the diagnostic groups. Older age, higher body mass index, and the use of antipsychotics, especially clozapine and olanzapine, were associated with an increased risk for metabolic syndrome.

Studies of metabolic syndrome in older patients, as a complication of using atypical antipsychotics, are very limited. In 100 older patients with schizophrenia and bipolar disorder, the prevalence of metabolic syndrome was not higher than in healthy controls and not related to the use of a specific class of antipsychotics (Konz et al. 2014). Possibly, older patients with bipolar disorder who survive into old age represent a healthy "survivor" subpopulation.

Thyroid and Parathyroid

A Cochrane review on lithium for maintenance treatment of mood disorders concluded that there were insufficient data on specific side effects to allow meta-analysis, except for hypothyroidism which occurred in 5% of patients on lithium and in none of those on placebo (Burgess et al. 2001). In a recent meta-analysis, lithium was associated with increased risk of endocrine side effects such as hypothyroidism and hyperparathyroidism (McKnight et al. 2012). Lithium inhibits thyroid hormone secretion by several different mechanisms. CBZ and VPA were shown to have this same effect, however less frequent and particularly when combined with lithium (Gau et al. 2010). In the majority of patients, compensatory mechanisms operate and prevent the development of hypothyroidism. Risk factors for development of hypothyroidism include iodine deficiency, cigarette smoking, and presence of thyroid antibodies. The prevalence of thyroid autoantibodies among lithium-treated patients varies across studies and may be more associated with affective disorder than with lithium (Kupka et al. 2002). Women, especially beyond the age of 50, more often express thyroid autoimmunity (Bocchetta et al. 2007), which makes them especially at risk for lithium-induced hypothyroidism (Kirov et al. 2005; Bocchetta and Loviselli 2006). Most patients are diagnosed with hypothyroidism in the first years of lithium treatment (van Melick et al. 2010; Johnston and Eagles 1999). The wide range of prevalence rates of hypothyroidism in lithium-treated patients (0–23%) is explained by differences in criteria (overt vs. subclinical hypothyroidism) and study population (gender, iodine intake, proportion of subjects with autoimmunity) (Bocchetta and Loviselli 2006). Up to 2% of lithium-treated patients require treatment with levothyroxine (Kirov et al. 2005; Bocchetta and Loviselli 2006).

A retrospective analysis of laboratory data with a median follow-up of 3 years (max. 28 years) on patients using lithium was found an increased risk for hypothyroidism, with women, especially younger women, and patients with diabetes at higher risk (Shine et al. 2015). Lithium levels over 0.6 mmol/L were associated with increased risk for adverse effects.

Monitoring of clinical symptoms provides useful guidance for treatment in addition to values of TSH or free T4, since management of even subclinical hypothyroidism may improve outcomes among bipolar patients (Kleiner et al. 1999; Najafi et al. 2015).

A meta-analysis of 14 observational studies found a 10% increase of calcium and parathyroid hormone concentrations in lithium users (McKnight et al. 2012). The risk for elevated adjusted calcium concentration was not raised with lithium treatment (Shine et al. 2015), only total calcium concentrations were. Women aged 60 and over were most at risk. It is recommended to measure calcium (total and adjusted) concentrations in all patients on lithium therapy at baseline and at least annually thereafter.

Kidney

The effect of lithium on renal function has been the subject of several large population-based studies and meta-analyses in the past decade (McKnight et al. 2012; Kessing et al. 2015; Shine et al. 2015). Rates of kidney failures appear lower than previously reported and feared, possibly as a result of modern treatment principles (Aiff et al. 2014). Here, we will describe the two most common forms of kidney disease associated with lithium use: nephrogenic diabetes insipidus and chronic renal failure.

Nephrogenic diabetes insipidus is the result of lithium inhibiting the stimulating effect of antidiuretic hormone on the resorption of water in the collecting ducts of the nephron (Bendz and Aurell 1999). This causes polyuria, dehydration, thirst, and compensatory polydipsia. On average, urine-concentrating ability is reduced by 15% of normal maximum after long-term lithium use (McKnight et al. 2012) with a urinary production of more than 3 L a day. Other causes of polyuria and polydipsia such as diabetes mellitus have to be excluded as well as central diabetes insipidus and primary stimulation of the thirst center following lithium use (Cox and Singer 1975). Primary (psychogenic) polydipsia occurs predominantly in schizophrenia (Mercier-Guidez and Loas 1998), and dry mouth as a result of the anti-cholinergic side effects of drugs such as tricyclic antidepressants has to be considered.

Renal function is measured by glomerular filtration rate (GFR). Stage 3 chronic renal failure is defined as a GFR <60 mL/min per 1.73 m^2; at this point patients may develop symptoms, such as high blood pressure, anemia, and/or early bone disease. Only a very small subset of patients with stage 3 chronic renal failure will progress to end-stage renal failure; the risk has been estimated to be 0.5–1.0% (Tredget et al. 2010; Bendz et al. 2010).

In long-term lithium users, the mean GFR reduction is −6.22 mL/min over a mean observation time of 1 year (McKnight et al. 2012). Lithium users have a greater risk for renal failure compared to general population (Shine et al. 2015; Kessing et al. 2015). In bipolar patients the risk for renal failure is increased when using lithium or anticonvulsants and not with antipsychotics or antidepressants (Kessing et al. 2015). No effect of stable lithium maintenance therapy with a mean duration of 55 months was found on the rate of change in GFR over time; nephrotoxicity was determined by episodes of acute intoxications, duration of therapy, and cumulative dose (Clos et al. 2015).

In elderly patients renal failure is more prevalent, which can be attributed to the use of supratherapeutic lithium levels, accidental intoxications, co-medication (mostly diuretics and ACE inhibitors), medical comorbidity (mostly diabetes mellitus and hypertension), and age-related renal function decline (Rej et al. 2012). The casual relationship of long-term lithium use with renal dysfunction (Bendz et al. 2010; Paul et al. 2010) remains to be confirmed in geriatric populations (Rej et al. 2013). In older patients using lithium, potential correlates of renal disease include the use of diuretics and ACE inhibitors and higher lithium levels in the context of inadequate lithium monitoring (Ghose 1991). The most robust renal risk factors in older adults are diabetes, hypertension (Coresh et al. 2007), and age-related renal decline (Rej et al. 2012).

Thus, especially in the relatively large group of lithium users with only mild loss of renal function, treatable risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and proteinuria have to be addressed (Boton et al. 1987; Aiff et al. 2014). Throughout lithium prophylaxis, it is essential to monitor renal function in lithium levels at regular intervals, keeping lithium levels as low as possible, and avoid intoxication.

A serum creatinine of ~200 μmol/l (Manjunath et al. 2003) or GFR <40 mmol/l (Lepkifker et al. 2004) is considered to indicate a point of no return, and when approaching this point, one should consider stopping lithium prophylaxis (Presne et al. 2003; Markowitz et al. 2000). When this is not an option, impeding entry of lithium into the principal cells of the collecting ducts by blocking epithelial sodium channel with amiloride or drugs with a similar mode of action would provide a logical strategy to decelerate further renal lithium toxicity, with simultaneous reduction of the lithium dose. However, this strategy has not yet been proven effective; amiloride 5–20 mg/day has levels I and II evidence in the acute treatment of nephrogenic diabetes insipidus (Batlle et al. 1985; Bedford et al. 2008). Induction of increased potassium levels can be managed with potassium binders, e.g., Sorbisterit.

Syndrome of Inappropriate ADH Secretion (SIADH)

Particularly SSRIs but also TCAs may cause hyponatremia and disturbed secretion of antidiuretic hormone (ADH). Symptoms that may point to this disturbance are fatigue, sleep problems, and lethargy, but these are also symptoms of depression and thus are sometimes missed as a new somatic problem. Older persons appear to be

more vulnerable for this syndrome, and the use of other drugs that affect the same system, such as diuretics, increases the risk. It is not dose related, and crossover effects are found, which means that change to another SSRI will probably lead to the same problem. In older people, it is advised to check serum sodium before starting an SSRI, and again some weeks after the optimal dosage is found, and to be alert on symptoms of hyponatremia during the first 4 weeks after the start of the SSRI.

Eyes

Visual problems are due to decreased ability of the circular muscle of the lens to accommodate, an anticholinergic effect. This may cause blurred vision and impairment in reading and may worsen when the antidepressant is combined with other anticholinergic agents. There is an (rarely seen) elevated risk of (worsening of) glaucoma, and consultation of an ophthalmologist is advised (Carvalho et al. 2016).

Liver

Elevated levels of alkaline phosphatase, transaminases, and bilirubin are sometimes seen in treatment with antidepressants (Voican et al. 2016). It is not clear if this is a real pathophysiological change and what it means. Most of the changes have a temporary character. Rarely intrahepatic cholestasis is found, a severe condition with a peak incidence in the second month of treatment. Symptoms include sudden fever or abdominal pain, and discontinuation of the antidepressant is necessary. This complication is found in many antidepressants, and recent warnings have been given for agomelatine and mirtazapine (Stadlmann et al. 2012; Gahr et al. 2014).

Asymptomatic elevation of transaminases during treatment with valproate is seen in about 40% of cases. Abnormal liver function tests are mostly nonprogressive and not necessarily an indication for ceasing valproate. Transaminases will often normalize after simple dose reduction (Ghozzi et al. 2011). Hepatological complications leading to valproate discontinuation are estimated to occur in about 1:15,000 cases (Lackmann 2004). Severe hepatotoxicity is rare (0.01%) and is potentiated by the combination with other antiepileptic drugs (Ghozzi et al. 2011).

Hyperammonemia in the absence of abnormal liver function has been reported in 16–100% of patients treated with valproate (Chicharro et al. 2007), even with therapeutic serum levels, but is asymptomatic in most cases (Chicharro et al. 2007; Dealberto 2007; Hung et al. 2011; Shan et al. 2009). In rare cases it can lead to changes in consciousness and encephalopathy: valproate-induced hyperammonemic encephalopathy (VIHE). First symptoms occur most frequently within weeks after initiating or increasing the dose of valproate, but cases occurring during several years of maintenance therapy are also reported. Most frequent signs and symptoms include (flapping) tremor, ataxia, drowsiness, lethargy, disorientation, and "inappropriate behavior" (Dealberto 2007; Shan et al. 2009). The nonspecific presentation is frequently overlooked and regarded as a worsening of the psychiatric condition or as

side effect of concomitant medication (Shan et al. 2009). EEG shows symmetrical generalized slowing (Dealberto 2007). VIHE seems to occur equally in both genders. Possible risk factors include polypharmacy, mental retardation, vegetarian diet, urea cycle enzyme deficiency, and carnitine deficiency. The mechanism of VIHE remains unknown. The mean increase of serum ammonia level is about double the baseline level (Chicharro et al. 2007). Although no clear correlation was found between valproate serum levels, ammonia levels, and clinical symptoms, decreasing dose or discontinuing is advised.

Blood

Heightened levels of eosinophilic cells or lowered levels of leucocytes are often observed in all antidepressants, in about 10% of patients taking carbamazepine (Bertolino 1990; Sobotka et al. 1990) and rarely in patients treated with valproate (Lackmann 2004). It is mostly a harmless and temporarily effect.

There is no evidence that transient leukopenia progresses to aplastic anemia. The elderly (Askmark and Wiholm 1990) and patients whose total neutrophil or leucocyte count is low before treatment initiation (Bertolino 1990; Sobotka et al. 1990) are at increased risk of developing blood dyscrasias. Seldom seen but life threatening is agranulocytosis, which may develop after several weeks of treatment, with symptoms of sore throat, fever, difficulty in swallowing, infections in the mouth, or enlarged lymph nodes. Immediate discontinuation of the antidepressant is necessary, and antibiotics are given for prophylaxis.

Skin

Most patients experience dermatological side effects as distressing, and without proper attention and treatment, there is an increased risk for poor compliance. A frequent complaint in TCAs is perspiration, often during the night or in waves, and is due to blockage of alpha-1-receptors and/or serotonin reuptake inhibition (Kennedy et al. 2001; Bet et al. 2013). It is reported to lead to feeling uncomfortable, particularly in social contact with other people, and to disturbance of the sleep.

Exanthema is seen in 2–4% of patients with a TCA or fluoxetine and 6–8% in maprotiline. It is harmless, and changing the antidepressant may improve the complaints (Kennedy et al. 2001).

Although a meta-analysis showed no significant difference in the prevalence of skin disorders between patients given lithium and those given placebo (McKnight et al. 2012), in controlled trials, 3.4–45% of patients treated with lithium developed dermatological side effects, mainly acne and psoriasis (Yeung and Chan 2004). Acne is one of the most common side effects; it can develop within weeks after the initiation of lithium treatment. Psoriasis may develop after a refractory period of few weeks to several months. The incidence has been reported to be 1.8–6%. Preexisting psoriasis should not be regarded as a contraindication to lithium

prescription, but patients with a positive family history of psoriasis should be monitored carefully (Pande et al. 1986).

A benign rash occurs in 8.3% of lamotrigine patients in controlled settings ($n = 1{,}198$) and 13.1% of patients ($n = 257$) in an open-label setting (Calabrese et al. 2002). A serious rash as part of Stevens-Johnson syndrome or toxic necrolysis was reported 0.0% and 0.1%, respectively.

Intoxications and Anticholinergic and Serotonergic Syndrome

Intoxications in older people may be due to prescription of too high dosages (for this particular patient) and can be evaluated by monitoring serum levels. Of course, suicidal gestures with medication may also lead to dangerous serum levels.

Intoxications with TCAs can be dangerous because of the anticholinergic properties, and a broad range of symptoms can be found, like suppression of breathing and aspiration pneumonia, conduction disturbances leading to arrhythmias, heart block, PVCs, tachycardia, disturbances of consciousness, seizures, and coma. Treatment is possible, but often hospital admission and intensive care treatment are necessary.

Intoxications with modern antidepressants like SSRIs are less dangerous but may lead to the serotonergic syndrome.

Intoxication with lithium is, as in younger adults, based on clinical judgment and not lithium serum levels alone. Supratherapeutic lithium serum levels and intoxicates are major risk factors for renal failure and should be avoided at all times.

Anticholinergic Syndrome

In toxic doses of antidepressant medication with strong anti-muscarinic potential, a confusional state (delirium) may develop, consisting of anxiety, agitation, disorientation, hallucinations, myoclonus, seizures, hyperthermia, stupor, and even coma. Typical for the anticholinergic syndrome, and discriminating from other causes of delirium, are specific systemic symptoms such as tachycardia, widened pupils, a warm and dry skin, and dry saliva. Often prodromal confusion and agitation are seen, particularly during the night, and nightmares. The risk for the development of an anticholinergic syndrome is elevated when the antidepressants are combined with other psychotropic drugs with anticholinergic potential, such as an anti-Parkinson medication and some antipsychotics. Treatment consists of lowering the dose or discontinuation of the antidepressant, and in severe cases physostigmine 2–4 mgs i.v. or i.m. can be given.

Serotonergic Syndrome

This serious condition is due to stimulation of serotonin neurotransmission, and in most cases a combination of two or more serotonergic agents is necessary to provoke this syndrome. Symptoms are hyperthermia, motor symptoms (particularly extrapyramidal:

rigidity, cogwheel phenomenon, tremor, myoclonus, hyperreflexia, ataxia, agitation), autonomous disturbances (tachycardia, tachypnoea, tension changes, perspiring, nausea, diarrhea, urine incontinence), and consciousness changes (sedation, somnolence, anxiety, agitation, disorientation, hallucinations, seizures). The serotonergic syndrome may be life threatening or even lethal. It may be difficult to diagnose, because it looks like other deliriums or malign neuroleptic syndrome. Treatment consists of discontinuation of the medication.

Discontinuation of Antidepressants, Withdrawal Symptoms, and Interactions with Other Drugs

Please refer to the chapter on "► Pharmacotherapy for Mood and Anxiety Disorders" for depression and anxiety disorders in the elderly.

Subtypes of Mood Disorders Directly Related to Physical Health

Parkinson's Disease and Depression

Depression is a common comorbidity in Parkinson's disease (PD). In the literature prevalence up to 50% is found; however, most studies report prevalence between 20% and 30% (Evans et al. 2005). Depression may be found at any stage of the Parkinson's disease. In a longitudinal study with 400 Parkinson patients, 20% had a depression and approximately half of cases showed a persistent course. Risk factors were female gender, more severe disability, more severe motor fluctuations, autonomic and cognitive dysfunction, poorer nighttime sleep, and daytime sleepiness. Apart from motor fluctuations, depressive symptoms in PD were mainly associated with non-dopaminergic factors (Zhu et al. 2016). This underscores the idea that Parkinson's disease is not only a dopamine problem but that other neurotransmitter systems are involved as well, evoking all kinds of symptoms among which disturbances of mood and affect. The process starts in the medulla oblongata and from there spreads out to the higher regions (Braak and Tredici 2009). Although dopamine dysregulation often provokes the first obvious signs, i.e., motor signs such as rigidity and/or tremor, serotonergic dysregulation may occur earlier and cause depression and lability. In a longitudinal study in general practice, 9% of patients had depression in 3 years before the diagnosis of Parkinson's disease was confirmed, against 4% in the non-Parkinson patients (Leentjens et al. 2003).

Psychological factors may play a role as well, through the whole process. In the beginning or even before Parkinson's disease is diagnosed, the (future) patient may notice subtle changes in functioning that make him insecure or anxious. In later stages of the disease, when functioning is more hampered or motor problems are more difficult to treat, it may also increase the risk for depression.

The symptom profile of depression in Parkinson's disease may vary. A kind of "mental slowing" may occur, with apathy, lack of initiative, bradyphrenia, difficulty getting started in the morning, concentration problems, and diminished interest. However, also severe melancholic depression with vital symptoms and psychotic features may be seen, as well as in the beginning or even prodromal phase of the Parkinson's disease as later on in the disease process.

As mentioned above, many Parkinson symptoms are similar to depressive symptoms, and it is very important to investigate mood and affect in the case of Parkinson's disease because of the high common prevalence. Depression should be regarded as a separate problem and treated along the guidelines for depression. Antidepressant medication may worsen the Parkinson symptoms, and close collaboration with the neurologist is necessary. Electroconvulsive therapy (ECT) is often very effective and may improve the Parkinson symptoms as well as the mood symptoms.

Dementia and Depression

In 25–35% of patients with dementia, depressive symptoms are found, and in 10–20% criteria for MDD are fulfilled (Enach et al. 2011). Depression can be found in every stage of dementia, although in end stages, it is rare or very difficult to diagnose. Cognitive problems, such as concentration problems, memory problems, and problems in executive functioning, are often found in late-life depression. Sometimes these problems persist when the depression goes into remission, and this is found to be a predictor for the development of dementia (Kessing and Nilson 2003; Korczyn and Halperin 2009). Particularly in the early phase of dementia, it can be difficult to differentiate between depression and dementia. More elaborate diagnostic procedures, with interviewing the patient and the family on symptoms and course of the depression, gathering information on the psychiatric history, and neuropsychological tests may be helpful. However, many symptoms of depression are also found in several types of dementia, and sometimes it is not possible to differentiate between these two disorders. In that case it is important to treat a possible depression and follow the course of symptoms and functioning over time.

Depression in dementia may have a psychological basis, e.g., a psychological reaction to the perceived changes in cognitive function or to expected problems in the future. However, neurobiological processes play a role as well. In the case of white matter changes, as seen in vascular dementia but also in Alzheimer's dementia, a cluster of symptoms is found consisting of diminished interest, lack of initiative, lessened emotional reactivity, psychomotor slowing, and decreased ability to enjoy (Alexopoulos et al. 2008). Although motivational problems are most prominent and mood symptoms may be less clear, the criteria for depression are often met. Specific criteria for depression in Alzheimer's disease were proposed and have more emphasis on social withdrawal (Olin et al. 2002). More information on this so-called vascular depression can be found in the next paragraph.

Neurotransmitter loss, a core problem in many types of dementia, may also lead to depressive symptoms, particularly when there are disturbances in the

monoaminergic systems (serotonin, dopamine, (nor-)epinephrine, and melatonin) (Reinikainen et al. 1990). These neurotransmitter systems are all involved in several aspects of mood disorders.

Medial temporal lobe atrophy (MTA) or hippocampal atrophy and global cortical atrophy (GCA) are characteristic features in Alzheimer's dementia but are also seen in depression (Sheline et al. 2003). This finding may point to a common mechanism for depression and dementia, with differential clinical manifestations in the cognitive and mood domains.

Stress and the elevated levels of cortisol in depression may contribute to the higher risk of dementia in depressed persons, with the notion that this may cause death of hippocampal cells (Sapolsky et al. 2000).

Vascular Depression

In the late 1990s of the past century, the "vascular depression" hypothesis was postulated by Alexopoulos and Krishnan (Alexopoulos et al. 1997; Krishnan et al. 1997). This vascular depression was considered to be a subtype of late-life depression, found in patients with late-onset depression and substantial deep white matter hyperintensities on brain MRI. A typical clinical presentation was found, with psychomotor retardation, apathy, and more neuropsychological impairment, particularly executive dysfunction, compared to early-onset depression and a poorer response to treatment. The cerebrovascular disease was supposed to be the cause of this type of depression, with structural damage to the frontostriatal circuits that are involved in emotion regulation and executive functioning. It is not clear if the poor treatment response is associated with the white matter abnormalities, or with the executive dysfunction (Taylor et al. 2006; Sneed and Culang-Reinlieb 2011). As already mentioned, response to pharmacological treatment is worse than in other types of depression. In a study on post-stroke depression, nortriptyline was found more effective than fluoxetine, but the anticholinergic properties of the TCAs may be a problem in these patients with higher cerebral vulnerability (Robinson et al. 2000). SSRIs were found to even deteriorate the depression, showing a worsening compared to placebo (Sneed et al. 2010). Electroconvulsive therapy however has shown to be effective in this type of depression.

Next to treatment of the depression, management of the cardiovascular risk factors is important. Hypertension, diabetes mellitus, hyperlipidemia, smoking, and alcohol use should be evaluated and treated when necessary. A problem may be that antihypertensive medication may have a depression-inducing effect (see the chapter below section on "Medication-Induced Depression").

Metabolic Depression

A subtype of depression, defined by a specific pattern of symptoms among which weight gain instead of weight loss and increased need of sleep instead of diminished

sleep, appears to be connected with specific disturbances in metabolic processes and inflammation: the so-called metabolic depression.

In the Netherlands Study of Depression and Anxiety (NESDA), adult patients with an atypical depression had significantly higher levels of inflammatory markers, body mass index, waist circumference and triglycerides, and lower high-density lipid cholesterol than persons with melancholic depression and controls (Lamers et al. 2013).

In a Dutch community-based study, a high plasma level of the inflammation factor interleukin-6 (IL-6) was associated with an increased prevalence of major depression in late life, independent of age, chronic diseases, cognitive functioning, and antidepressants (Bremmer et al. 2008).

In the Netherlands Study of Depression in Older persons (NESDO), inflammatory factors (C-reactive protein, IL-6) and metabolic factors (waist circumference, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, fasting glucose) were investigated in depressed patients aged 60–93. Patients with atypical depression presented with metabolic upregulation, whereas immunometabolic downregulation was found in depressed patients with less severe symptoms and those with late-life onset (Vogelzangs et al. 2014a). In patients in NESDO using antidepressants, inflammatory and metabolic dysregulations predicted a more chronic course, suggesting a negative effect on antidepressant treatment response (Vogelzangs et al. 2014b). In the longitudinal Health, Aging, and Body Composition (HABC) Study, obesity, in particular visceral fat, increased the risk of onset of significant depressive symptoms in older men, suggesting that specific mechanisms might relate visceral fat to the onset of depression (Vogelzangs et al. 2010).

So, the presence of increased weight and other metabolic disturbances in depression is probably not a coincidence but part of the pathophysiology of depression, and (visceral) fat may be an active component in the (dys)regulation of affective processes. Screening for and treatment of metabolic factors are advised, also because there may be a link with worse outcome of antidepressant therapy.

Medication-Induced Depression

In the literature, a lot of reports can be found on medication associated with the onset or worsening of depression. Anticonvulsants, medication for Parkinson's disease, migraine and multiple sclerosis, a wide range of cardiovascular medications, anti-infective agents, oncologic agents, corticosteroids, and other hormonal agents are mentioned to play a role in evoking depression or even MDD.

However, for most drugs, only small studies or case reports have been performed, while prospective studies are lacking or did not find an association (Celano et al. 2011).

Furthermore, many of these drugs are given because of diseases that are associated with depression itself, and the link of medication and depression may be a more coincidental finding, not a real causal relationship.

However, there is evidence that some of the agents mentioned above are associated with depression. Furthermore, individual factors such as genetic vulnerability or concurrent medication may cause a depressive syndrome in single patients but not in the general population. It is advised to be alert on temporal associations of depression with the start or change of medication use, to perform an "on-off-on" trial and in case of doubt to change the medication (Dhondt et al. 1999; Celano et al. 2011).

Secondary Mania

Late-life manic symptoms and physical health are highly linked, and different hypotheses have been proposed. Somatic factors may be a true cause of mania (secondary mania), or merely triggering mania as a first manifestation of bipolar disorder in a person with a latent vulnerability, and with or without a previous history of depressive episodes. Somatic comorbidity may also be a coincidental finding without any causal relationship to mania.

Manic symptoms, as disturbed sleep, irritability, and impaired attention, in later life have a broad differential diagnosis including a psychiatric diagnosis such as (late-onset) bipolar disorder and schizoaffective disorder (primary mania) or an organic syndrome such as delirium, dementia, and secondary mania. Late-life mania is not rare; the overall prevalence is estimated to be 6.0% in older psychiatric inpatients with about one third experiencing their first manic episode (i.e., late-onset mania) (Dols et al. 2014a). Although the management of both primary and secondary mania may be similar, the etiology of mania is of importance as the appropriate treatment of secondary mania includes addressing the cause (Krauthammer and Klerman 1978).

The concept of secondary mania was introduced by Krauthammer and Klerman in 1978 (Krauthammer and Klerman 1978) as a condition with manic symptomatology resulting from an underlying medical illness that could develop in people with no history of mood disorder. For manic symptoms to be classified as secondary mania, the patient should have no history of primary mood disorder or evidence of delirium. The list of various neurological conditions, systemic disturbances, and medications that have been described to cause secondary mania is very extensive (Van Gerpen et al. 1999). While it can occur at any age, it is more common in older patients; this is understandable given the higher prevalence of potentially causative medical conditions and treatments in older adults. On the contrary, one could argue that coincidental somatic findings should not be attributed to have caused manic symptoms, since the vast majority of patients with these somatic comorbidities do not develop manic symptoms. Presently data are lacking to label "due to a somatic condition or medication" as specifier in bipolar disorder. As we know from other psychiatric disorders (e.g., schizophrenia), certain substances (e.g., cannabis) can prime the development of a psychiatric disease.

Analogous to delirium, many somatic conditions can cause mania in patients of any age; however, some patients seem more at risk, for example, older patients and patients with vascular non-symptomatic) brain damage; perhaps vascular risk factors

prime these patients to develop manic symptoms without matching bipolar patients in other aspects.

Vascular Mania

Although far less common than depression, mania can occur in 1% of stroke patients, in 2–12% of patients with movement disorders as Huntington's disease, and in patients with epilepsy or infections of the brain (Mendez 2000). Tumors, neurosurgery, and traumatic head injury can result in manic symptoms (Brooks and Hoblyn 2005), occasionally with a delay of up to 12 months before the manic symptoms develop (Jorge et al. 1993; Robinson et al. 1988). Focal brain lesions in the right hemisphere have been associated with mania (Braun et al. 1999).

Steffens and Krishnan (1998) proposed criteria for vascular mania and depression subtype specifiers, and their concept of vascular mania appears to have some overlap with the neurological disinhibition syndrome. Vascular mania is defined as a subtype when mania occurs in the context of cerebrovascular disease or neuropsychological impairment. Late-life mania may occur not infrequently in patients with non-symptomatic) vascular brain damage. Some (Martino et al. 2013; Samame et al. 2013; Schouws et al. 2009) but not all (Subramaniam et al. 2007) reports suggest that late-onset bipolar disorder is associated with significant cognitive impairment. One study noted that those with late-onset bipolar disorder had a greater prevalence of white matter hyperintensities (WMH) in the deep parietal region and basal ganglia compared to bipolar patients with an earlier onset and healthy controls (Tamashiro et al. 2008). In a recent sample of older bipolar patients, including both early and late onset, the self-reported prevalence of cerebrovascular disease was 3%, (Dols et al. 2014a); however, silent cerebral infarctions may be present in over half of older bipolar patients, regardless of age at onset (Huang et al. 2012).

Differentiating between "frontal disinhibition" and "bipolar mania" can be challenging; many symptoms are overlapping; nevertheless, "bipolar mania" may be more characterized by elevated mood and lack of need for sleep, contrary to disturbed sleep. The presence of a positive family history of affective disorder may indicate that a somatic cause resulted in mania by triggering an existing bipolar predisposition (Krauthammer and Klerman 1978).

Conclusion

In older adults with a mood disorder, an inclusive approach with investigation of symptoms of both depression and comorbid physical problems is warranted. It may be hard to disentangle physical complaints from primary mood symptoms, but it is advisable to treat the most important cause of the physical problems, together with treatment of the depressive component, dependent on the severity of symptoms. An example may be a severe depression with psychotic features and hypothyroidism:

restore the hormonal balance and consider an in-patient trajectory, addition of psychological treatment and support, and biological treatment of depression in case of persistence of the depression part.

Other important physical interventions that should be given together with depression treatment may be supplying nutritional deficiencies and treatment of infections. These factors may undermine the physical strength necessary for recovery from the depression. Even surgery for hip fracture may be very important to improve the possibilities for recovery from the depression (as well as for successful revalidation). In daily practice, this may feel as a moral dilemma to give such an extensive treatment to a sad and down old patient, and it is important not to join the defeatist and hopeless attitude often found in depressed patients (and their family).

And of course, it is wise to check the medication for side effects of depression.

Optimizing physical health will include interventions on lifestyle and unhealthy behavior, such as smoking, alcohol, sedentary lifestyle, and overweight. They may be part of the problem in disturbing mood balance and worsen treatment outcome.

Physical disease is a risk factor for the development of depression, and it can be difficult to discriminate a developing depression from the somatic problems that already exist. Indications for depression in somatic disease may be slow recovery or even a fallback, poor initiative, diminished appetite, sleep problems, dependency for functions of daily living, behavioral changes (irritability, drawback), memory problems, mistrust, or delusions.

Physical investigation with special attention to vascular risk factors is advised for every depressed older patient and laboratory tests comprising at least hematological tests, Na, K, Ca, glucose, liver function tests, renal function tests, TSH, vitamin B12 and folate, and other tests when indicated (Baldwin et al. 2002).

It is important to evaluate somatic complaints before the start with antidepressants or other agents, to prevent labeling them wrongly as side effects.

Somatic health is so key in the diagnosis and treatment of mood disorders in older adults that psychiatrists and other mental health workers caring for these vulnerable patients should be educated in somatic medicine as well as in mental health.

Cross-References

▶ Pharmacotherapy for Mood and Anxiety Disorders

References

Aiff H, Attman PO, Aurell M, Bendz H, Schon S, Svedlund J (2014) The impact of modern treatment principles may have eliminated lithium-induced renal failure. J Psychopharmacol 28:151–154

Alexopoulos GS, Meyers BS, Young RC et al (1997) 'Vascular depression' hypothesis. Arch Gen Psychiatry 54:915–922

Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S et al (2008) Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry 165:238–244

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders DSM-IV. APA, Washington, DC

Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A et al (1993) Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. Epidemiology 4:285–294

Askmark H, Wiholm BE (1990) Epidemiology of adverse reactions to carbamazepine as seen in a spontaneous reporting system. Acta Neurol Scand 81:131–140

Association, A. P (2013) Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Publishing (DSM5), Washington, DC

Baldwin RC, Chiu E, Katona C, Graham N (2002) Guidelines on depression in older people. Martin Dunitz, London

Batlle DC, Von Riotte AB, Gaviria M, Grupp M (1985) Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 312:408–414

Bedford JJ, Weggery S, Ellis G, Mcdonald FJ, Joyce PR, Leader JP, Walker RJ (2008) Lithium-induced nephrogenic diabetes insipidus: renal effects of amiloride. Clin J Am Soc Nephrol 3:1324–1331

Beekman AT, Penninx BW, Deeg DJ, Ormel J, Braam AW, van Tilburg W (1997) Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). J Affect Disord 46(3):219–231

Beekman AT, Penninx BW, Deeg DJ, de Beurs E, Geerlings SW, van Tilburg W (2002) The impact of depression on the well-being, disability and use of services in older adults: a longitudinal perspective. Acta Psychiatr Scand 105:20–27

Bendz H, Aurell M (1999) Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 21:449–456

Bensenor IM, Olmos RD, Lotufo PA (2012) Hypothyroidism in the elderly: diagnosis and management. Clin Interv Aging 7:97–111

Bendz H, Schon S, Attman PO, Aurell M (2010) Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int 77:219–224

Bertolino JG (1990) Carbamazepine. What physicians should know about its hematologic effects. Postgrad Med 88:183–186

Bet PM, Hugtenburg JG, Pennninx BW, Hoogendijk WJ (2013) Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol 23:1443–1451

Bocchetta A, Loviselli A (2006) Lithium treatment and thyroid abnormalities. Clin Pract Epidemiol Ment Health 2:23

Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A (2007) Fifteen-year follow-up of thyroid function in lithium patients. J Endocrinol Investig 30:363–366

Boton R, Gaviria M, Batlle DC (1987) Prevalence, pathogenesis, and treatment of renal dysfunction associated with chronic lithium therapy. Am J Kidney Dis 10:329–345

Bowden CL (2003) Valproate. Bipolar Disord 5:189–202

Bowden CL, Calabrese JR, Ketter TA, Sachs GS, White RL, Thompson TR (2006) Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. Am J Psychiatry 163:1199–1201

Braam AW, Prince MJ, Beekman AT, Delespaul P, Dewey ME, Geerlings SW, Kivela SL, Lawlor BA, Magnusson H, Meller I, Peres K, Reischies FM, Roelands M, Schoevers RA, Saz P, Skoog I, Turrina C, Versporten A, Copeland JR (2005) Physical health and depressive symptoms in older Europeans. Results from EURODEP. Br J Psychiatry 187:35–42

Braak, Tredici KC (eds) (2009) Neuroanatomy and pathology of sporadic Parkinson's Disease. Springer, Berlin

Braun CM, Larocque C, Daigneault S, Montour-Proulx I (1999) Mania, pseudomania, depression, and pseudodepression resulting from focal unilateral cortical lesions. Neuropsychiatry Neuropsychol Behav Neurol 12:35–51

Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, Hoogendijk WJ (2008) Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord 106(3):249–255

Brooks JO 3rd, Hoblyn JC (2005) Secondary mania in older adults. Am J Psychiatry 162:2033–2038

Burgess S, Geddes J, Hawton K, Townsend E, Jamison K, Goodwin G (2001) Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev 2001:CD003013

Calabrese JR, Sullivan JR, Bowden CL, Suppes T, Goldberg JF, Sachs GS, Shelton MD, Goodwin FK, Frye MA, Kusumakar V (2002) Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. J Clin Psychiatry 63:1012–1019

Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA (2016) The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom 85(5):270–288

Celano CM, Freudenreich O, Huffman JC (2011) Depressogenic effects of medications: a review. Dialogues Clin Neurosci 13:109–125

Cole MG, Dendukuri N (2003) The risk factors for depression among elderly community subjects: a systematic review and meta-analysis. Am J Psychiatry 13:41–48

Chicharro AV, De Marinis AJ, Kanner AM (2007) The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? Epilepsy Behav 11:361–366

Clos S, Rauchhaus P, Severn A, Cochrane L, Donnan PT (2015) Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. Lancet Psychiatry 2:1075–1083

Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS (2007) Prevalence of chronic kidney disease in the United States. JAMA 298:2038–2047

Cox M, Singer I (1975) Lithium and water metabolism. Am J Med 59:153–157

Creed F, Dickens C (2007) Depression in the medically ill. In: Steptoe A (ed) Depression and physical illness. Cambridge University Press, Cambridge, UK

Daban C, Martinez-Aran A, Torrent C, Sanchez-Moreno J, Goikolea JM, Benabarre A, Comes M, Colom F, Vieta E (2006) Cognitive functioning in bipolar patients receiving lamotrigine: preliminary results. J Clin Psychopharmacol 26:178–181

De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ (2009) Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychol 24:412–424

Dealberto MJ (2007) Valproate-induced hyperammonaemic encephalopathy: review of 14 cases in the psychiatric setting. Int Clin Psychopharmacol 22:330–337

Demyttenaere K, De Fruyt J, Sienaert P (1998) Psychotropics and sexuality. Int Clin Psychopharmacol 13(Suppl 6):S35–S41

Dhondt T, Derksen P, Hooijer C, van Heycop ten HB, van Gent PP, Heeren TJ (1999) Depressogenic medication as an etiological factor in major depression. An analysis in a clinical population of depressed elderly. In J Geriatr Psychiatry 14:875–881

DiMatteo MR, Lepper HS, Croghan TW (2000) Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 16:2101–2107

Djernes JK (2006) Prevalence and predictors of depression in population of elderly: a review. Acta Psychiatr Scand 113:372–387

Dols A, Kupka RW, Van Lammeren A, Beekman AT, Sajatovic M, Stek ML (2014a) The prevalence of late-life mania: a review. Bipolar Disord 16:113–118

Dols A, Rhebergen D, Beekman A, Kupka R, Sajatovic M, Stek ML (2014b) Psychiatric and medical comorbidities: results from a bipolar elderly cohort study. Am J Geriatr Psychiatry 22:1066–1074

Eaton WW, Fogel J, Armenian HK (2006) The consequences of psychopathology in the Baltimore epidemiologic catchment area follow-up. In: Eaton WW (ed) Medical and psychiatric comorbidity over the life span. American Psychiatric Publishing, Washington, DC, pp 21–38

Enach D, Winblad B, Aarsland D (2011) Depression in dementia: epidemiology, mechanisms and treatment. Curr Opin Psychiatry 24:461–472

Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KRR et al (2005) Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 58:175–189

Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J et al (2014) Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. Prev Med 63:36–42

Fenn HH, Bauer MS, Altshuler L, Evans DR, Williford WO, Kilbourne AM, Beresford TP, Kirk G, Stedman M, Fiore L, Team VACS (2005) Medical comorbidity and health-related quality of life in bipolar disorder across the adult age span. J Affect Disord 86:47–60

Fenton WS, Stover ES (2006) Mood disorders: cardiovascular and diabetes comorbidity. Curr Opin Psychiatry 19:421–427

Gahr M, Kratzer W, Fuchs M, Connemann BJ (2014) Safety and tolerability of agomelatine: focus on hepatotoxicity. Curr Drug Metab 15(7):694–702

Gau CS, Chang CJ, Tsai FJ, Chao PF, GAU SS (2010) Association between mood stabilizers and hypothyroidism in patients with bipolar disorders: a nested, matched case-control study. Bipolar Disord 12:253–263

Gelenberg AJ, Jefferson JW (1995) Lithium tremor. J Clin Psychiatry 56:283–287

Ghadirian AM, Annable L, Belanger MC (1992) Lithium, benzodiazepines, and sexual function in bipolar patients. Am J Psychiatry 149:801–805

Ghose K (1991) The need for a review journal of drug use and the elderly. Drugs Aging 1:2–5

Ghozzi H, Hakim A, Sahnoun Z, Ben Mahmoud L, Atheymen R, Hammami S, Zeghal K (2011) Relationship between plasma concentrations of valproic acid and hepatotoxicity in patients receiving high doses. Rev Neurol (Paris) 167:600–606

Gildengers AG, Whyte EM, Drayer RA, Soreca I, Fagiolini A, Kilbourne AM, Houck PR, Reynolds CF 3rd, Frank E, Kupfer DJ, Mulsant BH (2008) Medical burden in late-life bipolar and major depressive disorders. Am J Geriatr Psychiatry 16:194–200

Goodwin FK, Jamison KR, Ghaemi SN (2007) Manic-depressive illness: bipolar disorders and recurrent depression. Oxford University Press, New York

HALLAM (2010) Managing the impact of mood stabiliser-induced tremors in patients with bipolar disorder. Acta Neuropsychiatrica 22:259–260

Harden CL (2008) Sexual dysfunction in women with epilepsy. Seizure 17:131–135

Huang SH, Chung KH, Hsu JL, Wu JY, Huang YL, Tsai SY (2012) The risk factors for elderly patients with bipolar disorder having cerebral infarction. J Geriatr Psychiatry Neurol 25:15–19

Hung CC, Li TM, Wei IH, Huang CC (2011) The real mechanism of VPA-induced hyperammonemia remains unknown. Gen Hosp Psychiatry 33(84):e3–e4

Jacobson SA, Pies RW, Katz IR (2007) Clinical manual of geriatric psychopharmacology. American Psychiatric Publishing, Arlington

Joffe RT, Macdonald C, Kutcher SP (1988) Lack of differential cognitive effects of lithium and carbamazepine in bipolar affective disorder. J Clin Psychopharmacol 8:425–428

Johnston AM, Eagles JM (1999) Lithium-associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry 175:336–339

Jorge RE, Robinson RG, Starkstein SE, Arndt SV, Forrester AW, Geisler FH (1993) Secondary mania following traumatic brain injury. Am J Psychiatry 150:916–921

Kamphuis MH, Kalmijn S, Tijhuis MA, Geerlings MI, Giampaoli S, Nissinen A et al (2006) Depressive symptoms as a risk factor of cardiovascular mortality in older European men: the Finland, Italy and Netherlands Elderly (FINE). Eur J Cardiovasc Prev Rehabil 13:199–206

Keck PE, Mcelroy SL (2003) Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. J Clin Psychiatry 64:1426–1435

Kendler KS, Gardner CO, Fiske A et al (2008) Major depression and coronary heart disease in the Swedish twin registry. Arch Gen Psychiatry 66(8):857–863

Kennedy SH, Lam RW, Cohen NL, Ravindran AV, CANMAT Depression Work Group (2001) Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can J Psychiatry 46(Suppl 1):38S–58S

Kessing LV, Nilsson FM (2003) Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord 73:261–269

Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW (2015) Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. JAMA Psychiatry 72:1182–1191

Kirov G, Tredget J, John R, Owen MJ, Lazarus JH (2005) A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. J Affect Disord 87:313–317

Kleiner J, Altshuler L, Hendrick V, Hershman JM (1999) Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. J Clin Psychiatry 60:249–255

Konz HW, Meesters PD, Paans NP, Van Grootheest DS, Comijs HC, Stek ML, Dols A (2014) Screening for metabolic syndrome in older patients with severe mental illness. Am J Geriatr Psychiatry 22:1116–1120

Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A (2007) Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry 22(7):613–626

Korczyn AD, Halperin I (2009) Depression and dementia. J Neurol Sci 15(283):139–142

Krauthammer C, Klerman GL (1978) Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 35:1333–1339

Krishnan KR, Hays JC, Blazer DG (1997) MRI-defined vascular depression. Am J Psychiatry 154:497–501

Kroenke K (2003) The interface between physical and psychological symptoms. Primary care companion. J Clin Psychiatry 5(Suppl):11–18

Kupka RW, Nolen WA, Post RM, Mcelroy SL, Altshuler LL, Denicoff KD, Frye MA, Keck PE Jr, Leverich GS, Rush AJ, Suppes T, Pollio C, Drexhage HA (2002) High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry 51:305–311

Lackmann GM (2004) Valproic-acid-induced thrombocytopenia and hepatotoxicity: discontinuation of treatment? Pharmacology 70:57–58

Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS (1997) Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischaemic heart disease. Biol Psychiatry 42:290–295

Lala SV, Sajatovic M (2012) Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: a literature review. J Geriatr Psychiatry Neurol 25:20–25

Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW (2013) Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry 18(6):692–699

Leboyer M, Kupfer DJ (2010) Bipolar disorder: new perspectives in health care and prevention. J Clin Psychiatry 71:1689–1695

Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, Kupfer DJ (2012) Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 141:1–10

Leentjens AFG, van den Akker M, Metsemakers JFM, Lousberg R, Verhey FRJ (2003) Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord 18:414–418

Lepkifker E, Sverdlik A, Iancu I, Ziv R, Segev S, Kotler M (2004) Renal insufficiency in long-term lithium treatment. J Clin Psychiatry 65:850–856

Lett HS, Sherwood A, Watkins L, Blumenthal JA (2007) Depression and prognosis in cardiac patients. In: Steptoe A (ed) Depression and prognosis in cardiac patients. Cambridge University Press, Cambridge, UK

Lipscombe LL, Levesque L, Gruneir A, Fischer HD, Juurlink DN, Gill SS, Herrmann N, Hux JE, Anderson GM, Rochon PA (2009) Antipsychotic drugs and hyperglycemia in older patients with diabetes. Arch Intern Med 169:1282–1289

Lyness JM, Heo M, Datto CJ, ten Have TR, Katz IR, Drayer R et al (2006) Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Ann Intern Med 144:496–504

Manjunath G, Tighiouart H, Ibrahim H, Macleod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ (2003) Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 41:47–55

Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD (2000) Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol 11:1439–1448

Martinez-Aran A, Vieta E, Colom F, Torrent C, Reinares M, Goikolea JM, Benabarre A, Comes M, Sanchez-Moreno J (2005) Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother Psychosom 74:295–302

Martino DJ, Strejilevich SA, Manes F (2013) Neurocognitive functioning in early-onset and late-onset older patients with euthymic bipolar disorder. Int J Geriatr Psychiatry 28:142–148

van Marwijk HW, van der Kooy KG, Stehouwer CD, Beekman AT, van Hout HP (2015) Depression increases the onset of cardiovascular disease over and above other determinants in older primary care patients, a cohort study. BMC Cardiovasc Disord 12(15):40

Mavrides N, Nemeroff C (2013) Treatment of depression in cardiovascular disease. Depress Anxiety 30:328–341

Mcknight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR (2012) Lithium toxicity profile: a systematic review and meta-analysis. Lancet 379:721–728

Melle JP, de Jonge P, Ormel J, Crijns HJ, van Veldhuijsen DJ, Honig A et al (2005) Relationships between left ventricular dysfunction and depression following myocardial infarction: data from the MIND-IT. Eur Heart J 26:2650–2656

Mendez MF (2000) Mania in neurologic disorders. Curr Psychiatry Rep 2:440–445

Mercier-Guidez E, Loas G (1998) Polydipsia: review of the literature. Encéphale 24:223–229

Miller JM, Kustra RP, Vuong A, Hammer AE, Messenheimer JA (2008) Depressive symptoms in epilepsy: prevalence, impact, aetiology, biological correlates and effect of treatment with antiepileptic drugs. Drugs 68:1493–1509

Miodownik C, Witztum E, Lerner V (2002) Lithium-induced tremor treated with vitamin B6: a preliminary case series. Int J Psychiatry Med 32:103–108

Mitchell AJ, Rao S, Vaze A (2010) Do primary care physicians have particular difficulty identifying late-life depression? A meta-analysis stratified by age. Psychother Psychosom 79:285–294

Najafi L, Malek M, Hadian A, Ebrahim Valojerdi A, Khamseh ME, Aghili R (2015) Depressive symptoms in patients with subclinical hypothyroidism – the effect of treatment with levothyroxine: a double-blind randomized clinical trial. Endocr Res 40:121–126

Nemeroff CB (2003) Safety of available agents used to treat bipolar disorder: focus on weight gain. J Clin Psychiatry 64:532–539

Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, Beaulieu S, Yatham LN, Berk M, International Society For Bipolar, D (2009) The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 11:559–595

Olin JT, Katz IR, Meyers BS, Schneider LS, Lebowitz BD (2002) Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. Am J Geriatr Psychiatry 10:129–141

Pande AC, Max P, Donnelly RF (1986) Lithium associated with psoriasis. J Clin Psychiatry 47:330

Patten SB, Beck CA, Williams JV, Barbui C, Metz LM (2003) Major depression in multiple sclerosis: a population based perspective. Neurology 61:1524–1527

Paul R, Minay J, Cardwell C, Fogarty D, Kelly C (2010) Meta-analysis of the effects of lithium usage on serum creatinine levels. J Psychopharmacol 24:1425–1431

Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT (1999) Minor and major depression and the risk of death in older persons. Arch Gen Psychiatry 56(10):889–895
Pijl H, Meinders AE (1996) Bodyweight change as an adverse effect of drug treatment. Mechanisms and management. Drug Saf 14:329–342
Pollock BG, Laghrissi-Thode F, Wagner WR (2000) Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. J Clin Psychopharmacol 20:137–140
Polsky D, Doshi JA, Marcus S, Oslin D, Rothbard A, Thomas N et al (2005) Long-term risk for depressive symptoms after a medical diagnosis. Arch Intern Med 165:1260–1266
Presne C, Fakhouri F, Noel LH, Stengel B, Even C, Kreis H, Mignon F, Grunfeld JP (2003) Lithium-induced nephropathy: rate of progression and prognostic factors. Kidney Int 64:585–592
Regulies R (2002) Depression as a predictor for coronary heart disease. A review and meta-analysis. Am J Prev Med 23:51–61
Reinikainen KJ, Soininen H, Riekkinen PJ (1990) Neurotransmitter changes in Alzheimer's disease: implications to diagnostics and therapy. J Neurosci Res 27:576–586
Rej S, Herrmann N, Shulman K (2012) The effects of lithium on renal function in older adults – a systematic review. J Geriatr Psychiatry Neurol 25:51–61
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. Int J Geriatr Psychiatry 28:450–453
Robinson RG, Boston JD, Starkstein SE, Price TR (1988) Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry 145:172–178
Robinson PG, Starkstein SE (1990) Current research in affective disorders following stroke. J Neuropsychiatr Clin Neurosci 2:1–14
Robinson RG, Schultz SK, Castillo C et al (2000) Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry 157(3):351–359
Rodin G, Nolan RP, Katz MR (2005) Depression. In: Levenson JL (ed) Depression. American Psychiatric Publishing, Arlington, pp 193–217
Rottenberg J (2007) Cardiac vagal control in depression: a critical analysis. Biol Psychol 74:200–211
Sachs GS, Guille C (1999) Weight gain associated with use of psychotropic medications. J Clin Psychiatry 60(Suppl 21):16–19
Samame C, Martino DJ, Strejilevich SA (2013) A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disord 15:633–644
Sapolsky RM (2000) The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry 48:713–714
Schouws SN, Comijs HC, Stek ML, Dekker J, Oostervink F, Naarding P, Van Der Velde I, Beekman AT (2009) Cognitive impairment in early and late bipolar disorder. Am J Geriatr Psychiatry 17:508–515
Senturk V, Goker C, Bilgic A, Olmez S, Tugcu H, Oncu B, Atbasoglu EC (2007) Impaired verbal memory and otherwise spared cognition in remitted bipolar patients on monotherapy with lithium or valproate. Bipolar Disord 9(Suppl 1):136–144
Setoguchi S, Wang PS, Alan Brookhart M, Canning CF, Kaci L, Schneeweiss S (2008) Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications. J Am Geriatr Soc 56:1644–1650
Shan JC, Hsieh MH, Liu CC, Wen CC, Liu CM (2009) Clinical alertness to valproic acid-induced hyperammonemia – two case reports. J Psychopharmacol 24:943–945
Sheline YI, Gado MH, Kraemer HC (2003) Untreated depression and hippocampal volume loss. Am J Psychiatry 160:1516–1518
Shine B, Mcknight RF, Leaver L, Geddes JR (2015) Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet 386:461–468

Shimoda K, Robinson RG (1999) The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry 45:187–192
Sienaert P, De Fruyt J (2001) Seksuele bijwerkingen van psychofarmaca. In: Schene AH, Boer F, Heeren TJ (eds) Jaarboek voor psychiatrie en psychotherapie. Bohn Stafleu Van Loghum, Houten/Diegem, pp 2001–2002
Smaldone M, Sukkarieh T, Reda A, Khan A (2004) Epilepsy and erectile dysfunction: a review. Seizure 13:453–459
Sneed JR, Culang-Reinlieb ME (2011) The vascular depression hypothesis: an update. Am J Ger Psychiatry 19:99–103
Sneed JR, Culang ME, Keilp JG et al (2010) Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. Am J Geriatr Psychiatr 18:128–135
Sobotka JL, Alexander B, Cook BL (1990) A review of carbamazepine's hematologic reactions and monitoring recommendations. DICP 24:1214–1219
Stadlmann S, Portmann S, Tschopp S, Terracciano LM (2012) Venlafaxine-induced cholestatic hepatitis: case report and review of literature. Am J Surg Pathol 36(11):1724–1728
Steffens DC, Krishnan KR (1998) Structural neuroimaging and mood disorders: recent findings, implications for classification, and future directions. Biol Psychiatry 43:705–712
Stoll AL, V. A, Mcelroy SL (1991) Histamine$_2$-receptor antagonists for the treatment of Valproate-induced gastrointestinal distress. Ann Clin Psych 3:301–304
Subramaniam H, Dennis MS, Byrne EJ (2007) The role of vascular risk factors in late onset bipolar disorder. Int J Geriatr Psychiatry 22:733–737
Tamashiro JH, Zung S, Zanetti MV, De Castro CC, Vallada H, Busatto GF, De Toledo Ferraz Alves TC (2008) Increased rates of white matter hyperintensities in late-onset bipolar disorder. Bipolar Disord 10:765–775
Taylor WD, Steffens DC, Krishnan KR (2006) Psychiatric disease in the twenty-first century: the case for subcortical ischemic depression. Biol Psychiatry 60(12):1299–1303
Torelli P, Lambru G, Manzoni GC (2006) Psychiatric comorbidity and headache: clinical and therapeutical aspects. Neurol Sci 27(Suppl 2):S73–S76
Torrent C, Amann B, Sanchez-Moreno J, Colom F, Reinares M, Comes M, Rosa AR, Scott J, Vieta E (2008) Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatr Scand 118:4–18
Tredget J, Kirov A, Kirov G (2010) Effects of chronic lithium treatment on renal function. J Affect Disord 126:436–440
Tsai SY, Kuo CJ, Chung KH, Huang YL, Lee HC, Chen CC (2009) Cognitive dysfunction and medical morbidity in elderly outpatients with bipolar disorder. Am J Geriatr Psychiatry 17:1004–1011
Van Gerpen MW, Johnson JE, Winstead DK (1999) Mania in the geriatric patient population: a review of the literature. Am J Geriatr Psychiatry 7:188–202
Van Melick EJ, Wilting I, Meinders AE, Egberts TC (2010) Prevalence and determinants of thyroid disorders in elderly patients with affective disorders: lithium and nonlithium patients. Am J Geriatr Psychiatry 18:395–403
Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU (2015) Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14:339–347
Vestergaard P, Poulstrup I, Schou M (1988) Prospective studies on a lithium cohort. 3. Tremor, weight gain, diarrhea, psychological complaints. Acta Psychiatr Scand 78:434–441
Vinkers DJ et al (2004) Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus study. Int J Geriatric Psychiatry 19:852–857
Vogelzangs N, Kritchevsky SB, Beekman AT, Brenes GA, Newman AB, Satterfield S, Yaffe K, Harris TB, Penninx BW, Health ABC Study (2010) Obesity and onset of significant depressive symptoms: results from a prospective community-based cohort study of older men and women. J Clin Psychiatry 71(4):391–399

Vogelzangs N, Comijs HC, Oude Voshaar RC, Stek ML, Penninx BW (2014a) Late-life depression symptom profiles are differentially associated with immunometabolic functioning. Brain Behav Immun 41:109–115

Vogelzangs N, Beekman AT, van Reedt Dortland AK, Schoevers RA, Giltay EJ, de Jonge P, Penninx BW (2014b) Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. Neuropsychopharmacology 39(7):1624–1634

Voican CS, Martin S, Verstuyft C, Corruble E, Perlemuter G, Colle R (2016) Liver function test abnormalities in depressed patients treated with antidepressants: a real-world systematic observational study in psychiatric settings. PLoS One 12(5):11

Wahlbeck K, Westman J, Nordentoft M, Gissler M, Munk Laursen T (2011) Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. Br J Psychiatry 199:453–458

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart MA (2005) Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353:2335–2341

Wassertheil-Smollers S et al (2004) Depression and cardiovascular sequelae in postmenopausal women. Arch Intern Med 164:289–298

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:e002373

Whooley MA (2006) Depression and cardiovascular disease. JAMA 295:2874–2881

Wingo AP, Harvey PD, Baldessarini RJ (2009) Neurocognitive impairment in bipolar disorder patients: functional implications. Bipolar Disord 11:113–125

Yeung CK, Chan HH (2004) Cutaneous adverse effects of lithium: epidemiology and management. Am J Clin Dermatol 5:3–8

Young RC, Murphy CF, Heo M, Schulberg HC, Alexopoulos GS (2006) Cognitive impairment in bipolar disorder in old age: literature review and findings in manic patients. J Affect Disord 92:125–131

Zhu K, van Hilten JJ, Marinus J (2016) Associated and predictive factors of depressive symptoms in patients with Parkinson's disease. J Neurol 263:1215–1225

Cognitive and Neuropsychiatric Screening Tests in Older Adults

15

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Abstract

A number of instruments are available to clinicians to assess cognitive and neuropsychiatric features of neurocognitive disorders in older adults, from preclinical and prodromal stages through to more severe stages of dementia. This chapter provides a comprehensive overview and discussion of the key characteristics to consider when selecting a screening instrument to support accurate and timely assessment of cognitive changes and neuropsychiatric symptoms, both of which are core features of neurocognitive disorders. Particular consideration must be given to factors such as the assessment setting (e.g., acute care versus residential care environment), the population for which a measure was developed, and the context in which the instrument was validated. When selecting an instrument, clinicians must also consider possible population-based bias effects as a result of use in culturally and linguistically diverse populations or due to differences in educational attainment. Improving understanding of the diversity in measures available to assist clinicians in differing care contexts is fundamental so that the best possible care and treatment plans can be implemented, and better support provided to next of kin and caregivers (both formal and informal caregivers).

Keywords

Cognitive screening instruments • Dementia • Mild cognitive impairment • Cognitive impairment • Neuropsychiatric symptoms • Mild behavioral

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_16

impairment • Behavioral and psychological symptoms of dementia • Neurocognitive disorders

Contents

Introduction

Early Detection of Neurodegenerative Disease

Early identification of neurodegenerative disease allows for earlier intervention with the aim of modifying disease course. By and large, disease-modifying agents in neurodegenerative diseases have not been successful in treating cognitive and functional decline, in part due to poor signal detection and advanced pathology at time of trial enrollment (Gauthier et al. 2016). Thus, there are great efforts to identify earlier, people with neurodegenerative disease, in order to administer secondary prevention interventions. These include pharmacological and non-pharmacological treatments. Historically, dementia screening focused extensively on cognitive tests, especially in the domain of memory, but evidence is emerging that neuropsychiatric symptoms and other neurological functions may manifest early in disease course and be additional targets for screening to improve diagnostic accuracy (see below).

Importance of Cognitive Screening

There are several reasons supporting the use of cognitive screening in older adults. First, as mentioned, earlier identification of neurodegenerative disease allows for earlier intervention across the whole host of treatment modalities. It is at this stage that non-pharmacological interventions have the greatest likelihood of impacting

outcomes. Lifestyle changes, including increasing exercise, decreasing inflammatory burden in diet, optimizing risk factors, optimizing weight, and increasing social activity are more likely to improve quality of life and outcomes earlier in the course of neurodegenerative disease (Baumgart et al. 2015). In the context of routine clinical care, it is therefore important to preselect at risk individuals and administer cognitive screening interventions to them. Second, implementation of cognitive screening is the first step toward a dementia diagnosis. Early identification of neurodegenerative disease is important as it allows for the implementation of support structures to help family members and caregivers to better understand the changes in behavior and function being experienced by their loved ones. Finally, the implementation of systematic cognitive screening is also important in terms of forward care planning. Early identification of cognitive impairment as a result of cognitive screening means provisions to ensure legal documentation such as powers of attorney, personal directives, and last will and testaments have been drafted or are up-to-date (Ismail et al. 2010). However, it is important that cognitive screening test scores are not over-interpreted, rather, that they are used to direct further investigations and discussion.

Cognitive Screening Basic Principles

Detecting cognitive impairment, or ruling it out, is the most important role of a cognitive screening instrument. If mild cognitive impairment (MCI) is detected, a scale should be able to prognosticate dementia, bearing in mind that brief screening instruments are prone to false positives for MCI (Klekociuk et al. 2014). When significant cognitive impairment is detected, an ideal scale would be able to distinguish between different types of dementia or help narrow the differential diagnosis. Finally, as well as indicating dementia severity, measuring change over time is an important feature of a screening instrument. Changing nomenclature and definitions of cognitive syndromes complicates the interpretation of cognitive screening. Specifically, with the emergence of DSM-5-defined mild and major neurocognitive disorders, traditionally used instruments may have different psychometric properties compared to their performance in detecting MCI or dementia (Heinik and Kavé 2015).

Features of an Ideal Instrument

Ideally, a cognitive screening instrument should be easy to administer and acceptable to both the patient and family members. Instruments should be valid and reliable, measure change over time, and not be biased by language, education, or culture.

It is also important to consider the setting in which the measure will be implemented, as this will also determine the utility of a specific cognitive screening instrument. In primary care, shorter and less costly instruments are more useful given time constraints. However, in specialist care longer and more detailed instruments

are more likely to be used. Longer instruments provide a more comprehensive assessment, which facilitates the development and implementation of a treatment plan. Irrespective of the type of measures used in the different settings, the same principles apply in terms of validity and reliability. A survey of psychogeriatric clinicians determined that effectiveness, ease of administration, and speed of administration as being the main characteristics of instruments which were most correlated with frequency of use by clinicians (Ismail et al. 2013b). It was therefore concluded that these features are, in part, drivers of use of specific cognitive screening instruments (Ismail et al. 2013b). The following sections will describe a number of commonly used cognitive screening instruments.

Cognitive Screening Instruments

Historically, the most frequently used cognitive screening instrument has been the Folstein ***Mini-Mental State Exam*** (MMSE) (Folstein et al. 1975). When published it was a great advancement in cognitive screening, operationalizing assessment, and dividing the process of cognitive screening into the domains of orientation, registration, attention and calculation, recall, and language. The MMSE has proven to be resilient in clinical and research use, but in the context of becoming a pay-per-use instrument, identification of limitations in its interpretation, and the emergence of viable alternatives, it may no longer be the "gold standard" for cognitive screening. The MMSE performs optimally for ruling out dementia, but it does not perform adequately as a case-finding tool (Mitchell 2013). Notably, recent Cochrane reviews have determined that the MMSE should not be used in isolation to confirm or exclude neurocognitive disease (Creavin et al. 2016), nor should the MMSE stand as a single-administration test to identify MCI patients who are at risk of developing dementia (Arevalo-Rodriguez et al. 2015).

A number of alternatives to the MMSE have emerged and are the focus of extensive research and investigation. In an International Psychogeriatric Association survey of cognitive screening instruments administered in 2004, 92% of respondents used the MMSE often or routinely (Shulman et al. 2006). A primary care survey administered in 2007 found the MMSE and variants thereof were used most frequently (76%), with the Montreal Cognitive Assessment (MoCA) being used by 5% of respondents (Iracleous et al. 2010). A significant shift in use of cognitive screening instruments was observed by 2010, when it was found, that specialists were using the CDT more often than the MMSE, followed by the MoCA, which was used often or routinely by 80% of survey respondents (Ismail et al. 2013b).

***The clock-drawing test* (*CDT*)** is an extremely simple to administer test that assesses the ability to draw the numbers and hands on a clock, with one hand as a concrete representation of the hour and the second hand as an abstract representation of minutes (Shulman 2000). The CDT has been studied extensively and used independently in addition to being subsumed under other instruments such as Mini-Cog, Addenbrooke's cognitive exam (ACE), and the MoCA. Diagnostic

accuracy of the CDT for dementia is increased when combined with activities of daily living (ADL) questionnaire (Satukijchai and Senanarong 2013). For detecting MCI, the CDT has greater specificity when combined with other tools such as the MMSE (Rubínová et al. 2014) but is likely to be insufficient when used on its own to reliably screen for MCI (Ehreke et al. 2011). A very recent review assessed longitudinal CDT studies to assess its utility in monitoring decline in cognitive function over time as well as predicting incident dementia in older adults with normal cognition or MCI. Study consensus suggested that time misrepresentation detected cognitive decline most effectively. Additionally, the CDT appears to differentiate at baseline, cognitively intact older adults who will develop dementia up to 2 years later, and MCI individuals who will progress to dementia up to 6 years later (Amodeo et al. 2015). Thus the CDT is a simple cost-effective way to prognosticate dementia and monitor change over time, thus explaining this simple test's penetration into multiple screening assessment methods.

In recent years, the most studied cognitive screening instrument has been the *Montreal* ***Cognitive Assessment*** **(*MoCA*)** (Nasreddine et al. 2005). Initially developed as a screening instrument to detect MCI, which the MMSE could not do with good sensitivity and specificity, the MoCA is now used for all stages of cognitive impairment, across numerous disease states including FTD (Freitas et al. 2012) and vascular cognitive impairment (Koski 2013). The MoCA has demonstrated convergent validity with existing screening tools and global measures of cognition, as well as criterion validity, with highest sensitivity in the domains of memory, executive, and visuospatial functions (Lam et al. 2013). While the original cutoff score for detecting cognitive impairment was <26, recent literature suggests a lower score may be more specific. In a subsequent validation study of the MoCA including 90 participants with MCI and 90 with AD, as well as 180 controls, the MoCA showed consistently superior psychometric properties compared with the MMSE. At an optimal cutoff <22 for MCI and <17 for AD, the MoCA achieved significantly superior values in comparison with the MMSE for sensitivity, specificity, positive predictive value, negative predictive value, and classification accuracy. The MoCA also revealed higher sensitivity to cognitive decline in longitudinal monitoring (Freitas et al. 2013).

A pragmatic prospective study of 150 memory clinic patients compared the MMSE to the MoCA. The MoCA was more sensitive than the MMSE (0.97 vs. 0.65) but less specific (0.60 vs. 0.89) with greater area under the receiver operator characteristic (ROC) curve. Utilizing a cutoff of <20 maximized MoCA accuracy, improving specificity to 0.95, but at the expense of sensitivity (0.63) (Larner 2012). This cutoff is similar to an optimal cutoff of <21, determined in a validation study in a veteran population (Waldron-Perrine and Axelrod 2012). However, the MoCA is subject to education bias, despite the 1-point corrective factor for education of fewer than 12 years. Furthermore, a Chinese validation study determined cutoff points based on education with optimum cut points of 13/14 for illiterate individuals, 19/20 for those with 1–6 years of education, and 24/25 for individuals with 7 or more years of education (Lu et al. 2011). Thus in summary, it can be said that the MoCA is a useful tool with a relatively short administration time and significant utility in

cognitive screening in a number of settings, with the advantage of being free and readily available (www.mocatest.org).

The Veterans Affairs ***Saint Louis University Mental Status* (*SLUMS*)** *exam* is a 30-point screening test that assesses orientation, memory, attention, and executive function, and initially demonstrated superiority to the MMSE for detecting mild neurocognitive disorder (Tariq et al. 2006). Similar to the MoCA, the SLUMS incorporates five-word recall and the CDT. In a study of veterans over the age of 60 with at least a high school education, the SLUMS performed comparably to the MoCA. Using the Clinical Dementia Rating (CDR) scale as a reference standard, area under the ROC curve for MCI was 0.74, for the SLUMS examination 0.74, and 0.77 for the MoCA. For dementia, SLUMS AUC was 0.98 and MoCA 0.96 (Cummings-Vaughn et al. 2014). The Rapid Cognitive Screen (RCS) is a very brief (<3 min) tool derived from the SLUMS. The three items of the RCS include five-word recall, clock-drawing test, and story recall. In a study of 702 participants, ages 65–92, the RCS demonstrated very good psychometric properties for detection of cognitive impairment, given its rapid administration time. For dementia sensitivity was 0.89 and specificity 0.94, and for MCI, sensitivity was 0.87 and specificity 0.70 (Malmstrom et al. 2015).

***Addenbrooke's Cognitive Exam* (*ACE*)** is a screening tool that is frequently used in specialty care. It may also have great utility in other settings when briefer instruments are inconclusive. ACE was developed to detect mild dementia and differentiate AD from FTD and takes 15–20 min to administer. ACE incorporates and expands on the MMSE and adds assessments of episodic memory, phonemic and categorical fluency, perceptual ability, and clock drawing. ACE has good psychometric properties for dementia detection with sensitivity of 93% at a cutoff of 88 and 82% at a cutoff of 83. Using a ratio of verbal fluency + language/orientation + memory, ACE also differentiates between AD and FTD (Mathuranath et al. 2000). A systematic review of screening tools for predicting the development of dementia recommended the ACE based on its psychometric properties, especially high specificity (Lischka et al. 2012). In order to improve sensitivity, cross-cultural use, and ease of administration, ACE was revised to ACE-R. The naming component was improved to address ceiling effects in ACE, and the visuospatial component was expanded as well. Two cutoffs were defined (88, sensitivity = 0.94, specificity = 0.89; 82, sensitivity = 0.84, specificity = 1.0). The ACE-R generates five domain subscores and has three alternative versions (Mioshi et al. 2006).

However, the use of ACE-R has also highlighted areas of relative weakness, stemming specifically from its MMSE roots. For example, the verbal repetition item ("no ifs, ands, or buts") has low sensitivity and specificity. Failure on this item might be related to poor hearing or attention or due to cultural bias. Measures of comprehension (such as the three-stage command and "close your eyes") lack sensitivity to cognitive impairment with performance often at ceiling. The equivalent use of "world" backward and serial 7 s also affects psychometric properties due to differences in difficulty (Hsieh et al. 2013).

Furthermore, although dementia and depression have different cognitive profiles (Ting et al. 2010), clinicians often have difficulty distinguishing dementia from

late-life depression (Ismail et al. 2014). ACE-R may have a role in differentiating between severe depression and AD, based on a study of 295 older adults. In participants with severe late-life depression, ACE-R scores reflected milder memory impairment and greater deficits in letter fluency versus semantic fluency, compared to participants with AD (Rotomskis et al. 2015).

A newer version of ACE has been developed (ACE-III) and has demonstrated validity in AD and FTD, with comparable performance with its predecessor (Hsieh et al. 2013). Whether or not the ACE-III is culturally sensitive and avoids ceiling effects is yet to be fully determined. However, early experience with the ACE-III demonstrates excellent accuracy for dementia detection in day-to-day clinical practice (Jubb and Evans 2015). However, it must be noted that this was the case when lower cutoffs than specified in the index paper were used and that there is a need to consider education years in order to optimize diagnostic performance (Jubb and Evans 2015).

A mini-ACE (M-ACE) has also been developed using the orientation, address registration and recall, animal fluency, and letter identification items from ACE. This mini-ACE is much briefer to administer and scored out of 30. A validation study in a heterogeneous dementia population found the M-ACE to be more sensitive than the MMSE in detecting all-cause dementia and that also was linked to a lower likelihood of ceiling effects (Hsieh et al. 2014).

Brief Screening Instruments

A number of very brief screening tools may serve as alternatives to the MMSE based on comparable scale performance. The ***Mini-Cog*** is remarkably simple to administer and combines the CDT with three-word recall in a two-step algorithm (Borson et al. 2000). The Mini-Cog was shown to have comparable psychometric properties to the MMSE, but is less confounded by language and education (Borson et al. 2005). A German memory clinical study assessed utility of the Mini-Cog in comparison to the MMSE and CDT in an analysis of 502 participants. For all age and educational groups, the Mini-Cog outmatched the CDT and MMSE and was less affected by education than MMSE and less susceptible for the dementia stage than the CDT (Milian et al. 2012). In a large validation study of 8,063 veterans with no previous diagnosis of cognitive impairment, multiple versions of the Mini-Cog were utilized including five different three-word lists and three different clock times. Additionally, the cutoff score was increased to 4/5 (i.e., correct time and 2/3 words correct) to increase sensitivity. While scores declined with age, age did not predict pass or fail. Of note, ~26% of participants failed the screening, with choice of word lists producing different screen failure rates (McCarten et al. 2011). While very well tolerated and easy to administer, Mini-Cog version choice may influence results, reminding clinicians and researchers that even subtle changes in instrument construction and administration can affect scores, and not all versions are necessarily comparable. More research is required in this regard.

Developed as an alternative to the MMSE, the ***Sweet 16*** has no need for props, such as pen, paper, or special forms, and takes 2–3 min to administer. The Sweet

16 consists of questions on orientation, three-word registration, digit span, and recall. The performance of the Sweet 16 was comparable to the MMSE across all levels of education (Fong et al. 2011).

The ***General Practitioner Assessment of Cognition* (*GPCOG*)** was designed for primary care and combines tests of learning and memory with a CDT (Brodaty et al. 2002). Despite being very memory focused, the GPCOG benefits from embedding a six-item informant questionnaire, of which three items assess impairment in instrumental ADL (IADL) function (finances, medication, and transportation). The addition of informant information may improve psychometric properties of this easy to administer test.

Importance of Brief Screening Instruments for Acute Settings

In very acute settings, like an emergency department (ED) or acute inpatient ward, very brief instruments are more likely to be used. A study of 163 geriatric ED patients compared the ***Ottawa 3DY* (*O3DY*), *Brief Alzheimer's Screen* (*BAS*), *Short Blessed Test* (*SBT*)**, and caregiver-completed ***AD8*** (cAD8), in comparison to the MMSE ($\leq$23) as the criterion standard. Of these instruments, the SBT provided the optimal overlap with the MMSE, and the addition of the cAD8 did not enhance diagnostic accuracy (Carpenter et al. 2011). A very brief informant-rated instrument, ***Dementia* = (*MC*)^2**, may also have utility in the ED. Derived from the Clinical Dementia Rating (CDR) Scale , this instrument consists of only four questions on memory, consistency of memory difficulties, financial abilities, and comprehension. Dementia = $(MC)^2$ demonstrated excellent psychometric properties for detecting MCI or dementia and has potential to identify patients who warrant further cognitive evaluation in busy clinical settings (Douglas et al. 2011).

Addressing Bias in Cognitive Screening

While cognitive screening instruments have normative values that are based on their validation sample, certain populations may not be well represented in the sample due to differences in language, education, and culture. Testing in these populations may be susceptible to false positives and false negatives. Some instruments have been designed to minimize the bias and may be more appropriate in a culturally diverse population or in those with limited education.

An a priori development protocol that included multicultural input on cultural appropriateness of items resulted in the ***Rowland Universal Dementia Assessment Scale* (*RUDAS*)** being the most studied instrument for diverse populations. This instrument is scored out of 30 and assesses the domains of memory (four-item grocery list), gnosis (body orientation), praxis (fist-palm alternating task), visuospatial function (cube copying), judgment (street crossing scenario), and language (animal fluency). A cut point of 23 has a sensitivity of 89% and specificity of 98% in the original validation sample (Storey et al. 2004). A systematic review and meta-

analysis assessed the psychometric properties of the RUDAS to reference standards in 1,236 participants. Pooled sensitivity was 77.2% and pooled specificity was 85.9%, with the RUDAS less affected by language and education than the MMSE (Naqvi et al. 2015). The RUDAS has successfully been translated into Chinese (Chen et al. 2015) and combined with the caregiver-rated Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) to detect dementia in an Arabic-speaking population (Nielsen et al. 2015).

A New Zealand study assessed performance of the RUDAS, MoCA, and ACE-III as alternatives to the MMSE for detecting dementia. All three instruments had comparable diagnostic accuracy, but the data-derived optimal cutoffs were lower for the MoCA and ACE-III than in published recommendations (Cheung et al. 2015).

The ***Visual Cognitive Screening Test*** **(*VCAT*)** was developed specifically to minimize cultural bias in cognitive testing and allow for administration irrespective of language without translation or adaptation. Unambiguous and culturally neutral pictures were identified from the International Picture Naming Project. Shortlisted pictures were then used to construct test items in the five cognitive domains of memory, executive function, visuospatial function language, and attention. The VCAT has been validated for detection of MCI and dementia with sensitivity and specificity comparable to the MoCA, with an administration time of approximately 15 min (Kandiah et al. 2016).

The ***Phototest*** **(*PT*)** is a very simple and short instrument (<3 min), not influenced by level of education that can be applied to illiterates to assess multiple cognitive fields (language, executive function, episodic memory). It comprises three parts: a naming task with six color photographs of common objects in prototypic position, a verbal fluency test (names of people) demonstrated to be uninfluenced by educational level, and free recall and recall facilitated by cues using the six objects in the naming test. There are two parallel versions of the test. Version A is usually applied in Spain, but version B is more suitable in English-speaking countries because the first two objects in version A are virtually homophonous in English (cards, car) (Carnero-Pardo et al. 2011). In an Argentinian validation, the diagnostic accuracy of the PT for a-MCI and AD was shown to be 0.93 and 0.97 [UAC], respectively, and was higher than that of the MMSE and the CDT. The optimal cutoffs were 27/28 for AD (sensitivity = 89.29, specificity = 96.67) and 30/31 for a-MCI (sensitivity = 85.25, specificity = 90.00) (Russo et al. 2014).

Accessibility Issues in Cognitive Screening

While face-to-face cognitive testing is considered ideal, it is not always accessible or feasible. Telephone cognitive testing may be an alternative to in-person testing. Telephone cognitive testing has shown promise and may have applications in clinical care and research, but further validation is still required (reviewed in Castanho et al. 2014).

Similarly, computerized cognitive testing may also address accessibility issues, but further research is needed to assess its utility in cognitive screening. A recent

review suggested caution in implementing computerized cognitive testing. The authors stated that the psychometric quality, standardization, normative data, and administration advice of computerized cognitive testing for neurocognitive disorders are lacking (Gates and Kochan 2015).

A newly developed propriety test, called the ***Cognitive Assessment for Dementia*** iPad version (CADi), does hold promise as a new screen for dementia. The CADi consists of items involving immediate recognition memory for three words, semantic memory, categorization of six objects, subtraction, backward repetition of digits, cube rotation, pyramid rotation, trail making A, trail making B, and delayed recognition memory for three words. It has thorough psychometric analysis which revealed large concurrent validity with the MMSE and internal consistency (Onoda et al. 2013).

The ***CogState Brief Battery (CBB)*** is a computerized proprietary screening tool that may address issues of access to clinical care, unstandardized administration, test-retest reliability, and cultural bias. The CBB, administered in approximately 10 min, is based on a card-playing paradigm and generates composite scores in the domains of learning/working memory and attention/psychomotor speed. The CBB has demonstrated utility in detecting MCI and AD, with optimal performance with cutoffs on the learning/working memory of −1 SD for MCI and −1.7 SD for AD (Maruff et al. 2013).

The ***Test Your Memory (TYM)*** screen (Hancock and Larner 2011) and the ***Self Test*** (de Leonni Stanonik et al. 2005) are both very brief screens and self-administered under supervision which may identify quickly patients with cognitive impairment. The Self Test has a computerized derivative (CST), which has demonstrated utility in assessing cognitive impairment and addressing accessibility issues to clinical cognitive testing. The CST is an interactive internet-based tool designed to assess cognitive domains impaired by AD and MCI. In a study of 215 participants, the CST outperformed both the MMSE and the Mini-Cog, accurately classifying 96% of the cognitively impaired individuals (versus controls), compared to 54% for the MMSE and 48% for the Mini-Cog (Dougherty et al. 2010).

Longer and more involved than TYM or ST, the ***Self-Administered Gerocognitive Exam (SAGE)*** has demonstrated promise in detecting cognitive impairment in community settings. In a study of 1,047 community-dwelling adults, principal component and correlation analysis indicate that SAGE is an internally consistent test that is very well balanced, with language, cognition, visuospatial, executive, and memory domains (Scharre et al. 2014).

Caregiver-Rated Scales

While impairment in basic activities of daily living function (BADLs) are the hallmark of dementia, more subtle functional impairments are often seen in MCI. Assessment of function may offer insights into the development of neurodegenerative disease, and caregivers may have a role in this assessment. Informants are sensitive to subtle early cognitive change in individuals with MCI, and their ratings are related to objectively measured neuropsychological performance (Tsang et al. 2012).

Mild IADL changes can be predictive of future cognitive decline, but more sensitive and reliable questionnaires are required (Gold 2012).

Both the MoCA and MMSE have demonstrated improved diagnostic accuracy when combined with an informant-based functional measure (Roalf et al. 2013). Similarly, a Brazilian primary care study in persons with little education demonstrated that adding the Functional Assessment Questionnaire to a simple cognitive screening tool, such as category verbal fluency or the CDT, resulted in excellent psychometric properties compared to using the instruments alone (Jacinto et al. 2014). The *AD8* is a simple eight-item caregiver questionnaire assessing whether there has been a change in function or cognition over the last several years. The AD8 queries judgment, apathy, date orientation, financial matters, and memory (Galvin et al. 2005).

***The Informant Questionnaire on Cognitive Decline in the Elderly* (*IQCODE*)** is a 26-item scale that queries an informant's opinion on multiple aspects of cognition at the time of assessment compared to 10 years previously. Initial validation demonstrated that the IQCODE performed at least as well as the MMSE in detecting dementia (Jorm et al. 1991). In a study of 186 patients in a community neurology practice, both the AD8 and IQCODE were able to detect dementia. The AD8, however, was more successful than IQCODE in detecting MCI (Razavi et al. 2014).

The ***Instrumental Activities of Daily Living – Compensation scale* (*IADL-C*)** is a novel approach to functional assessments. The instrument captures early functional difficulties and quantifies compensatory strategies that precede overt functional impairment. For example, the questionnaire assesses the use of aids such as mnemonics, lists, and GPS devices in addition to performance on IADLS. These informant-rated scale queries function in the domains of money and self-management, home daily living, travel and event memory, and social skills. The IADL-C total score and subscales show convergent validity with other IADL measures, discriminant validity with psychosocial measures, and the ability to discriminate between diagnostic groups. Of note, the money and self-management subscale showed notable difficulties for individual with MCI (Schmitter-Edgecombe et al. 2014). The IADL-C is a promising scale, which may contribute to the early detection of early neurodegenerative disease. With little burden on clinical resources, the IADL-C warrants further exploration.

Neurological and Neuropsychiatric Screening

Noncognitive Aspects of Neurodegeneration

It is also important to consider later-life changes in neurological function as potential indicators of neurodegenerative disease, even in advance of obvious or overt cognitive impairment. Increasingly, evidence supports noncognitive symptoms as possible early indicators of neurodegenerative disease. These noncognitive symptoms include sensory and motor changes such as slowing of gait (Del Campo et al. 2016), changes in oculomotor function (Hellmuth et al. 2012; Ladas et al. 2014), loss of hearing (Lin et al. 2011), and olfactory changes (Stanciu et al. 2014).

Assessment of neurological function can be part of a neurodegenerative screening visit, and even a simple assessment of the palmomental reflex can improve diagnostic accuracy of the basic cognitive screening tests (Streit et al. 2015).

Neuropsychiatric symptoms (NPS) are very important components of dementia and neurodegenerative disease. NPS in dementia are associated with greater caregiver burden, higher rates of institutionalization, and faster cognitive decline in greater neuropathological burden (Ismail et al. 2016). While late-life depression has long been considered a risk factor for and/or early indicator of dementia (Ismail et al. 2014), evidence suggest other NPS may also be important (Lanctôt et al. 2016). NPS can be present at initial diagnosis of dementia and impact outcomes in mild cognitive impairment (MCI), with the presence of NPS conferring greater cognitive and functional burden and incidence of dementia (Rosenberg et al. 2013). Further, later-life NPS in advance of cognitive impairment have been shown to increase risk of cognitive decline and incident dementia, with the syndrome of mild behavioral impairment operationalizing the measurement and assessment of these later-life onset NPS (Ismail et al. 2016). In addition to affecting the course of cognitive decline, NPS also affect function. A recent analysis of a longitudinal study of older adults at the University of California Davis Alzheimer's Disease Center demonstrated the impact of NPS on function. In an assessment of 344 older adults, cognitive performance, as well as ratings of depressive symptoms and apathy, all made largely independent contributions to informant-based ratings of functional capacities in older adults (Rog et al. 2014). Findings such as these highlight the importance of assessing NPS when screening older adults for neurodegenerative disease and when monitoring them over time.

Neuropsychiatric Symptoms Screening: Basic Principles

NPS represent an important clinical dimension of neurocognitive disorders and prodromal states (e.g., MCI). NPS are typically brought to the attention of clinicians by concerned family members or healthcare providers, usually after an extreme behavioral event, or when troublesome behaviors persistently disrupt the provision of care or compromise safety (patient or caregiver) (Gitlin et al. 2014). Nonetheless, NPS typically remain under-identified and thus undertreated in clinical settings. According to Gitlin et al. (2014) this may in part be due to a lack of understanding by health professionals of the importance of monitoring behavioral symptoms as well as a lack of adequate assessment tools to detect such behaviors.

Accurate and timely identification of NPS, using reliable and validated instruments, is fundamental to ensure appropriate diagnosis and treatment. The Physician Consortium for Performance Improvement (PCPI) suggests that people with dementia should be assessed for NPS on a yearly basis; however, there are currently no clear guidelines to advise on which measures should be used, how behaviors should be assessed, and who should be assessing them (Odenheimer et al. 2013; Gitlin et al. 2014). Furthermore, it is also not clear to what extent this recommendation is currently being practiced by clinicians (Gitlin et al. 2014).

In fact, a recent review by Kales et al. (2015) concluded that while there are numerous measures to assess NPS, these are infrequently used in clinical settings to guide NPS management.

Neuropsychiatric Symptoms Assessment

A number of caregiver and clinician-rated measures of NPS are available to assist with the variable needs of clinicians and researchers when assessing behaviors. The variety of measures available may in part reflect a lack of consensus as to what constitutes NPS and how behaviors should be identified, characterized, classified, and assessed (Gitlin et al. 2014). Measures differ in terms of the focus of what is assessed (e.g., symptoms of a particular NPS domain or symptom domains), scale properties such as the targeted informant (e.g., caregiver, clinician, patient), and the rating approach used (e.g., rating frequency, severity, or other) (de Medeiros et al. 2010). Additionally scales can detect the presence of symptoms and their response to treatment differently and may be selected based on the anticipated effect size of treatment. In a pharmacological trial of agitation in dementia, the **Empirical Behavioral Rating Scale** (**EBRS**), **the Neurobehavioral Rating Scale** (**NBRS**), and the **Neuropsychiatric Inventory** (**NPI**) performed differently. The instruments were equally likely to detect agitation. The NBRS was most likely to detect psychosis. Although the NPI best detected improvement in agitation, the instruments were equal for detecting improvement in psychosis. In the receiver operating characteristic analysis for overall clinical improvement in response to treatment, there were no differences in the areas under the correlated curves for the three instruments, but they demonstrated different sensitivity and specificity at different cutoff points for target symptom reduction (Ismail et al. 2013a).

In a systematic review of 45 commonly used measures of NPS (16 general behavior scales and 29 specific behavior scales; see Table 1 for summary) with established validity and/or reliability, Gitlin et al. (2014) concluded it was not possible to indicate whether one measure is superior to another. It is therefore recommended that selection and use of a measure to assess NPS should be context specific and dependent on a number of key factors. Accordingly, the selection of a measure to assess NPS should be guided by the purpose of measurement (i.e., is there a need for a general screen of NPS or a more targeted behavioral assessment; the setting in which the assessment will be complete; who will assess the behaviors and how the assessment will be conducted (e.g., observation, proxy interview); and the amount of time and resources available to assess the behaviors) (Gitlin et al. 2014). Clinicians should therefore start with a general measure of NPS (e.g., Neuropsychiatric Inventory) which serves as an all-purpose screen for a wide variety of behavioral symptoms. Based on the findings of such a general screen, specific behavior-targeted measures can then be used in follow-up assessments to provide greater specificity with regard to the type of behaviors manifested so that a more nuanced understating of the presenting behavior can be obtained (Gitlin et al. 2012, 2014). The following section describes a subsample of commonly used measures.

Table 1 Global and specific measures used in the assessment of NPS (Adaptation from Gitlin et al. 2014)

	Number of domains	NPS domains assessed
Global measures		
Alzheimer's Disease Assessment Scale Non-Cog	10	Tremors, pacing, motor restlessness, tearfulness, depression, delusions, hallucinations, appetite, concentration, and uncooperativeness
Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)	7	Delusions, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxiety/phobia
Behavioral Syndromes Scale for Dementia (BSSD)	5	Disinhibition (including agitation, aggression, and wandering), catastrophic reactions, apathy indifference, sundowning, and denial
CERAD Behavior Rating Scale for Dementia (BRSD)	8	Depressive features, psychotic features, defective self-regulation, irritability/agitation, vegetative features, apathy, aggression, and affective lability
Clinical Dementia Rating Scale (CDR)	6	Memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care
Computer-assisted Behavioral Observation Systems (CABOS)	1	Disruptive vocalization, but could be applied to other behaviors too
Dementia behavior Disturbance Scale (DBS)	6	Passivity, agitation, eating disturbances, aggressiveness, diurnal rhythm disturbances, and sexual misdemeanor
Dementia Signs and Symptoms Scale (DSS)	8	Anxiety, mania, depression, restlessness, social disruptiveness, aggressiveness, delusions, and hallucinations
Frontal System Behavior Scale (FrSBe)	3	Apathy, disinhibition, and executive dysfunction
Key Behavior Change Inventory (KBCI)	8	Inattention, impulsivity, unawareness of problems, apathy, interpersonal difficulties, communication problems, somatic difficulties, and emotional adjustment
Multidimensional Observation Scale for Elderly Patients (MOSES)	5	Self-care, disoriented behavior, depressed/anxious mood, irritable behavior, and withdrawn behavior
The Neurobehavioral Rating Scale (NRS)	6	Cognition, agitation/disinhibition, behavioral retardation, anxiety/depression, verbal output disturbance, and psychosis
Neuropsychiatric Inventory (NPI) Cummings et al. (1994)	12	An informant-rated assessment of the presence, frequency, and severity of ten neuropsychiatric symptom domains of delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety,

(*continued*)

Table 1 (continued)

	Number of domains	NPS domains assessed
		irritability, disinhibition, euphoria, apathy, and aberrant motor behavior and two neurovegetative domains of sleep and nighttime behavior change and appetite/eating change. The NPI also assesses caregiver distress associated with each of the 12 domains
Neuropsychiatric Inventory – Clinician (NPI-C)	13	A clinician-rated version of the NPI in which they assess the presence, frequency, and severity of the 12 NPI domains (see above) as well as aberrant vocalization and caregiver distress
Neuropsychiatric Inventory – Questionnaire (NPI-Q)	12	An informant-rated version assesses only the presence and frequency of the 12 NPI domains (see above) and caregiver distress
Nurses' Observation Scale for Geriatric Patients (NOSGER)	6	Memory, instrumental activities of daily living, activities of daily living, mood, social behavior, and disturbing behavior
The Nursing Home Behavior Problem Scale (NHBPS)	6	Uncooperative or aggressive, irrational or restless, sleep problems, annoying, inappropriate, and dangerous
Revised Memory and Behavior Problem Checklist (RMBPC)	3	Memory-related problems, depressive problems, disruptive problems, as well as caregiver reaction
Specific measures		
Agitation		
Agitated Behavior in Dementia Scale (ABID)		
Brief Agitation Rating Scale (BARS)		
Cohen-Mansfield Agitation Inventory (CMAI)		
Disruptive Behavior Rating Scales (DBRS)		
Overt Agitation Scale (OASS)		
Pittsburgh Agitation Scale (PAS)		
Scale for the Observation of Agitation in Persons with Dementia of the Alzheimer's Type (SOAPD)		
Apathy		
Apathy Evaluation Scale (AES)		
Apathy Inventory (IA)		
Dementia Apathy Interview and Rating Scale (DAIR)		
Irritability-Apathy Scale (IAS)		
Lille Apathy Rating Scale (LARS)		
Aggression		
Aggressive Behavior Scale (ABS)		
Overt Aggression Scale (OAS); also available as the Modified Overt Aggression Scale (MOAS)		

(*continued*)

Table 1 (continued)

	Number of domains	NPS domains assessed
Rating Scale for Aggressive Behavior in the Elderly (RAGE)		
Ryden Aggression Scale (RAS)		
Anxiety		
Beck Anxiety Inventory (BAI)		
Geriatric Anxiety Inventory (GAI); also available in short form (CAI-SF)		
Rating Anxiety in Dementia (RAID); structured interview also available		
The Worry Scale		
Depression		
Cornell Scale for Depression in Dementia (CSDD)		
The Dementia Mood Assessment Scale (DMAS)		
The Geriatric Depression Scale (GDS)		
Patient Health Questionnaire-9 (PHQ-9)		
Sleep		
Epworth Sleepiness Scale (ESS)		
Pittsburgh Sleep Quality Index (PSQI)		
The Sleep Disorders Inventory (SDI)		
Depression and Anxiety		
Hospital Anxiety and Depression Scale (HADS)		
Wandering		
Algase Wandering Scale (AWS)		

The **Neuropsychiatric Inventory (NPI)** (Cummings et al. 1994) is a well-known global assessment scale which is widely used in both research and clinical practice. The NPI is a structured informant interview with established reliability and validity (Cummings et al. 1994). Using the NPI, a clinician obtains a subjective assessment from the caregiver of the presence, frequency, and severity of ten neuropsychiatric symptom domains (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior) and two neurovegetative domains (sleep and nighttime behavior change and appetite/eating change). The informant also provides an assessment of the level of distress experienced by themselves in relation to the specific symptom domain. Several important methodological approaches to NPS are addressed by the NPI. These include: (1) items which are behavior based and observable, facilitating informant report of frequency and severity of symptoms; (2) items grouped into domains under a screening question in order to enable quick completion and interpretation of results; (3) items which are specific to populations with dementia; and (4) standardized rating of domain frequency, severity, and caregiver distress (de Medeiros et al. 2010).

While the NPI is the most applied measure to assess NPS, both in a clinical and research setting, there are a number of caveats associated with this measure which need to be considered. These include:

1. That data is acquired from the informant and not the patient, making the results susceptible to caregiver recall and interpretation bias. Reports may be influenced by caregiver mood, cultural beliefs, denial, and/or caregiver's education.
2. That there is unknown reliability of ratings for individual items compared to global domain ratings.
3. Few items which are specific to severe or mild dementia.
4. Limited depth of items in domains, making it difficult to use individual domains as stand-alone measures (e.g. individual assessment of depression or agitation).
5. Limited sensitivity to change compared to other measures which include clinician's assessment (de Medeiros et al. 2010; Stella 2013).

To address some of these limitations, de Medeiros et al. (2010) developed, in collaboration with J. L. Cumming, the original creator of the NPI, the **Neuropsychiatric Inventory – Clinician Rating Scale** (**NPI-C**). For this the NPI was restructured and expanded to include psychopathological items into multiple domains (Stella 2013). Additional items were added to the domains of dysphoria, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, and appetite and eating disorders (de Medeiros et al. 2010). The domains of delusion and hallucinations are the only two domains to remain unchanged. Importantly, the NPI domain of agitation/aggression was divided to represent the two separate domains of agitation and aggression (de Medeiros et al. 2010). Furthermore, a new domain of aberrant vocalization is included in the NPI-C, which is to be understood in the context of behavioral disturbance and which is more common in patients with severe dementia (de Medeiros et al. 2010). The NPI-C therefore consists of 14 psychopathological domains. A further significant change relates to the scoring of the NPI-C, which is now completed by the clinician. In the NPI-C, the clinician rates the severity of each item and each domain by drawing on information from caregiver reports, data from the patient interview, and direct observation of the patient's behaviors. If required, clinicians can also draw on clinical records to assist in their assessment.

The **Behavioral Pathology in Alzheimer's Disease** (**BEHAVE-AD**) (Reisberg et al. 1996) is a validated and reliable caregiver-rated measure used to assess behavioral disturbances in Alzheimer's disease patients. Caregivers provide information about the level of severity of behaviors over a 2-week period by completing a 25-item assessment. The BEHAVE-AD assesses seven major categories of behavior disorders, including paranoid and delusional ideation, hallucinations, disturbances of daily activities, aggression, sleep disturbances and circadian rhythm disorders, affective disorder, and anxiety or phobias. This measure allows for the assessment of whether behavioral disturbances are proving detrimental to the patient and the caregiver.

The **Cohen-Mansfield Agitation Index** (**CMAI**) (Cohen-Mansfield et al. 1989) is a frequently used clinician-rated measure which systematically assesses frequency of agitated psychopathological behaviors in elderly. The CMAI divides agitation into four subtypes: (1) physically nonaggressive behaviors (e.g., restlessness, pacing, mannerisms, hiding things, inappropriate dressing/undressing), (2) physically aggressive behaviors (e.g., hitting, pushing, scratching, biting kicking, and

grabbing), (3) verbally nonaggressive behaviors (e.g., negativism, repetitions, interruptions, constant request for attention), and (4) verbally aggressive behaviors (e.g., screaming, marking strange noises, cursing, and temper outbursts). It is primarily used in primary care settings and clinical sites; however its reliability has also been established in community-dwelling AD patients (Weiner et al. 2002).

The CMAI is based on clinician scoring based on subjective information provided by the caregiver of the frequency of agitated behaviors over a 2-week period. It is valid, reliable, and quick to administer, taking approximately 15 min. It does not assess psychosis, mood disturbances, negative symptoms (e.g., loss of initiative), or vegetative symptoms (e.g., sleep/wake disturbances, changes in eating patterns or appetite, incontinence) (Weiner et al. 2002). Later versions of the CMAI also include, in addition to the assessment of frequency of agitated behavior episodes, a description which considered whether these symptoms cause difficulty for patients and caregiver burden.

The **Cornell Scale for Depression in Dementia** (**CSDD**) (Alexopoulos et al. 1988) assesses the frequency and severity of depressive symptoms in patients with dementia over the previous week. Originally developed as a measure of depressive symptoms in dementia patient undergoing psychopharmacological treatment, the CSDD aims to quantify depressive symptoms and support clinical diagnosis.

The **Apathy Inventory** (**AI**) (Robert et al. 2002, 2010) is an effective measure used to assess the three apathy domains including: (1) a reduction or loss of affective and emotional reactivity, (2) a reduction or loss of cognitive interest or goal-directed activity, and (3) a reduction or loss of initiative or goal-directed behavior. Methodological strengths of the AI are reflected in its high level of accuracy (Stella 2013). Scoring of the AI is similar to the NPI-C and is based on caregiver responses; however the clinician ultimately decides on the scoring of the items and domains by rating the severity. The final score of the AI is determined by the clinician after considering the patient interview and the patient's reactions during the evaluation (Stella 2013).

While the **Global Deterioration Scale** (**GDS**) (Reisberg et al. 1982) was originally developed to measure cognitive decline and its impact on overall functioning of dementia patients, it can also be used to assess neuropsychiatric disturbances including aggressiveness, agitation, and disorganized behavior in advanced stages of dementia.

Diagnosis and treatment of co-occurring NPS also pose a major challenge to clinicians (Lyketsos and Miller 2012), as symptoms can occur individually or in combination, affecting an individuals' ability to perform everyday activities, thus reducing quality of life and increasing disease burden (Mortby and Anstey 2015). NPS can vary in severity, fluctuate over time, and occur episodically for limited time periods (Selbaek et al. 2014), making it, at times, more difficult for clinicians to observe and diagnose.

When selecting a measure to assess NPS, it is important to consider the setting and population in which a measure was validated, as a measure developed and validated for hospital use may not be appropriate for use in nursing home settings (Gitlin et al. 2014). Further important considerations when selecting a measure

include whether the measure requires clinical input. The majority of measures rely on proxy reports to assess NPS. However, challenges associated with the provision of care may affect caregivers (e.g., depression, caregiver burden); caregiver cognitive decline or even cultural expectations may bias caregiver recognition and reporting of patient symptoms (Stella et al. 2015; Gitlin et al. 2014). Furthermore, it has been suggested that measures which are exclusively based on caregiver information may not capture the essential nature of psychopathological manifestations, particularly when presentation is subtle (Stella et al. 2015). These factors need to be considered by clinicians when implementing a proxy-based assessment of NPS.

NPS in Prodromal Stages

The onset of NPS is a further important issue to consider. NPS can occur in prodromal phases of dementia (e.g., MCI) and also in preclinical individuals without any cognitive impairment. NPS are increasingly being recognized as an intrinsic aspect of prodromal stages of dementia and as an early marker of dementia risk which precedes the onset of cognitive symptoms and clinical diagnosis (Mortby and Anstey 2015).

The concept of "mild behavioral impairment" (MBI) has been proposed as a late-life transitional state between normal aging and dementia (i.e., prodromal stage of dementia), in which the presence of NPS in the absence of cognitive symptoms (i.e., cognitively normal individuals) confers an increased risk of developing dementia (Ismail et al. 2016). This concept has been proposed as a diagnostic construct aimed at identifying individuals at an increased risk of developing dementia who do not exhibit cognitive symptoms and which will enable earlier detection of incipient neurodegenerative illness.

MBI is hallmarked by changes in behavior or personality which start in later life (after the age of 50 years) and which persist, at least intermittently, for 6 months. These represent a clear change from the person's usual behavior or personality and are evidenced by at least one of the following:

- Decreased motivation (e.g., apathy, aspontaneity, indifference)
- Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
- Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
- Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
- Abnormal perception or thought content (e.g., delusions, hallucinations)

In order to meet the operationalized criteria for MBI, the behaviors must be of sufficient severity to produce at least minimal impairment to either interpersonal relationships, other aspects of social functioning, or ability perform in the workplace.

Individuals with MBI generally maintain independence of function in daily life and require minimal aids or assistance.

According to the operationalized criteria for MBI, individuals may have comorbid conditions; however behavioral or personality changes may not be attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication, nor may they meet clinical criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). However, mild cognitive impairment can be concurrently diagnosed with MBI (Ismail et al. 2016).

The concept of MBI recognizes another population at risk of developing dementia and provides a further dimension relevant to clinicians and diagnostics. Acceptance of the syndrome of MBI as a prodromal stage of dementia and implementation of screening will have significant implications for improving early detection, prevention, and treatment of dementia by providing a better understanding of the very early consequences of neurodegenerative disease. The newly developed **Mild Behavioral Impairment Checklist** (**MBI-C**) is a questionnaire based on the five MBI domains. Specifically designed for a pre-dementia population, the MBI-C is a two-page questionnaire with 34 questions designed to elicit early but sustained and impactful behavioral changes that may be precursors to cognitive decline and dementia. Initially developed for an English-speaking population, the MBI-C is currently subject to multiple translation-validation studies. The MBI-C is free for clinical and research use and can be found at www.MBItest.org.

Conclusion

In summary, there are many validated and reliable cognitive and neuropsychiatric screening instruments which can assist clinicians in the diagnostic process. Clinicians must pay particular consideration to the selection process of instruments to ensure they are context appropriate (e.g., applicability to culturally diverse populations, level of education bias, population for which the measure was developed and in which it was validated). By selecting context-specific and suitable instruments, clinicians can help ensure timely diagnosis, implementation of case-specific treatment, and appropriate provision of support for next of kin and caregivers (both formal and informal caregivers).

Cross-References

► (Neurobiology of) Dementia: Causes, Presentation, and Management
► Pharmacotherapy of Dementia
► Prevention of Alzheimer's Disease and Alzheimer's Dementia

References

Alexopoulos GS, Abrams RC, Young RC, Shamoian CA (1988) Cornell scale for depression in dementia. Biol Psychiatry 23:271–284

Amodeo S, Mainland BJ, Herrmann N, Shulman KI (2015) The times they are a-changin' clock drawing and prediction of dementia. J Geriatr Psychiatry Neurol 28:145–155

Arevalo-Rodriguez I, Smailagic N, Roqué I, Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A, Pedraza OL, Bonfill Cosp X, Cullum S (2015) Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Dat Syst Rev 3:CD010783. doi:10.1002/14651858.CD010783.pub2

Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H (2015) Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 11:718–726

Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A (2000) The Mini-Cog: a cognitive'vital signs' measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry 15:1021–1027

Borson S, Scanlan JM, Watanabe J, Tu SP, Lessig M (2005) Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample. J Am Geriatr Soc 53:871–874

Brodaty H, Pond D, Kemp NM, Luscombe G, Harding L, Berman K, Huppert FA (2002) The GPCOG: a new screening test for dementia designed for general practice. J Am Geriatr Soc 50:530–534

Carnero-Pardo C, Espejo-Martinez B, Lopez-Alcalde S, Espinosa-Garcia M, Saez-Zea C, Vilchez-Carrillo R, Hernandez-Torres E, Navarro-Espigares JL (2011) Effectiveness and costs of phototest in dementia and cognitive impairment screening. BMC Neurol 11:1

Carpenter CR, Bassett ER, Fischer GM, Shirshekan J, Galvin JE, Morris JC (2011) Four sensitive screening tools to detect cognitive dysfunction in Geriatric Emergency Department Patients: brief Alzheimer's screen, short blessed test, Ottawa 3DY, and the caregiver-completed AD8. Acad Emerg Med 18:374–384

Castanho TC, Amorim L, Zihl J, Palha JA, Sousa N, Santos NC (2014) Telephone-based screening tools for mild cognitive impairment and dementia in aging studies: a review of validated instruments. Front Aging Neurosci 6:16

Chen CW, Chu H, Tsai CF, Yang HL, Tsai JC, Chung MH, Liao YM, Chi MJ, Chou KR (2015) The reliability, validity, sensitivity, specificity and predictive values of the Chinese version of the Rowland Universal Dementia Assessment Scale. J Clin Nurs 24:3118–3128

Cheung G, Clugston A, Croucher M, Malone D, Mau E, Sims A, Gee S (2015) Performance of three cognitive screening tools in a sample of older New Zealanders. Int Psychogeriatr 27:981–989

Cohen-Mansfield J, Marx MS, Rosenthal AS (1989) A description of agitation in a nursing home. J Gerontol 44:M77–M84

Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJE, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton GF, Neale BE, Watton ME, Cullum S (2016) Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Dat Syst Rev 1:CD011145. doi:10.1002/14651858.CD011145.pub2

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314

Cummings-Vaughn LA, Chavakula NN, Malmstrom TK, Tumosa N, Morley JE, Cruz-Oliver DM (2014) Veterans Affairs Saint Louis University mental status examination compared with the Montreal cognitive assessment and the short test of mental status. J Am Geriatr Soc 62:1341–1346

de Leonni Stanonik M, Licata CA, Walton NC, Lounsbury JW, Hutson RK, Dougherty JH (2005) The self test: a screening tool for dementia requiring minimal supervision. Int Psychogeriatr 17:669–678

de Medeiros K, Robert P, Gauthier S, Stella F, Politis A, Leoutsakos J, Taragano F, Kremer J, Brugnolo A, Porsteinsson AP, Geda YE, Brodaty H, Gazdag G, Cummings J, Lyketsos C (2010) The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. Int Psychogeriatr 22:984–994

del Campo N, Payoux P, Djilali A, Delrieu J, Hoogendijk EO, Rolland Y, Cesari M, Weiner MW, Andrieu S, Vellas B (2016) Relationship of regional brain β-amyloid to gait speed. Neurology 86:36–43

Dougherty JH Jr, Cannon RL, Nicholas CR, Hall L, Hare F, Carr E, Dougherty A, Janowitz J, Arunthamakun J (2010) The computerized self test (CST): an interactive, internet accessible cognitive screening test for dementia. J Alzheimers Dis 20:185–195

Douglas VC, Neuhaus J, Johnson J, Racine C, Miller BL, Josephson SA (2011) Dementia = (MC) 2: a four-item screening test for mild cognitive impairment and dementia. Alzheimer Dis Assoc Disord 25:220

Ehreke L, Luck T, Luppa M, König H-H, Villringer A, Riedel-Heller SG (2011) Clock drawing test–screening utility for mild cognitive impairment according to different scoring systems: results of the Leipzig Longitudinal Study of the Aged (LEILA 75+). Int Psychogeriatr 23:1592–1601

Folstein MF, Folstein SE, Mchugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198

Fong TG, Jones RN, Rudolph JL, Yang FM, Tommet D, Habtemariam D, Marcantonio ER, Langa KM, Inouye SK (2011) Development and validation of a brief cognitive assessment tool: the sweet 16. Arch Intern Med 171:432–437

Freitas S, Simões MR, Alves L, Duro D, Santana I (2012) Montreal Cognitive Assessment (MoCA): validation study for frontotemporal dementia. J Geriatr Psychiatry Neurol 25:146–154

Freitas S, Simões MR, Alves L, Santana I (2013) Montreal cognitive assessment: validation study for mild cognitive impairment and Alzheimer disease. Alzheimer Dis Assoc Disord 27:37–43

Galvin J, Roe C, Powlishta K, Coats M, Muich S, Grant E, Miller J, Storandt M, Morris J (2005) The AD8 A brief informant interview to detect dementia. Neurology 65:559–564

Gates NJ, Kochan NA (2015) Computerized and on-line neuropsychological testing for late-life cognition and neurocognitive disorders: are we there yet? Curr Opin Psychiatry 28:165–172

Gauthier S, Albert M, Fox N, Goedert M, Kivipelto M, Mestre-Ferrandiz J, Middleton LT (2016) Why has therapy development for dementia failed in the last two decades? Alzheimers Dement 12:60–64

Gitlin LN, Kales HC, Lyketsos CG (2012) Nonpharmacologic management of behavioral symptoms in dementia. JAMA 308:2020–2029

Gitlin LN, Marx KA, Stanley IH, Hansen BR, van Haitsma KS (2014) Assessing neuropsychiatric symptoms in people with dementia: a systematic review of measures. Int Psychogeriatr 26:1805–1848

Gold DA (2012) An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. J Clin Exp Neuropsychol 34:11–34

Hancock P, Larner A (2011) Test your memory test: diagnostic utility in a memory clinic population. Int J Geriatr Psychiatry 26:976–980

Heinik J, Kavé G (2015) An investigation of the efficiency of the mini-Kingston standardized cognitive assessment-revised in classifying patients according to DSM-5 major and mild neurocognitive disorders due to possible Alzheimer's disease. Int Psychogeriatr 27:785–791

Hellmuth J, Mirsky J, Heuer H, Matlin A, Jafari A, Garbutt S, Widmeyer M, Berhel A, Sinha L, Miller B (2012) Multicenter validation of a bedside antisaccade task as a measure of executive function. Neurology 78:1824–1831

Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013) Validation of the Addenbrooke's cognitive examination III in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 36:242–250

Hsieh H, Mcgrory S, Leslie F, Dawson K, Ahmed S, Butler CR, Rowe JB, Mioshi E, Hodges JR (2014) The mini-Addenbrooke's cognitive examination: a new assessment tool for dementia. Dement Geriatr Cogn Disord 39:1–11

Iracleous P, Nie JX, Tracy CS, Moineddin R, Ismail Z, Shulman KI, Upshur RE (2010) Primary care physicians' attitudes towards cognitive screening: findings from a national postal survey. Int J Geriatr Psychiatry 25:23–29

Ismail Z, Rajji TK, Shulman KI (2010) Brief cognitive screening instruments: an update. Int J Geriatr Psychiatry 25:111–120

Ismail Z, Emeremni CA, Houck PR, Mazumdar S, Rosen J, Rajji TK, Pollock BG, Mulsant BH (2013a) A comparison of the E-BEHAVE-AD, NBRS, and NPI in quantifying clinical improvement in treatment of agitation and psychosis associated with dementia. Am J Geriatr Psychiatry 21:78–87

Ismail Z, Mulsant BH, Herrmann N, Rapoport M, Nilsson M, Shulman K (2013b) Canadian Academy Of Geriatric Psychiatry survey of brief cognitive screening instruments. Can Geriatr J 16:54–60

Ismail Z, Malick A, Smith EE, Schweizer T, Fischer C (2014) Depression versus dementia: is this construct still relevant? Neurodegener Dis Manag 4:119–126

Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, Agüera-Ortiz L, Sweet R, Miller D, Lyketsos CG (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement 12:195–202

Jacinto AF, Brucki SMD, Porto CS, de Arruda Martins M, de Albuquerque Citero V, Nitrini R (2014) Suggested instruments for general practitioners in countries with low schooling to screen for cognitive impairment in the elderly. Int Psychogeriatr 26:1121–1125

Jorm A, Scott R, Cullen J, Mackinnon A (1991) Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. Psychol Med 21:785–790

Jubb MT, Evans JJ (2015) An investigation of the utility of the Addenbrooke's cognitive examination III in the early detection of dementia in memory clinic patients aged over 75 years. Dement Geriatr Cogn Disord 40:222–232

Kales HC, Gitlin LN, Lyketsos CG (2015) Assessment and management of behavioral and psychological symptoms of dementia. BMJ 350:h369

Kandiah N, Zhang A, Bautista DC, Silva E, Ting SKS, Ng A, Assam P (2016) Early detection of dementia in multilingual populations: visual Cognitive Assessment Test (VCAT). J Neurol Neurosurg Psychiatry 87:156–160

Klekociuk S, Summers J, Vickers J, Summers MJ (2014) Reducing false positive diagnoses in mild cognitive impairment: the importance of comprehensive neuropsychological assessment. Eur J Neurol 21:1330. e83

Koski L (2013) Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. Cerebrovasc Dis 36:6–18

Ladas A, Frantzidis C, Bamidis P, Vivas AB (2014) Eye blink rate as a biological marker of mild cognitive impairment. Int J Psychophysiol 93:12–16

Lam B, Middleton LE, Masellis M, Stuss DT, Harry RD, Kiss A, Black SE (2013) Criterion and convergent validity of the Montreal cognitive assessment with screening and standardized neuropsychological testing. J Am Geriatr Soc 61:2181–2185

Lanctôt KL, Agüera-Ortiz L, Brodaty H, Francis PT, Geda YE, Ismail Z, Marshall GA, Mortby ME, Onyike CU, Padala PR (2016) Apathy associated with neurocognitive disorders: recent progress and future directions. Alzheimers Dement 13(1):84–100. doi:10.1016/j.jalz.2016.05.008. Epub 2016 Jun 27

Larner A (2012) Screening utility of the Montreal Cognitive Assessment (MoCA): in place of–or as well as–the MMSE? Int Psychogeriatr 24:391–396

Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L (2011) Hearing loss and incident dementia. Arch Neurol 68:214–220

Lischka AR, Mendelsohn M, Overend T, Forbes D (2012) A systematic review of screening tools for predicting the development of dementia. Can J Aging/La Rev Can Vieil 31: 295–311

Lu J, Li D, Li F, Zhou A, Wang F, Zuo X, Jia X-F, Song H, Jia J (2011) Montreal cognitive assessment in detecting cognitive impairment in Chinese elderly individuals: a population-based study. J Geriatr Psychiatry Neurol 24:184–190

Lyketsos CG, Miller DS (2012) Addressing the Alzheimer's disease crisis through better understanding, treatment, and eventual prevention of associated neuropsychiatric syndromes. Alzheimers Dement 8:60–64

Malmstrom TK, Voss V, Cruz-Oliver D, Cummings-Vaughn L, Tumosa N, Grossberg G, Morley J (2015) The Rapid Cognitive Screen (RCS): a point-of-care screening for dementia and mild cognitive impairment. J Nutr Health Aging 19:741–744

Maruff P, Lim YY, Darby D, Ellis KA, Pietrzak RH, Snyder PJ, Bush AI, Szoeke C, Schembri A, Ames D (2013) Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. BMC Psychol 1:1

Mathuranath P, Nestor P, Berrios G, Rakowicz W, Hodges J (2000) A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology 55:1613–1620

Mccarten JR, Anderson P, Kuskowski MA, Mcpherson SE, Borson S (2011) Screening for cognitive impairment in an elderly veteran population: acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc 59:309–313

Milian M, Leiherr A-M, Straten G, Müller S, Leyhe T, Eschweiler GW (2012) The Mini-Cog versus the mini-mental state examination and the clock drawing test in daily clinical practice: screening value in a German Memory Clinic. Int Psychogeriatr 24:766–774

Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 21:1078–1085

Mitchell AJ (2013) The Mini-Mental State Examination (MMSE): an update on its diagnostic validity for cognitive disorders. In: Cognitive screening instruments. Springer, London

Mortby ME, Anstey KJ (2015) Mental health and aging. In: Pachana AN (ed) Encyclopedia of geropsychology. Springer Singapore, Singapore

Naqvi RM, Haider S, Tomlinson G, Alibhai S (2015) Cognitive assessments in multicultural populations using the Rowland Universal Dementia Assessment Scale: a systematic review and meta-analysis. Can Med Assoc J 187:E169–E175

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695–699

Nielsen TR, Phung TKT, Chaaya M, Mackinnon A, Waldemar G (2015) Combining the rowland universal dementia assessment scale and the informant questionnaire on cognitive decline in the elderly to improve detection of dementia in an arabic-speaking population. Dement Geriatr Cogn Disord 41:46–54

Odenheimer G, Borson S, Sanders AE, Swain-Eng RJ, Kyomen HH, Tierney S, Gitlin L, Forciea MA, Absher J, Shega J, Johnson J (2013) Quality improvement in neurology: dementia management quality measures (executive summary). Am J Occup Ther 67:704–710

Onoda K, Hamano T, Nabika Y, Aoyama A, Takayoshi H, Nakagawa T, Ishihara M, Mitaki S, Yamaguchi T, Oguro H (2013) Validation of a new mass screening tool for cognitive impairment: cognitive assessment for dementia, iPad version. Clin Interv Aging 8:353–360

Razavi M, Tolea MI, Margrett J, Martin P, Oakland A, Tscholl DW, Ghods S, Mina M, Galvin JE (2014) Comparison of two informant questionnaire screening tools for dementia and mild cognitive impairment: AD8 and IQCODE. Alzheimer Dis Assoc Disord 28:156

Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 139:1136–1139

Reisberg B, Auer SR, Monteiro IM (1996) Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. Int Psychogeriatr 8(Suppl 3):301–308; discussion 351–4

Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE (2013) Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. Alzheimers Dement 9:529–537

Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, Caci H, Borg M, Brocker P, Bedoucha P (2002) The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry 17:1099–1105

Robert PH, Mulin E, Mallea P, David R (2010) Apathy diagnosis, assessment, and treatment in Alzheimer's disease. CNS Neurosci Ther 16:263–271

Rog LA, Park LQ, Harvey DJ, Huang C-J, Mackin S, Farias ST (2014) The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. Clin Neuropsychol 28:215–236

Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG (2013) The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. Am J Geriatr Psychiatry 21:685–695

Rotomskis A, Margevičiūtė R, Germanavičius A, Kaubrys G, Budrys V, Bagdonas A (2015) Differential diagnosis of depression and Alzheimer's disease with the Addenbrooke's Cognitive Examination-Revised (ACE-R). BMC Neurol 15:1

Rubínová E, Nikolai T, Marková H, Šiffelová K, Laczó J, Hort J, Vyhnálek M (2014) Clock drawing test and the diagnosis of amnestic mild cognitive impairment: can more detailed scoring systems do the work? J Clin Exp Neuropsychol 36:1076–1083

Russo MJ, Iturry M, Sraka MA, Bartoloni L, Carnero Pardo C, Allegri RF (2014) Diagnostic accuracy of the phototest for cognitive impairment and dementia in Argentina. Clin Neuropsychol 28:826–840

Satukijchai C, Senanarong V (2013) Clock drawing test (CDT) and activities of daily living (ADL) questionnaire as a short screening test for dementia in Thai population. J M Assoc Thai = Chotmaihet Thangphaet 96:S39–S46

Scharre DW, Chang SI, Nagaraja HN, Yager-Schweller J, Murden RA (2014) Community cognitive screening using the self-administered gerocognitive examination (SAGE). J Neuropsychiatr Clin Neurosci 26:369–375

Schmitter-Edgecombe M, Parsey C, Lamb R (2014) Development and psychometric properties of the instrumental activities of daily living: compensation scale. Arch Clin Neuropsychol 29:776–792, acu053

Selbaek G, Engedal K, Benth JS, Bergh S (2014) The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month follow-up period. Int Psychogeriatr 26:81–91

Shulman I (2000) Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry 15:548–561

Shulman KI, Herrmann N, Brodaty H, Chiu H, Lawlor B, Ritchie K, Scanlan JM (2006) IPA survey of brief cognitive screening instruments. Int Psychogeriatr 18:281–294

Stanciu I, Larsson M, Nordin S, Adolfsson R, Nilsson L-G, Olofsson JK (2014) Olfactory impairment and subjective olfactory complaints independently predict conversion to dementia: a longitudinal, population-based study. J Int Neuropsychol Soc 20:209–217

Stella F (2013) Assessment of neuropsychiatric symptoms in dementia: toward improving accuracy. Dementia Neuropsychol 7:244–251

Stella F, Forlenza OV, Laks J, de Andrade LP, de Castilho Cacao J, Govone JS, de Medeiros K, Lyketsos CG (2015) Caregiver report versus clinician impression: disagreements in rating neuropsychiatric symptoms in Alzheimer's disease patients. Int J Geriatr Psychiatry 30:1230–1237

Storey JE, Rowland JT, Conforti DA, Dickson HG (2004) The Rowland universal dementia assessment scale (RUDAS): a multicultural cognitive assessment scale. Int Psychogeriatr 16:13–31

Streit S, Limacher A, Zeller A, Bürge M (2015) Detecting dementia in patients with normal neuropsychological screening by Short Smell Test and Palmo-Mental Reflex Test: an observational study. BMC Geriatr 15:1

Tariq SH, Tumosa N, Chibnall JT, Perry MH, Morley JE (2006) Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder – a pilot study. Am J Geriatr Psychiatry 14:900–910

Ting C, Rajji TK, Ismail Z, Tang-Wai DF, Apanasiewicz N, Miranda D, Mamo D, Mulsant BH (2010) Differentiating the cognitive profile of schizophrenia from that of Alzheimer disease and depression in late life. PLoS ONE 5:e10151

Tsang RS, Diamond K, Mowszowski L, Lewis SJ, Naismith SL (2012) Using informant reports to detect cognitive decline in mild cognitive impairment. Int Psychogeriatr 24:967–973

Waldron-Perrine B, Axelrod BN (2012) Determining an appropriate cutting score for indication of impairment on the Montreal Cognitive Assessment. Int J Geriatr Psychiatry 27:1189–1194

Weiner MF, Tractenberg RE, Jin S, Gamst A, Thomas RG, Koss E, Thal LJ (2002) Assessing Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory: scoring and clinical implications. J Psychiatr Res 36:19–25

Capacity Assessment

16

Carmelle Peisah

Abstract

Capacity is the ability to make decisions. Autonomy in decision-making and being safeguarded against abuse and undue influence are fundamental human rights. This chapter will demonstrate how "good" capacity assessment can support these human rights. The assessment of capacity is a complex and highly specialized task, governed by principles of the presumption of capacity, that capacity is not diagnosis bound, and the need for individualized, task-, and situation-specific assessments. The clinician engaged to undertake a capacity assessment has a responsibility to act as gatekeeper, and sometimes advocate, for the actualization of human rights. Capacity assessment presents opportunities to identify strengths and weaknesses to inform and enable supported decision-making. It also provides opportunities and obligations to identify abuse. When people with disability such as mental illness are empowered to make the decisions they are capable of making, while protected from making the decisions they are incapable of making, human rights are supported. Such principles are universal, regardless of the jurisdictional variations in the laws that govern capacity and competency determinations internationally.

Keywords

Capacity • Human rights • Assessment • Abuse • Supported decision-making • Mental illness • Dementia

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_17

Contents

Introduction

Capacity is the ability to make decisions. The term "capacity" has been used interchangeably with the word "competence," although some consider competence a legal determination and capacity a health-care professional's determination (Kolva and Rosenfeld 2012). In this chapter, the two concepts will be regarded synonymously. What is more important is the distinction between decisional capacity and legal capacity, the former an ability, the latter a human right (Quinn 2010). Flynn and Arstein-Kerslake (2012, p1) define legal capacity as:

> a possession of the individual. It includes the ability to be a holder of rights as well as an actor in law. Legal capacity obligates the state to protect, promote, and enforce an individual's rights. Simultaneously, an individual's legal capacity allows her to interact with the law to have her rights enforced. Furthermore, an individual's legal capacity allows her to take actions that the law must recognise; such as signing a contract, getting married, voting, and making medical decisions. Legal capacity is the law recognizing an individual's personhood. Without legal capacity, you are a mere 'object' under the law (not a 'subject' within it).

This chapter will demonstrate how "good" capacity assessment can support legal capacity and other related human rights. Such principles are universal, regardless of the jurisdictional variations in the laws that govern capacity and competency determinations internationally. These variations arise out of the legal systems that govern different countries. Common law legal systems are governed by case law, which is law developed by judicial rulings or precedents, i.e., developed by judges through decisions of

courts or tribunals. Common law countries are also governed by statutory law which is law determined by legislation. Common law (which originated in England) is in practice in Commonwealth countries such as Canada, Australia, New Zealand, South Africa, India, Fiji, as well as the USA on a state level (except Louisiana).

In contrast to common law, civil law (also known as continental European law) is based on codified statutes and ordinances. Countries governed by civil law include China, Japan, most African nations, all South American nations (except Guyana), and most of Europe. Some jurisdictions such as South Africa and Hong Kong use a combination of civil and common law. It is beyond the scope of this chapter to address both civil and common law so where legal principles are referred to in this chapter, they will reference the common law. For a comparative review of capacity and substitute decision-making across Asia and Australia, see Tsoh et al. (2015).

Capacity and Human Rights

The United Nations Convention on the Rights of Person with Disabilities (CRPD), the first binding international human rights instrument explicitly to address disability (Australian Law Reform Commission (ALRC) 2014), opened for signature in March 2007 and entered into force in May 2008. As of February 2016, it had 160 signatories and 162 parties to it (United Nations Treaty Collection 2016). The CRPD consolidates and clarifies the application of existing human rights to persons with disabilities and can assist with the interpretation and the development of the common law domestically. For example, in the Australian Capital Territory (ACT), Section 30 of the Human Rights Act [2004] [ACT] states that:

> Territory law must be interpreted in a way that is compatible with human rights

The CRPD provides the framework for many of the legal and ethical principles espoused in this chapter. In particular, maximizing individual autonomy, choice, and personhood, while safeguarding against undue influence and abuse, underpins the exploration and study of the concept of capacity. The CRPD Articles which have special relevance to these constructs are Articles 1, 12, and 16.

Article 1 states that the purpose of the convention is to promote full and equal enjoyment of human rights and freedoms by persons with disabilities and respect for their dignity. Notably, included in those persons with disabilities are people with long-term "mental or intellectual impairments."

Article 12 – "Equal recognition before the law" is perhaps the cornerstone for all human rights discourse in relation to capacity. It states:

1. States parties reaffirm that persons with disabilities have the right to recognition everywhere as persons before the law.
2. States parties shall recognize that persons with disabilities enjoy legal capacity on an equal basis with others in all aspects of life.

3. States parties shall take appropriate measures to provide access by persons with disabilities to the support they may require in exercising their legal capacity.
4. States parties shall ensure that all measures that relate to the exercise of legal capacity provide for appropriate and effective safeguards to prevent abuse in accordance with international human rights law. Such safeguards shall ensure that measures relating to the exercise of legal capacity respect the rights, will, and preferences of the person, are free of conflict of interest and undue influence, are proportional and tailored to the person's circumstances, apply for the shortest time possible, and are subject to regular review by a competent, independent, and impartial authority or judicial body. The safeguards shall be proportional to the degree to which such measures affect the person's rights and interests.
5. Subject to the provisions of this article, states parties shall take all appropriate and effective measures to ensure the equal right of persons with disabilities to own or inherit property, to control their own financial affairs, and to have equal access to bank loans, mortgages, and other forms of financial credit and shall ensure that persons with disabilities are not arbitrarily deprived of their property.

Article 16 – "Freedom from exploitation, violence and abuse" states that parties shall take all appropriate legislative, administrative, social, educational, and other measures to protect persons with disabilities, both within and outside the home, from all forms of exploitation, violence, and abuse. In particular, support should include the provision of information and education on how to avoid, recognize, and report instances of exploitation, violence, and abuse.

An interesting and oft-forgotten human right in the capacity field is Article 25, the right to health, which states that parties recognize that persons with disabilities have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability. In particular, states parties shall provide persons with disabilities with the same range, quality, and standard of free or affordable health care and programs as provided to other persons. Further, health professionals shall provide care of the same quality to persons with disabilities as to others, including on the basis of free and informed consent by, inter alia, raising awareness of the human rights, dignity, autonomy, and needs of persons with disabilities through training and the promulgation of ethical standards for public and private health care.

How is Article 25 relevant to capacity? The role of free and informed consent is clearly stated, the assessment of which is crucial to the enactment of human rights. For example, a noncompetent refusal to have health care or treatment should never be used as reason to deny a person that right and that rather, a decision should be made about the treatment by a proxy or substitute decision-maker based on the person's rights, will, and preferences, if known, and if not known, in their best interests. Clinicians may need to act as advocates in climates of limited public health resources where noncompetent refusals for treatment are seen as opportunities to save or divert health resources.

The Capacity Construct: Definitions and Key Principles

Although the legal standards that define capacity vary across jurisdictions internationally, operational definitions of the cognitive elements of capacity usually comprise combinations of the following abilities:

1. To understand the specific situation, relevant facts, or basic information about choices
2. To evaluate and use reasoned processes to weigh the risks, consequences, and benefits of the choices
3. To communicate relatively consistent or stable choices

Capacity is not a unitary concept but rather refers to specific decisions, tasks, or domains. To conceptualize capacity as a global construct – for example, by referring to someone as "lacking capacity" without specifying for what decisions the person lacks capacity – is antithetical to human rights of autonomy and minimizing intrusion, in essence antithetical to principles of legal capacity. The concept of an "incapable person" or an "incapacitated person," although sprinkled throughout legislation around the world, is similarly flawed. Rarely is anyone incapable of making any decisions or expressing any choices.

By stating that capacity is task or domain specific, we ensure that it is specific to the particular type of decision made (Peisah et al. 2009a). Accordingly, the capacity task is different for entering into a contract; executing a power of attorney, will, or deed; appointing an enduring guardian or an attorney under a power of attorney; or consenting to treatment, divorce, or marriage. Thus, capacity cannot be extrapolated from one capacity task to another. For example, a person's capacity to write a will cannot be inferred from their capacity to consent to medical treatment.

Even within a particular type of decision or task category, capacity may vary. Within a single domain or capacity task, there is a spectrum or hierarchy of decisions from simple (e.g., having a blood test) to complex (e.g., amputation) and accordingly, people may be capable of making simple decisions but not more complex ones. Further, the greater the complexity and conflict within the decision-maker's environment (the "situation-specific" nature of capacity), (Shulman et al. 2007) the higher the level of cognitive function or emotional stability/mental health necessary in order to be considered capable when making decisions which involve others. This might include, for example, the weighing up of potential beneficiaries in a will or potential appointees as attorneys under enduring powers of attorney or as enduring guardians or recipients of a gift, or whether to propose or accept a proposal to marry.

Accordingly, a person with dementia may have the capacity to make a simple will, for example, leaving a single asset such as their house to their spouse, but may not have capacity to make a complex will, for example, dividing a complex estate involving a real estate and share portfolio amongst multiple, conflicting beneficiaries with fractional bequests. It is for this reason that when making statements or writing reports about capacity, it is inappropriate to state that a person has or lacks capacity to write "a will" or "execute a power of attorney" but rather, to write "the will in question" or "the power of attorney appointing x for y matters."

Also, in any discussion about incapacity, it must be appreciated that there is, in common law jurisdictions, a presumption of capacity in relation to anyone 18 years or more. This concept originated from a case in the UK, re MB (An Adult: Medical Treatment) [1997] 2 FCR 541 (at [553]) which involved a 23-year-old woman with a needle phobia who required an emergency caesarian section, for whom capacity was presumed until it was rebutted because she [at paragraph 22]:

> *lacked the mental competence to make a decision about the treatment that was proposed because she was incapable of weighing up the considerations that were involved. She was called upon to make that decision at a time of acute emotional stress and physical pain in the ordinary course of labour made even more difficult for her because of her own particular mental history*

Consequently, incapacity is not "status" or diagnosis bound (Peisah et al. 2009a). This means that incapacity cannot be assumed because of a diagnosis, such as dementia or schizophrenia, which means nothing in relation to decision-making other than to raise a possible question as to capacity. The presumption may be rebutted by evidence to the contrary, but such evidence can only be derived when the person is given the opportunity to make the decision and appears to struggle as a result of a mental illness, disorder, or intellectual disability.

The question of whether or not a person has capacity is assessed in the context of their cognitive abilities and mental status in relation to the decision. A person with mild dementia may therefore have enough insight, memory, and reasoning to know they need help and accept it in the way of community services but not have enough reasoning to decide on the pros and cons of a colostomy for a necrotic bowel. A useful formula in this context might be:

$$\textbf{Capacity} = \textbf{brain reserve} / \textbf{decision}$$

Put another way, this means that the bigger and more complex the decision, the more brain reserve or intellectual ability one needs to have capacity. Freedom is maximized when a person is allowed to make the decisions they are capable of making.

Importantly, many of these basic capacity principles, namely, the importance of presumption of capacity, the acknowledgment that capacity is not status or diagnosis bound, and that it is task specific, have statutory support in the USA in the Californian Due Process in Competency Determinations Act (DPCDA), Probate Code sections 810–813, and Civil Code section 39(b).

Supported Decision-Making: The Link Between Capacity Assessment and Legal Capacity

Supported decision-making is a collaborative process (Browning et al. 2014) of decision-making between a person with impaired capacity and a supporter or supporters. The process involves knowledge building and shared learning that

facilitates the choices and decisions of the person with impaired capacity (Peisah et al. 2013).

This definition of supported decision-making, which is contingent upon a starting point of impaired capacity, needs to be reconciled with a presumption of capacity. Is this possible?

This model still starts with the presumption of capacity for all, including people with disabilities. If a decision needs to be made, or a choice or preference sought, then discussion should begin with ensuring that the person is equipped with adequate information to make the decision. This crucial "education step" – penned by Darzins et al. (2000) in their Six-Step Capacity Assessment Process – ensures that people are given every chance to understand their problems, choices, and the reasonably foreseeable consequences of these choices. This is crucial to equitable participation in decision-making, which should not be a guessing game for the person involved.

Supported decision-making is reliant on capacity assessment. Browning et al. (2014) suggest that supported decision-making is a process that enables some people to exercise their legal capacity and thus greater autonomy and self-determination.

An applied clinical example of such is in end-of-life decision-making. In a qualitative study of community living staff working with residents with intellectual disability, Wiese et al. (2014) emphasized the fundamental right of people with disability to know about dying and death, which can only occur in residential care settings if staff initiate discussions with residents. This study showed that there was little evidence that staff talked with, or assisted clients in understanding the end of life, both prior to and after a death, such discussions relying on sophisticated communication skills to ensure that clients can meaningfully engage with end-of-life issues as opportunities arise. Such opportunities included when family members die, incidental opportunities, when clients live with someone who is dying, and when a client is dying (Wiese et al. 2013), although to leave such discussions until the latter stage might preclude many from actively participating in decision-making. These principles of the right to early information must be extended to people with and without disabilities alike.

Parallel to the entire process of information sharing and exchange is the need to ensure that there are no adverse effects of, or distress arising from, decision-making. Put simply, decision-making should not be "shoved down people's throats." Again, when it comes to discussing end of life with people with disability, Wiese et al. (2015) noted:

> More evidence is needed, however, before a compelling case can be made that the balance between beneficence and non-maleficence is firmly in support of intervention. Researchers evaluating interventions should not only monitor benefits, such as increased knowledge, but also measure potential harms, such as anxiety, depression, and fear of death.

The most sensitive and person-centered solution to this dilemma is to treat each person as an individual and to monitor their responses to decision-making, particularly looking for any evidence of distress. Clinically, it is usually very obvious when a person doesn't want to talk about a subject, and our predominantly Western agenda of autonomy should not be the driver of whether a person has to participate in decision-making. People without disability frequently choose to defer decision-

making or abdicate their right to have a voice. People with disability similarly choose to (Bamford and Bruce 2000) and have an equal right to do so.

If the person wishes to be involved or proceed, the task of eliciting their will and preferences must start obviously with the person themselves, but may involve input from others. The assessment of capacity should proceed with a focus only on the decision at hand, according to the task-specific nature of capacity. If there are doubts about capacity, an assessment of strengths and weaknesses will assist with supported decision-making. Key to this model is the symbiotic relationship between capacity assessment and supported decision-making. Supported decision-making that is tailored, individualized, and person-centered can occur only if informed by strength- and deficit-based capacity assessment. This sort of capacity assessment is not to be confused with traditional, ill-informed, human rights-incompatible capacity assessment that was status or diagnosis bound (i.e., disability or diagnoses = lack of capacity) and dependent upon the "reasonableness" of the decision or whether the assessor agreed with the decision (Quinn 2010).

A systematic "how to" approach for supported decision-making, based on collaborative principles and a positive, relational concept of autonomy, can be captured with the acronym ASK ME (Peisah et al. 2013):

Step 1. ASSESS the person's strengths and deficits, starting with an assessment of mental state and cognitive abilities, particularly assessing crucial skills such as executive function and awareness. Important executive functions relevant to decision-making include holding information in working memory, weighing alternatives and consequences, projecting, and planning. Additionally, memory, language, and communication functions are important and, if found to be lacking following assessment, can be buttressed (Zuscak et al. 2015). Another important cognitive construct for capacity is awareness. As a more nuanced and inclusive concept than the traditional notion of insight, which tends to be categorical and exclusive, awareness is a more useful construct for supported decision-making. Importantly, awareness seems to lack the floor effects of insight and as such, is often present at severe ends of disability severity, providing it is identified. For example, Clare et al. (2013) demonstrated that even people with severe dementia show awareness, although this is influenced by the extent to which the environment provides opportunities for engagement and by the way in which care staff notice awareness and interact with residents. In addition to preserved awareness, other strengths that need to be identified during assessment include carer support, including friends, family members, and professional carers. Knowing strengths and weaknesses helps to determine exactly how best to approach the next test, to simplify the task and maximize the ability to understand.

Step 2. SIMPLIFY the task. The best way to maximize participation is to limit the capacity task to the specific decision at hand and not to overstate the decision. This might mean obtaining choices and preferences about the part of decision that the person understands. For example, a person may merely understand they have a problem or a dysphoric (negative, unpleasant) experience for which they want relief. Alternatively, they may be able to articulate what makes them happy. A person who

is not capable of understanding a full advance care directive may be capable of expressing a desire for care, pain relief, and comfort (i.e., participating in advance care planning), or where they want to have that care, rather than making a full advance care directive.

Step 3. KNOW the person. It is essential to ascertain the will and preferences of the person. This includes finding out what the person considers important and what their long-held values and decisions were. In particular, if there is a neurodegenerative condition such as dementia, it might be useful to cue past decisions (precedent autonomy) and check whether the person still affirms these values. Information about past trusts and allegiances might be evident in documents such as powers of attorney or wills. It is equally important to understand current preferences, understanding what is important and meaningful to the person in their life right now as it relates to the decision at hand (e.g., in an accommodation decision for residential care, the person may be more interested in food or family than accommodation). If possible respect the person's precedent autonomy, but also, where appropriate, "respect their right to change their mind when their mind has changed." Reconciling differences between precedent and current choices may involve updating a person's self-concept. For example, a person may have previously written an advance care directive consistent with their former values and subsequently, in the face of dementia and their "new self," change their mind (Hertogh 2015).

Step 4. MAXIMIZE the ability to understand by addressing and buttressing factors which hinder communication (Zuscak et al. 2015). This might include giving more time, optimizing the environment, simplifying, and concretizing information and providing it in an accessible format. Visual aids should be tailored to the person's cognitive deficits including either written or visual information, with simple pictorial or linear representations of the choices to be made. People with expressive or receptive language deficits, confrontational naming, visual agnosia, dyslexia will all require different aids, and supported decision-making can be usefully assisted by a speech pathologist or neuropsychologist (Zuscak et al. 2015). Provide interpreters where necessary or written cues in the person's language. Finally, it is respectful to elicit decisions when a person is at their best, when they are not delirious, when they are not sundowning, or when they are not in pain, drowsy, or fatigued. This might be first thing in the morning or after a treatment such as blood transfusion or dialysis.

Step 5. ENABLE participation in decision-making by using the assessment process outlined above to tailor the degree of support to the complexity and consequences of the decision. Assist and facilitate the communication and implementation of the decision.

Statutory support for supported decision-making is growing, and it is beyond the scope of this review. However, one illustrative and progressive example is Ireland's Assisted Decision-Making (Capacity) Act 2015 which emphasizes will and preferences and outlines three levels of decision-making assistance: "decision-making assistant," "co-decision-maker" (joint decision-maker), and "decision-making representative" (substitute decision-maker).

Capacity Assessment

Capacity assessment occurs in two contexts, in the medicolegal setting and in the clinical setting. The two roles are distinctly different and require different processes in regard to engagement of the assessor or "expert," setting up the assessment and the purpose and use of the report.

Assessing Capacity as a Medicolegal Expert

Capacity assessment that relates to execution of legal documents such as wills, powers of attorney, and enduring guardianship should be a truly medicolegal interaction. Ideally, formal assessments of capacity in that context should be requested by a lawyer who outlines the applicable legal test or procedures to apply. Clinicians should not take instructions from patients or fellow clinicians, and the duty of the clinician is to the court and not as an advocate for any party or lawyer. This process is governed by a code of conduct or civil procedure rules legislated in most common law legal systems around the world. Examples of the kind of principles embodied in such codes are:

i. An overriding duty to assist the court impartially.
ii. To restrict opinion to matters relevant to the expert witness's area of expertise.
iii. A paramount duty to the court and not to any party to the proceedings (including the person retaining the expert witness). An expert witness is not an advocate for a party.
iv. Duty to work cooperatively with other expert witnesses and endeavor to reach agreement with the other expert witness where possible.
v. To include in a report:
   (a) The expert's qualifications as an expert on the issue
   (b) The facts, and assumptions of fact, on which the opinions in the report are based
   (c) The expert's reasons for each opinion expressed
   (d) Any literature or other materials utilized in support of the opinions
   (e) Any examinations, tests, or other investigations on which the expert has relied
vi. To acknowledge limitations, i.e., to specifically state:
   (a) If a particular issue falls outside the expert's field of expertise
   (b) If the report is incomplete or inaccurate without some qualification
   (c) If the opinion is not a concluded opinion because of insufficient research or insufficient data or for any other reason
vii. If an expert witness changes opinion on a material matter after providing an expert's report then a supplementary report to that effect should be provided.

These "rules" or "codes" have emerged with the proliferation of experts and the perception of some experts as "hired guns" who give "opinions for sale." Courts have faced real difficulties in understanding and evaluating the reasoning and conclusions of expert witnesses, particularly in relation to abstruse areas of expertise (McDougall 2016). The court needs to know what facts opinion is based upon, if those facts are "assumed" or "accepted," and if the opinion is founded upon the expert's specialized knowledge. In an Australian case, *Makita (Australia) Pty Ltd v Sprowles* (2001), Heydon JA stated that *the prime duty of experts in giving opinion evidence: to furnish the trier of facts with criteria enabling the evaluation of the validity of the expert's conclusions.*

These concepts are held fairly widely in common law jurisdictions and resonate for with a ruling from the Queen's Bench Division of the High Court of the UK, Lawton LJ in *R v Turner* [1975] which stated that … *counsel calling an expert should in examination in chief ask his witness to state the facts upon which his opinion is based.*

Similarly, in an earlier Scottish decision in *Davie v Lord Provost, Magistrates and Councillors of the City of Edinburgh* (Davie 1953) SC 34 at 39–40 where Lord President Cooper stated of expert witnesses that:

> *Their duty is to furnish the Judge or jury with the necessary scientific criteria for testing the accuracy of their conclusions so as to enable the Judge or jury to form their own independent judgment by the application of these criteria to the facts proved in evidence.*

Capacity Assessments in Clinical Settings

Capacity assessments in clinical settings should be restricted to assessments that are related to clinical need, such as assessment of treatment consent and end-of-life decisions, guardianship applications for nursing home admissions, or action to address abuse. A valid "trigger" must exist to rebut the presumption of capacity and a need for assessment of capacity beyond merely a relative or lawyer's request. This is particularly so for inpatients within hospitals. For some people, assessment per se is perceived as intrusive, and they may be offended that their capacity is being doubted or challenged.

The General Approach to Capacity Assessment

Whenever tasked with the role of assessing capacity, it is useful for the clinician to consider the following protocol:

1. History. The clinician must first obtain a comprehensive medical and personal history, as well as obtaining the "history of documents" to obtain information about the person's precedent choices, their will, and preferences prior to the onset of mental disorder. They must be armed with relevant documentation such as, in

the case of assessment of financial capacity, a list of assets and bills; with Will making, the past Wills; or with power of attorney or enduring guardianship appointments any past documents of appointment.
2. General examination. This must include both an examination of mental and cognitive state.
3. Specific functional capacity assessment. Broadly, capacity assessment can be divided into a consideration of the "why," the "what," the "who," and the "freedom" of the decision:
   i. The why of the decision. The trigger for assessment must be ascertained. Who has initiated the assessment? Answering this question provides a useful screen for ensuring there is a valid reason to rebut the presumption of capacity or to identify possible undue influence or elder abuse. Ideally, assessments that are initiated or at least understood by the person, the subject of the assessment, are most robust to such screens. An example of an unnecessary trigger might be when a clinician is asked to do a capacity assessment for appointment of financial power of attorney by the brother of a woman who has recently been hospitalized with a stroke but had already made a valid enduring financial power of attorney a year earlier.
   ii. The what of the assessment. The specific tasks or domain being tested must be clarified and the relevant legal tests outlined if possible. Accordingly, an understanding of the specific nature of the decision and the facts and information relevant to the decision are integral to this part of the assessment. This must always be expressed in the person's own words. An answer to the closed question, "Do you understand?" is never sufficient proof of capacity.
   iii. The who of the assessment. When decisions are made that involve appointment of others or benefits to others, the person's understanding of their relationship with the appointee or beneficiary and rationale for this choice are an important part of the assessment. Ideally, the assessor should be informed of genograms and family relationship history.
   iv. The freedom of the assessment. It is an obligation of any capacity assessor to screen for the presence of coercion, undue influence (Peisah et al. 2009b), or abuse, regardless of the specific area of capacity being tested.

Clearly, this is but one of the enumerable approaches to capacity assessment that have been proposed (Wood and O'Bryan 2012). Regardless of which conceptual model that is used to frame clinical assessments of capacity, commonalities include combinations of a medical diagnosis (psychiatric, cognitive), assessment of values, a functional component (including risk assessment), a contextual component looking at the complexity of decision-making, and a reference to the appropriate legal standards and opportunities to enhance capacity (Wood and O'Bryan 2012). An example of statutory support for a schedule for capacity assessment, or "determination that a person is of unsound mind or lacks the capacity to make a decision or do a certain act," has been codified in the Californian Due Process in Competency Determinations Act (DPCDA), Probate Code sections 810–813, and Civil Code section 39(b).

Ethical Considerations

Many of the ethical issues which abound in the area of capacity assessment have already been discussed. Firstly, there are the aforementioned human rights of autonomy and dignity, safeguarding against abuse and undue influence, and equitable right to health. Secondly, many of these principles align with the medical ethical principles of autonomy, equitable justice, beneficence, and non-maleficence (Katona et al. 2009). Thirdly, in medicolegal settings, there are the ethical duties embodied within the aforementioned codes of conduct in each jurisdiction. Finally, in addition to these much studied or codified principles, there are a number of incidental ethical issues that arise in the process of capacity assessment.

An obvious example is the urgent or high-risk situation that arises during capacity assessment. When it is incidentally found that the person is acutely unwell or suicidal, a clinical responsibility and imperative to ensure safety and treatment obviously override the medicolegal role. Another example is the nonurgent need for clinical care. Sometimes the only impetus for bringing someone to the attention of a clinician are capacity issues driven by a financial or family conflict imperative, rather than a diagnostic or treatment-driven impetus. As a result, it is not unusual for the capacity assessor to be the first clinician to set eyes on a person with dementia or, in some cases, mental illness. In such circumstances, it may be appropriate with the person's permission to ask the lawyer to ensure that the person is referred to an appropriate clinician and to ask permission of the person to forward a copy of the report (which should contain a comprehensive report on cognition and diagnosis) to the clinician.

The Assessment of Specific Capacity Domains

The following presents a brief overview of the "what" of capacity assessment, the specific legal tests relevant to commonly assessed domains of capacity. Using the protocol outlined earlier, any assessment would proceed with history, general examination, and specific capacity testing including the why, the what, the who, and the freedom.

Capacity and Treatment Consent

The area of capacity and treatment consent provides us with ample opportunities for the actualization of human rights of autonomy, respect for will and preferences, and provision of supported decision-making for people with disability. Equally at stake is the right of people with disability to equitable access to health care, particularly for those who are unable to give consent to treatment. Again, a noncompetent refusal to have treatment should never be used as reason to deny a person that right.

In a recent case before the UK Supreme Court, *Montgomery v Lanarkshire Health Board (Scotland)* [2015] UKSC 11, the social and legal developments which are pointing away from a relationship of paternalism between doctor and patient were noted:

> *They also point away from a model based upon a view of the patient as being entirely dependent on information provided by the doctor. What they point towards is an approach to the law which, instead of treating patients as placing themselves in the hands of their doctors (and then being prone to sue their doctors in the event of a disappointing outcome), treats them so far as possible as adults who are capable of understanding that medical treatment is uncertain of success and may involve risks, accepting responsibility for the taking of risks affecting their own lives, and living with the consequences of their choices. [81]*

Capacity is essential for treatment consent. For a treatment consent to be valid, the person must be (i) competent (or have capacity) to make the decision, (ii) acting voluntarily without pressure or duress, and (iii) provided with enough relevant information about the treatment options and alternatives to enable them to make the decision.

Broadly speaking, using a simple derivation of the definition of capacity used above, capacity for treatment requires:

i. An understanding of the situation, facts, and information relevant to the decision (i.e., the illness or problem, treatment choices, risks, consequences, and alternatives)
ii. An ability to use and weigh that information
iii. An ability to communicate the decision

This broad-brush approach to capacity for treatment results from the infinite permutations of this concept that have emerged from research (Grisso and Appelbaum 1995; Grisso et al. 1997) common law and statutory law (Ryan et al. 2015).

Regardless of which definition is used, the pivotal role of information provision, Darzin and Molloy's (2000) "education step" referred to earlier, is clearly evident. Before assessing whether a person can understand the situation, facts, or information relevant to the decision, they must be informed of these. This includes discussing the material risks of the treatment. A risk is material if, in the circumstances of the particular case, a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it or if the medical practitioner is or should reasonably be aware that the particular patient, if warned of the risk, would be likely to attach significance to it. Importantly, this places the onus on the doctor to sufficiently inform the patient. As noted in *Montgomery v Lanarkshire Health Board (Scotland)* [2015] UKSC 11:

> *there is something unreal about placing the onus of asking upon a patient who may not know that there is anything to ask about* (Wiese et al. 2014)

In keeping with current societal, legal, and ethical expectations, this is not merely about enough information but also how that information is presented. It must be presented in a form that can be understood, and, that means, if we are to meet our obligations under Article 12 of the CRPD, providing supported decision-making for those who require it.

The Principle of Necessity: When Capacity for Treatment Is Not Needed

The principle of necessity evolved from an English Case, Re F (1990) 2 AC 1, 77; (also F v West Berkshire HA [1991] UKHL 1 (17 July 1990)], which upholds the actions of agents (doctors) who are unable to get instructions from their principals (the patient) but must act in an emergency provided they act in a way that, in the judgment of a wise and prudent person, is in the best interests of the patient. The intent from that case was to provide guidance for doctors dealing with patients who were likely to be incapable only for a short period because, for example, they were unconscious or delirious and, with care and treatment, would soon regain capacity. In such cases, doctors could treat patients by doing no more than was reasonably required in their best interests.

It is important to note that in the same judgment it was stated:

> *So intervention cannot be justified when another more appropriate person is available and willing to act; nor can it be justified when it is contrary to the known wishes of the assisted. Accordingly, if a person presents to the emergency department, is unable to give consent and treatment is urgent and necessary, there is no obvious advance treatment directive, and there is no-one available to give substitute consent, the person can be treated.* [p25]

Capacity and Advance Care Directives

Clinicians are sometimes asked to comment on or certify a person's capacity or, in some jurisdictions (e.g., Medical Treatment Act, 1988. (Victoria, Australia) Schedule 1. Section 3, 5(2)] "soundness of mind" to make an advance care directive (ACD). As an advanced treatment refusal, the approach to assessing capacity in this context is similar to that for treatment consent or refusal, particularly if the ACD relates to a current condition, as is required in some jurisdictions. In other words, does the person understand the condition, illness or problem, treatment choices, risks, alternatives, and consequences, which in this case is death? Can they weigh that information and communicate their decision? The moot point in this area of capacity is that using the risk hierarchy or threshold approach, death is perhaps the most "risky" decision a person can make.

A suggested approach to assessing capacity in this area is firstly to address all reversible or potentially irreversible conditions that will impact upon the ability to make a decision. This might include pain, sleep, noisy, or non-private environment. Most importantly, identify and address the two most common conditions facing people about to make an ACD, namely, delirium and depression.

Delirium is highly prevalent amongst older patients and dying patients, not only as a preterminal event but also in the last weeks of life, with a prevalence up to 85% (Friedlander et al. 2004; Massie et al. 1983). Delirium is frequently missed by health-

care professionals, both in hospital (Friedlander et al. 2004; Inouye et al. 2001) and in nursing homes (Voyer et al. 2008). Older patients (Voyer et al. 2008) and those with preexisting cognitive impairment or dementia (Fick and Foreman 2000) are more likely to have undetected delirium. Hypoactive presentations of delirium, characterized by less activity and more withdrawal and decreased speech (Meagher et al. 2007), are prevalent and frequently missed. For example, of 33% of 100 consecutive cases of delirium in a palliative care unit were classified as hypoactive, and these patients had the same impairment in cognitive functioning as patients with other types of delirium (Leonard et al. 2011), rendering them just as vulnerable to impaired capacity but perhaps less identifiably so.

With regard to major depression, thoughts of death and a wish to die are frequent symptoms of illness. In an interesting study undertaken some 20 years ago, 42% of 22 patients with major depression (mean age = 77) hypothetically expressed a preference for voluntary euthanasia in their present state, which reversed to 8% ($n = 1$) of those fully recovered and 11% of those improved from their depression (Hooper et al. 1997). Notably, there was less reversal when talking about hypothetical life-threatening illness with uncertain prognosis, where requests for euthanasia went from 83% before treatment to 58% after recovery.

Given the known association between depressive symptoms and interest in hastened death in patients who are seriously ill, and at some level in patients undergoing euthanasia/physician-assisted suicide (Levene and Parker 2011), depressive symptoms per se cannot be an exclusion criteria for making an ACD, but rather a pointer to potentially treatable or reversible conditions.

The next step after addressing reversible conditions in the approach to assessing capacity for an ACD is the education step. Ensure the person has been informed sufficiently about the nature of their current (or feared) condition to enable them to make a decision about whether or not to refuse medical treatment generally or of a particular kind. Secondly, ensure they are informed what an ACD is and its effect. Thirdly, ask the person to repeat this information in their own words. A person may not be capable of understanding all the risks, benefits, and consequences to make an ACD but still may be able to express a wish or preference and as such, a ripe opportunity for supported decision-making. Discussing an advance care directive may provide an opportunity for patients, families, and health professionals to discover and share values and expectation regarding end-of-life decisions (Tulsky 2005). Importantly, the ACD is not the "be all and end all" and that instead a higher-order priority is to engage in discussions around death or advance care planning with patients and their families or proxies as they confront the challenge of a progressive illness trajectory (Hertogh 2011; De Boer et al. 2010).

Although this section has started with the premise that a doctor might be involved in the assessment of capacity prior to making an ACD, and in some cases statutorily compelled to confirm soundness of mind, this is the exception rather than the rule. As stated by Hertogh (2011), "the presentation of the directive is customarily at the end of the enquiry instead of the beginning" (p. 512). In such cases, when presented with a directive, there is, as always, a presumption of capacity and, accordingly, of the

validity of the document. If there is any doubt and a valid trigger for rebutting that presumption exists, obtain further information as to the medical, cognitive or psychiatric condition of the person at the time the ACD was made.

Capacity and Relationships

The fundamental right of every person to make decisions about sexual behavior and to choose not to engage in sexual activity is enshrined within very basic civil liberties and human rights to autonomy, dignity, and the right to be safeguarded against abuse. The enactment of these rights is equitably owed to people with disabilities such as mental illness and cognitive impairment. Doctors or other health-care professionals are sometimes asked about the appropriateness of two people – either one or both of whom have mental illness, cognitive impairment, or intellectual disability – entering into a sexual relationship. On the one hand, health-care professionals must tread carefully in regard to any interference in or abrogation of a person's right to engage, in a non-abusive way, in a sexual relationship. On the other hand, there is a responsibility to identify when sexual expression impinges on the rights of others to be safeguarded against abuse. Complicating this are the various legal or statutory definitions of what constitutes a sexual offence and conversely what constitutes consent in this context. For example, consent in regard to sexual offences refers to free and voluntary agreement in some jurisdictions, although capacity to make the choice is included in others.

Generally speaking, when considering capacity for sexual activity, one might consider the person's understanding of sexual activity, the identity of the other and the nature and consequences of the relationship if any (e.g., anxiety, genital trauma/itch, etc.). Importantly, with people in residential care facilities, rather than polarizing participants into victims and perpetrators, we should consider the capacity of both parties (Peisah et al. 2014).

Responses to expression of sexuality in facilities are often treatment focused with a goal of extinguishing the behavior. Rather, responses need to be needs and risk management focused, with decisions to intervene or not based on some of the following considerations:

i. The relevant statutory definitions of consent and sexual offence in the jurisdiction.
ii. The nature of the relationship, including the presence of a power imbalance or element of coercion.
iii. Is the relationship associated with other exploitation, e.g., financial?
iv. Is there a significant discrepancy between the two people's age and cognitive capacity?
v. What pleasure (or otherwise) do they experience in the relationship? Are they willing or content for it to continue? Can they advocate for their interests, say "no" when they want to; Can they understand and respond appropriately when the partner says "no"?

vi. Is there evidence of protest, resistance, or coercion? Note that accession or assent does not equate to consent.
vii. Is there evidence of harm or injury: physical (e.g., bruising, bite marks, rash) or psychological? Consider in the nonverbal or dysphasic or apathetic patient other signs such as behavioral change after conjugal visits, increased agitation, behavioral psychological symptoms of dementia, sleep, or appetite disturbance (Peisah et al. 2014a).

Once again there is an obligation under Articles 12 and 16 of CRPD to safeguard people with disability against exploitation, violence, and abuse. Yet, one of the most complex and challenging issues for clinicians is when an older person with a mental illness or dementia, who is a long-standing victim of abuse, usually domestic violence, chooses to return to live with the perpetrator. It is important in such cases to discern the difference between consent (which is contingent upon both capacity and acting voluntarily without duress or influence) and assent, which is mere agreement.

Capacity and Guardianship

The appointment of a guardian or conservator, a proxy or substitute decision-maker on behalf of another person who lacks capacity, can be made in advance by the person themselves with an enduring guardianship appointment in jurisdictions where this is available, or subsequently when needed, by courts or tribunals. The decision-making powers of guardians or conservators depend on the jurisdiction and may range from decisions about personal matters such as where the person can reside (accommodation), health care, what services they can receive, access (i.e., with whom they can have contact), and sometimes property and finances. In some jurisdictions, orders are plenary – that is, giving the guardian complete control (Kolva and Rosenfeld 2012) while in others they are limited to specific functions (O'Neill and Peisah 2017). Ideally, when capacity for needing or appointing guardian is assessed, it should focus on the specific decision-making powers to be divested to the proxy decision-maker.

In some jurisdictions, the test for appointment is defined and includes a determination of capacity. Otherwise, the approach to capacity assessment should follow the same procedure of why, who, what, and freedom, namely:

(a) The "why" of the appointment:
   i. What is the trigger for the assessment? A mere diagnosis, for example, of dementia, is not per se sufficient justification for an assessment and application for a court or tribunal appointed guardian. In contrast, it is an entirely appropriate trigger for a self-appointed enduring guardian. For a court or tribunal appointed guardian, does a decision need to be made, and

are there risks involved in not appointing a decision-maker or can current informal arrangements continue? Ideally court- or tribunal-appointed decision-makers should be appointed as a last resort and not "just in case."

(b) The "what" of the appointment:
   i. For the appointment of an enduring guardian, does the person understand when it is explained to them that they are authorizing someone to make decisions in the future, when they are no longer capable, about the specific domains nominated in the document?
   ii. For the appointment of a court or tribunal appointed guardian, does the person have capacity to make decisions about the domains under application, such as accommodation, lifestyle, health, or access to others? For example, with regard to accommodation, does the person understand their disability, what services they need to help them, and what risks are involved in rejecting them? Do they understand the accommodation options, their benefits, and risk?

(c) The "who" of the appointment:
   i. For the appointment of an enduring guardian, why has the person been selected for appointment as an attorney?
   ii. Has the person executed any enduring guardian appointments previously? If so, how frequently have there been changes (i.e., revocations and new appointments)? Does the person recall making these past appointments and revocations?
   iii. Have they considered the trustworthiness and wisdom of the person they are appointing and any past conflict with that person?
   iv. Is this appointment in keeping with previous appointments (e.g., has someone else been consistently appointed as guardian in the past)?
   v. What is the history of the relationship between the person and the attorney and has there been any radical change in that relationship coinciding with the onset or course of dementia?

(d) The "freedom" of the appointment of an enduring guardian:
   i. Has all the relevant information been given to the person in a way they can understand?
   ii. Is the person making the appointment freely and voluntarily, not being unduly influenced or "schooled," to make the appointment?

Capacity and Powers of Attorney

A power of attorney is a written authorization (instrument) made by a competent *principal*, *grantor*, or *donor* of another person to represent or act on their behalf in personal, lifestyle, health, or financial affairs. A range of legislation dealing with POAs has been developed around the world. This includes, to name but a few, the

UK Mental Capacity Act 2005 (which created the Lasting Power of Attorney (LPA)), Adults with Incapacity (Scotland) Act (2000), Mental Health Ordinance Cap. 136 (MHO), Hong Kong Special Administrative Region of the People's Republic of China, and a range of Powers of Attorney Acts across different states in Australia and the USA and provinces across Canada.

Although the definitions of capacity to appoint a power of attorney (POA) and the powers conferred by POAs vary across jurisdictions, consider the following generic framework for assessment as used above:

i. The "why" of the appointment. Who has initiated the appointment? Is there a valid trigger to rebut the presumption of capacity? Is there already a valid document in place? Has it been revoked? Is the appointment in the best interests of the donor or someone else?
ii. The "what" of the appointment. Does the person understand when it is explained to them:
    i. That they are authorizing someone to look after and assume complete authority of their medical, personal, or financial affairs?
    ii. The nature and extent of what they are authorizing the attorney to do (the more extensive and complex a maker's affairs are, the greater their understanding needs to be)
    iii. The sort of things the attorney can do without further reference to them
    iv. Do the makers understand that the attorney can do anything with [their property or other decisions] which they themselves can do?
    v. When the authority will begin, i.e., immediately (general), or "springing" into action, or continuing (durable or enduring POAs), when they are incapable of managing their [financial or other] affairs
    vi. That they can revoke the POA while they have the capacity to do so

(e) The "who" of the appointment:
    i. Why has the person been selected for appointment as an attorney?
    ii. Has the person executed any powers of attorney previously? If so, how frequently have there been changes (i.e., revocations and new appointments)? Does the person recall making these past appointments and revocations?
    iii. Have they considered the trustworthiness and wisdom of the person they are appointing?
    iv. Is this appointment in keeping with previous appointments (e.g., has someone else been consistently appointed as attorney in the past)?
    v. What is the history of the relationship between the person and the attorney, and has there been any radical change in that relationship coinciding with the onset or course of dementia?
(f) The "freedom" of the appointment:
    i. Has all the relevant information been given to the person in a way they can understand?

ii. Is the person making the appointment freely and voluntarily, not being unduly influenced or "schooled" to make the appointment?

Financial Capacity (or Capacity to Manage Property)

The approach to the assessment of financial capacity must be driven by the same human rights and capacity assessment principles of presumption of capacity, maximization of autonomy with a task-specific focus and safeguarding against abuse. To that end, the clinician must always question the trigger for assessment: why am I being asked to do this? The intrusive nature of assessment and the potential affront to dignity and autonomy posed by questioning someone's ability to manage their own financial affairs, particularly an older person who has managed such all of their life, cannot be ignored. Conversely, while many of these assessments are initiated in the context of family conflict or a grapple for control of finances (Peisah et al. 2006), where there must be careful scrutiny for a valid trigger, there are also clinical circumstances such as concerns regarding neglect and/or financial abuse that will mandate an assessment.

The next step is to ensure that the assessor is equipped with sufficient corroborative information regarding the person's financial affairs, assets, bill payment, and provision of care to perform the assessment. A global mental state assessment must be performed remembering that mental disorders such as depression and psychosis, or specifically symptoms of depression, apathy and delusions can equally effect financial capacity as can impairment of cognition. It is sometimes useful to remind oneself that "it is not all about dementia." Notwithstanding this, assessment of cognition with an extended cognitive screen supplemented by frontal lobe testing at minimum is essential, if not full neuropsychological assessment. Finally, a performance-based financial capacity assessment must be undertaken.

Over the last 30 years, a plethora of instruments or methodologies to assess financial capacity have been developed. Sousa et al. (2014) have categorized these instruments into:

i. Neuropsychological assessment
ii. Functional assessment scales, mostly self-report, which assess a range of activities of daily living including capacity to manage financial affairs
iii. Performance-based functional assessment scales based on direct observation of performance of activities of daily living including ability to manage financial affairs
iv. Forensic assessment scales which specifically and directly address legal and clinical questions about financial capacity

There is no single gold standard instrument, although the forensic assessment scales specifically and comprehensively address financial capacity, rather than individual tasks such as counting money or purchasing items and giving change. For example, the Financial Capacity Instrument (Griffith et al. 2003) and the Financial Capacity Assessment Instruments (Kershaw and Webber 2008)

conceptualize financial capacity as comprising several domains, including basic monetary skills, financial knowledge, cash transactions, checkbook management, bank statement management, bill payment, financial judgment (including fraud risk), knowledge of personal assets/estate arrangements, and investment decision-making. Inclusion of fraud risk in the assessment of financial capacity is a significant advance in highlighting to clinicians their responsibilities in screening for and identifying financial abuse and undue influence, consistent with Article 16 of the United Nations Convention on the Rights of Person with Disabilities (CRPD).

Testamentary Capacity

Testamentary capacity refers to the capacity to make a will. Clinicians are commonly asked to do assessments of testamentary capacity for testators who are contemplating, or have recently made a will (contemporaneous assessment), and for deceased testators whose testamentary capacity has been challenged retrospectively (retrospective assessment).

The test for testamentary capacity is defined according to an English case of 1,870, Banks v Goodfellow, in which the court laid out four broad criteria to be satisfied, namely:

> *To understand the nature of the act [of making a will] and its effects;*
> *To understand the extent of the property of which he is disposing;*
> *To be able to comprehend and appreciate the claims to which he ought to give effect;*
> *That no disorder of mind will poison his affections, pervert his sense of right, prevent the exercise of his natural faculties that no insane delusion shall influence his will in disposing of his property and bring about a disposal of it which, if the mind had been sound, would not have been made*

Although this case has stood the test of time, Shulman et al. (2017) have proposed that these traditional *Banks v. Goodfellow* criteria be updated and attuned to advances in neuroscience and the modern environmental context of testamentary capacity. Specifically, cognitive disorders far outnumber "insane delusions" associated with schizophrenia (as suffered by John Banks) as the basis for modern will challenges. Proposed criteria (Shulman et al. 2017) for an updated test of testamentary capacity that assesses whether a testator, with a specific level of cognitive abilities, has the capacity to execute a particular will, in a particular life context at a particular time, are that the testator must be:

1. Capable of understanding the act of making a will and its effects
2. Capable of understanding the nature and extent of their property relevant to the disposition
3. Capable of evaluating the claims of those who might be expected to benefit from his estate and able to demonstrate an appreciation of the nature of any significant conflict and or complexity in the context of the testator's life situation

4. Capable of communicating a clear, consistent rationale for the distribution of their property, especially if there has been a significant departure from previously expressed wishes or prior wills
5. Free of a mental disorder, including delusions, that influences the distribution of the estate

Guides for performing contemporaneous (Peisah 2005; Shulman et al. 2007, 2009; Frost et al. 2015) and retrospective assessments of testamentary capacity (Shulman et al. 2005, 2007; Peisah 2005; Frost et al. 2015) have been developed. The issues of deathbed wills (Peisah et al. 2014), testamentary capacity and delirium (Liptzin et al. 2010), and wills and suicide notes (Sinyor et al. 2015) have been addressed. In addition to considering whether a testator had, or did not have testamentary capacity, the clinician must also screen for risk factors for "undue influence" (Peisah et al. 2009b). The term "undue influence" is a legal concept referring to coercion or subversion of will, specifically in the will-making process. However, the concept also has salience in circumstances where others seek to persuade vulnerable individuals including those with mental illness or cognitive impairment to make decisions or execute legal documents, including gifts, in their favor. This is inter vivos (between the living) or equitable undue influence. As outlined above, the importance of this broader more inclusive concept is acknowledged in Article 12 of the CRPD.

Risk factors for undue influence in both will-making and other document procurement include:

1. Relationship risk factors
   i. Anyone in position of trust or upon whom testator is dependent for emotional or physical needs
2. Social or environmental risk factors
   i. Isolation and sequestration of the person
   ii. Change in family relationships/dynamics
   iii. Recent bereavement
   iv. Family conflict
3. Psychological and physical risk factors
   i. Physical disability
   ii. Nonspecific psychological factors such as deathbed wills, sexual bargaining, serious medical illness with dependency, and regression
   iii. Personality disorders
   iv. Substance abuse
   v. Mental disorders including dementia, delirium, mood, and paranoid disorders
4. Legal risk factors
   i. Beneficiary instigates or procures the will
   ii. Contents of the will include unnatural provisions
   iii. Contents favor the beneficiary

iv. Contents not in keeping with previous wishes
v. Other documents have changed at the same time
vi. Evidence of inter vivos gifting

Capacity to Give Instructions and to Give Evidence

Sometimes clinicians are asked by lawyers to determine if a person has capacity to give instructions to the lawyer. Once again there is a presumption of legal capacity, until the contrary is established when a solicitor interviewing a client has caused to question or rebut this presumption, in which case they should seek assessment to determine whether or not the client can give instructions.

Two Australian cases provide guidance in relation to this. In an early Australian case, *Ranclaud v Cabban*, (1988) NSW ConvR 55-385, 57–548, Young J noted that a person must "*understand what a solicitor is and what one is doing when one is retaining a solicitor."* Although some may be *"well aware of the commercial risks involved to give a solicitor a retainer which just says "achieve result X by whatever means you think sufficient with no regard as to cost",* generally speaking *"a person retains a solicitor to advise one and one reserves to oneself the ultimate power of making decisions after receiving the solicitor's advice*.

Further to that, in *Dalle-Molle by his next friend Public Trustee v Manos,* [2004] SASC 102, at (Inouye et al. 2001; Katona et al. 2009; Kershaw and Webber 2008) and (Kim et al. 2011b). Debelle J noted the following matters:

1. The person must have the capacity not only to give sufficient instructions to prosecute or defend the action but also the capacity to give sufficient instructions to compromise the proceedings.
2. The term "sufficient instructions" in Rule 5 of the Supreme Court Rules (of the South Australian Supreme Court) signifies that the person is able, once an appropriate explanation has been given to them, to understand the essential elements of the action and is able then to decide whether to proceed with the litigation or, if it is a question of agreeing to a compromise (a settlement) of the proceedings, to decide whether or not to compromise (settle the case).
3. The person's understanding must be in relation to the facts and the subject matter of the particular case. Legal proceedings have a spectrum of complexity. They can extend from the most simple issues through a range of complexity to quite involved and complex litigation.
4. The person's level of understanding must be greater than the mental capacity to understand in broad terms what is involved in the decision to prosecute, defend, or settle the proceedings; they must be able to understand the nature of the litigation, its purpose, its possible outcomes, and the risks having to pay costs if they are unsuccessful in the case.

In a similar vein, in the UK case *Masterman-Lister v Brutton & Co* [2003] 3 All ER 162, at [75] Chadwick LJ described the test to be applied for capacity to give instructions:

> . . . the test to be applied, as it seems to me, is whether the party to legal proceedings is capable of understanding, with the assistance of such proper explanation from legal advisers and experts in other disciplines as the case may require, the issues on which his consent or decision is likely to be necessary in the course of those proceedings. If he has capacity to understand that which he needs to understand in order to pursue or defend a claim, I can see no reason why the law – whether substantive or procedural – should require the interposition of a next friend or guardian ad litem . . .

An important and familiar theme that emerges from these three common law rulings is that every case is different and that understanding must be commensurate with the complexity of facts and the subject matter of the particular case. Notwithstanding this specificity, the tests described above do necessitate a degree of mental flexibility, insight, judgment, and memory (Ashdown 2014) rendering a certain complexity to the task of giving instructions in general. For those unable to give instructions, a tutor, a next friend, or a guardian ad litem may be appointed in most jurisdictions.

Another aspect to court involvement is giving evidence. Not infrequently, people with mental or intellectual or cognitive impairment are asked to give "evidence about a fact" in either criminal or civil justice settings. Capacity to give evidence about a fact is usually defined in legislation, and is often stated in the negative, due to the presumption of capacity. Although the exact definition varies across jurisdictions, generally a person is considered not competent to give evidence if they are unable to understand a question about a fact and are unable to give an answer that can be understood to a question about the fact (O'Neill and Peisah 2017).

Clinically, an assessment of the capacity to give evidence includes consideration of factors related to the witness, for instance, the degree of cognitive impairment and any comorbid conditions that might exacerbate it, such as sensory impairment or anxiety. Cognitive impairment in one area should not be extrapolated to other areas of cognition such that a person may have impairment of semantic memory but relatively intact episodic memory, rendering them capable of giving evidence about a distressing personal event such as an instance of abuse (Sabat 2005).

The nature of the witness of fact also requires consideration. For example, a witness of fact such as the observer of a motor accident might take the stand for a shorter period, not undergo cross examination, and thus be less cognitively taxed when giving evidence than the victim of an alleged assault (O'Neill and Peisah 2017).

Finally, the capacity of a person to be a witness should also consider the ability of the court to assist the witness. For instance, support persons might be permitted on the stand, and the provision of hearing loops or assisted listening devices and aides memoire might mitigate impairments to a degree. Supported decision-making and the use of registered intermediaries (RIs) with vulnerable witnesses have been a focus of interest and extensively implemented in parts of the UK (Hepner et al. 2014; Stewart et al. 2015). Once again, there has been increasing recognition that the capacity to give evidence, for both witnesses and defendants, is decision specific, issue specific, and support dependent (Australian Law Reform Commission (ALRC) 2014).

Capacity to Consent to Research

Older people with mental illness and/or dementia have an equitable right to research being conducted in areas relevant to their care and treatment and are owed an equitable opportunity to participate in such research. These rights must be extended to both those with and without capacity, although adequate safeguards need to be in place to respect their wishes and protect their interests (Katona et al. 2009; Peisah et al. 2012). Generally, people who lack capacity to consent for themselves should only be involved in research from which they, or others with similar conditions should benefit, and which cannot be undertaken otherwise involving people able to give consent (BMA and the Law Society 2004).

Over the last 10 years, there has been a massive proliferation of regulations, legislation, and policies to provide governance over ethical conduct of research internationally. The Office for Human Research Protections (OHRP) US Department of Health and Human Services has compiled the International Compilation of Research Standards, a list of over 1,000 laws, regulations, and guidelines that govern human subject research in 120 countries (http://www.hhs.gov/ohrp/sites/default/files/internationalcomp2016%20.pdf. Accessed 31 June 2016)

Specifically in regard to the participation in research of adults with impaired capacity, in 2009, the Secretary's Advisory Committee on Human Research Protections (SACHRP) of the OHRP convened the subcommittee on inclusion of individuals with impaired decision-making in research making a number of recommendation in this area (SIIIDR).(http://archive.hhs.gov/ohrp/sachrp/20090715LetterAttach.html. Accessed 31 June 2016).

Research capacity is assessed using similar standards to treatment consent (Appelbaum and Roth 1982) although there are facts and issues that need to be understood and appreciated that are specific to research participation such as understanding the difference between treatment and research protocols, placebos, and randomization. An application of these standards to research consent includes:

i. Understanding of the facts and issues including an understanding of the procedure and/or treatment, the risks and side effects, the available options, the advantages, disadvantages, and consequences of participation and non-participation, including random allocation, the use of placebos, and the difference between treatment and research
ii. Rational manipulation of the above information and reasoning
iii. Appreciation of the nature of the situation as it applies to the person
iv. Communicating a choice, preferably a stable one (Resnick et al. 2007; BMA and the Law Society 2004)

These standards have been further operationalized to develop a range of instruments to structure and standardize the assessment of capacity due to the considerable variability in the judgment of capacity determination by clinicians (Peisah et al. 2012; Kim et al. 2011b).

The standards articulated above clearly reflect quite a high bar for understanding, and it has been suggested for over a decade that research involving older subjects who lack capacity will often need to rely on proxy or substitute consent (Mason et al. 2006). The role and obligations of such proxies and the types of research they may consent to on behalf of another varies from jurisdiction to jurisdiction. Notwithstanding these variations, whether it be individual proxies, tribunals, or courts who are providing consent, the kind of considerations they must take into account when making decisions about research participation usually include the past and current views of the person and the welfare and best interests of the person.

Although the notion of advance directives for research has been widely promulgated, it is generally held that the capacity for nominating a proxy for giving consent to research is probably less complex a task than giving consent for research or making an advance research directive. It is therefore probably retained longer in the course of neurodegenerative diseases such as Alzheimer's disease, and it has been suggested that over 90 % of persons with early Alzheimer's will likely be able to appoint a proxy decision-maker for research (Kim and Appelbaum 2006; Kim et al. 2011). It is therefore useful, as part of the advance care planning process that we encourage upon diagnosis of dementia, to encourage people to nominate not only a proxy for future health care but also for future research or at least document their wishes and preferences about such. In this way, we facilitate the equitable right to research and respect autonomous choice.

Conclusion

The assessment of capacity is a complex and highly specialized task and cannot be treated lightly by the clinician. Inevitably, when the question of capacity arises, a person's human rights for autonomy and/or being safeguarded against abuse are on the line. As such, clinicians who are engaged to undertake capacity assessment are imparted with responsibilities as gatekeepers for the actualization or denial of human rights. This is worthy of more than a one-line report. When approached using a systematic methodology that is rule driven, using principles of presumption of capacity and individualized, task- and situation-specific assessment, capacity assessment can facilitate the actualization of human rights. When people with disability such as mental illness are empowered to make the decisions they are capable of making, while protected from making the decisions they are incapable of making, human rights are supported. Such principles are universal.

References

Appelbaum PS, Roth LH (1982) Competency to consent to research. Arch Gen Psychiatry 39:951–958

Ashdown B (2014) Legal capacity and case guardians- part 1. Legal capacity. Fam Law Rev 4(1):25. Accessed May 2016 http://www.academia.edu/7850956/Legal_Capacity_and_Case_Guardians_-_Part_1_Legal_Capacity

Australian Law Reform Commission (ALRC) (2014) Equality, capacity and disability in commonwealth laws. Discussion Paper 81. www.alrc.gov.au/sites/default/files/pdfs/publications/whole_dp81.pdf. Accessed online 25 May 2015

Bamford C, Bruce E (2000) Defining the outcomes of community care: the perspectives of older people with dementia and their carers. Ageing Soc 20:543–570

British Medical Association and The Law Society (2004) Assessment of mental capacity – guidance for doctors and lawyers, 2nd edn. BMJ Books, London

Browning M, Bigby C, Douglas J (2014) Supported decision making: understanding how its conceptual link to legal capacity is influencing the development of practice. Res Pract Intellect Dev Disabil. doi:10.1080/23297018.2014.902726

Clare L, Whitaker R, Woods RT, Quinn C, Jelley H, Hoare Z, Woods J, Downs M, Wilson BA (2013) AwareCare: a pilot randomized controlled trial of an awareness-based staff training intervention to improve quality of life for residents with severe dementia in long-term care settings. Int Psychogeriatr 25:128–139

Darzins P, Molloy DW, Strang D (eds) (2000) Who can decide? The six step capacity assessment process. Memory Australia, Adelaide

Davie V (1953) Lord provost, magistrates and councillors of the city of Edinburgh, SC 34 at 39–40

de Boer ME et al (2010) Advance directives in dementia: issues of validity and effectiveness. Int Psychogeriatr 22:201–208

Fick D, Foreman M (2000) Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals. J Gerontol Nurs 26:30–40

Flynn E, Arstein-Kerslake A (2012) "Equal recognition before the law: exploring a support model of legal capacity" 10 March 2012, 'Equality: are we there yet?' The Kent Critical Law Society Conference at the University of Kent, Canterbury, p 1

Friedlander MM, Brayman Y, Breitbart WS (2004) Delirium in palliative care. Oncology 18:1541–1551

Frost M, Lawson S, Jacoby R (2015) Testamentary Capacity Law Practice and Medicine. Oxford, Oxford University Press

Griffith HR, Belue K, Sicola A et al (2003) Impaired financial abilities in mild cognitive impairment. Neurology 60:449–457

Grisso T, Appelbaum PS (1995) Comparison of standards for assessing patients' capacities to make treatment decisions. Am J Psychiatry 152(7):1033–1037

Grisso T, Appelbaum PS, Hill-Fotouhi C (1997) The MacCAT-T: a clinical tool to assess patients' capacities to make treatment decisions. Psychiatr Serv 48(11):1415–1419

Hepner IJ, Woodward MN, Stewart J (2014) Giving the vulnerable a voice in the criminal justice system: the use of intermediaries with individuals with intellectual disability. Psychiatry Psychol Law. doi:10.1080/13218719.2014.960032

Hertogh CMPM (2011) The misleading simplicity of advance directives. Int Psychogeriatr 23:511–515

Hertogh CMPM (2015) Capacity and awareness: how to include people with decision making disability second international conference on capacity. IPA Congress, Berlin

Hooper SC et al (1997) Preferences for voluntary euthanasia during major depression and following improvement in an elderly population. Aust J Ageing 16(1):3–7

Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM Jr (2001) Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Intern Med 161:2467–2473

Katona C, Chiu E, Adelman S, Baloyannis, Camus V, Firmino H, Gove D, Ghebrehiwet T, Graham N, Icelli I, Ihl R, Kalasic A, Leszek L, Kim S, Lima C d M, Peisah C, Tataru N, Warner J (2009) World psychiatric association section of old age psychiatry consensus conference on ethics and capacity in old people with mental disorders. Int J Geriatr Psychopharmacol 24:1319–1324

Kershaw MM, Webber LS (2008) Assessment of financial competence. Psychiatry Psychol Law 15:40–55

Kim SYH, Appelbaum PS (2006) The capacity to appoint a proxy and the possibility of concurrent proxy directives. Behav Sci Law 24:469–478
Kim SY, Karlawish JH, Kim HM, Wall IF, Bozoki AC, Appelbaum PS (2011a) Preservation of the capacity to appoint a proxy decision maker: implications for dementia research. Arch Gen Psychiatry 68(2):214–220
Kim SYH, Appelbaum PS, Kim HM et al (2011b) Variability of judgments of capacity: experience of capacity evaluators in a study of research consent capacity. Psychosomatics 52:346–353
Kolva EA, Rosenfeld B (2012) In: Demakis GJ (ed) Civil capacities in clinical neuropsychology. Oxford University Press, New York, pp 17–36
Lawton LJ in R v Turner [1975] QB 834 at 840
Leonard M, Donnelly S, Conroy M, Trzepacz P, Meagher DJ (2011) Phenomenological and neuropsychological profile across motor variants of delirium in a palliative care unit. J Neuropsychiatr Clin Neurosci 23:180–188
Levene I, Parker M (2011) Prevalence of depression in granted and refused requests for euthanasia and assisted suicide: a systematic review. J Med Ethics 37:205–211
Liptzin, B. Peisah C., Shulman K. Finkel S. for the International Psychogeriatric Association Task Force on Wills and Testamentary Capacity (2010) Testamentary capacity and delirium. Int Psychogeriatr 22:950–956
Makita (Australia) Pty Ltd v Sprowles (2001) 52 NSWLR 705, [at 743–744]
Mason S, Barrow H, Phillips A et al (2006) Brief report on the experience of using proxy consent for incapacitated adults. J Med Ethics 32:61–62
Massie MJ, Holland J, Glass E (1983) Delirium in terminally ill cancer patients. Am J Psychiatr 140:1048–1050
McDougall, R. Expert evidence http://www.supremecourt.justice.nsw.gov.au/Documents/mcdougall_2004.02.13.pdf. Accessed 1 April 2016
Meagher DJ et al (2007) Phenomenology of delirium. Assessment of 100 adult cases using standardised measures. Br J Psychiatry 190:135–141
O'Neill N., Peisah C (2017) Capacity and the law (2nd Edition), Australasian Legal Information Institute (AustLII) Communities. Available at http://austlii.community/wiki/Books/CapacityAndTheLaw/
Peisah C (2005) Reflections on changes in defining testamentary capacity. Int Psychogeriatr 17(4):709–712
Peisah C, Forlenza O, Chiu E. (2009a) Ethics, capacity, and decision-making in the practice of old age psychiatry: an emerging dialogue. Curr Opin Psychiatry 22(6):519–521
Peisah C., Finkel S., Shulman K., Melding P., Luxenberg J., Heinik J., Jacoby R., Reisberg B., Stoppe G., Barker A., Firmino H., Bennett H. for the International Psychogeriatric Association Task Force on Wills and Undue Influence (2009b) The wills of older persons: risk factors for undue influence. Int Psychogeriatr 21(1):7–15
Peisah C, Vollmer-Conna, SYH K (2012) Capacity to consent to research. Asia-Pac Psychiatry 4:219–227
Peisah C, Sorinmadeayo D, Mitchell L, Hertogh C (2013) Decisional capacity: towards an inclusionary approach. Int Psychogeriatr Assoc Task Force Capacit Int Psychogeriatr 25(10):1571–1579
Peisah C, Tiwana R, Benbow SM (2014a) Sexual expression, consent and capacity in residential care: a person-centered, human rights approach. In: Book of proceedings of the 1st annual international capacity conference. http://capacityaustralia.org.au/wp-content/uploads/2014/10/printed-Hong-kong-Booklet.pdf
Peisah C, Luxenberg J, Liptzin B, Wand A, Shulman K, Finkel S (2014b) Death bed wills: assessing testamentary capacity in the dying patient. Int Psychogeriatr Assoc Task Force Capacit (Int Psychogeriatr) 26(2):209–216
Resnick B, Gruber –Baldini A.L, Pretzer-Aboff, Galik E Custis Buie V, Russ K, Zimmerman S. (2007) Reliability and validity of the evaluation to sign consent measure. The Gerontol 47:69–77
Quinn G (2010) Personhood and legal capacity perspectives on the paradigm shift of article 12 CRPD HPOD Conference Harvard Law School

Ryan C, Callaghan S, Peisah C (2015) Assessing capacity to refuse psychiatric treatment: a guide for clinicians and tribunal members. Aust N Z J Psychiatry 49(4):324–333
Sabat S (2005) Capacity for decision making in Alzheimer's disease: selfhood, positioning and semiotic people. Aust N Z J Psychiatry 39:1030–1035
Shulman KI, Cohen CA, Hull I (2005) Psychiatric issues in retrospective challenges of testamentary capacity. Int J Geriatr Psychiatry 20(1):63–69
Shulman KI, Cohen CA, Kirsh FC, Hull IM, Champine PR (2007) Assessment of testamentary capacity and vulnerability to undue influence. Am J Psychiatr 164:722–727
Shulman KI, Peisah C, Jacoby R, Finkel S et al (2009) Contemporaneous assessment of testamentary capacity. A consensus report from the IPA task force on testamentary capacity and undue influence. Int Psychogeriatr 21(3):433–439
Shulman KI, Himel SG, Hull IM, Peisah C, Amodeo S, Barnes C (2017) Banks v Goodfellow 1870: time to update the test for testamentary capacity. Can Bar Rev (in press)
Sinyor M, Schaffer AM, Hull I, Peisah C, Shulman K (2015) Last will and testaments in a large sample of suicide notes: implications for testamentary capacity. Br J Psychiatry 206(1):72–76
Sousa LB, Simões MR, Firmino H, Peisah C (2014) Financial and testamentary capacity evaluations: procedures and assessment instruments underneath a functional approach. Int Psychogeriatr 26(2):217–228
Stewart S, Woodward M, Hepner I (2015) Fitness to stand trial, human rights and possibilities from England and Wales. J Law Med 22(4):886–899
Tsoh J, Peisah C, Narumuto J, Masaru Mimura M, Wongpakaran N, Kato (2015) Cross national comparisons of substitute decision making across. Asia Aust Int Psychogeriatr 27(6):1029–1037
Tulsky JA (2005) Beyond advance directives: importance of communication skills at the end of life. JAMA 294:359–365
United Nations Treaty Collection (2016) https://treaties.un.org/Pages/ViewDetails.aspx?src=TREATY&mtdsg_no=IV-15&chapter=4&lang=en. Accessed Mar 2016
Voyer P, Richard S, Doucet L, Danjou C, Carmichael PH (2008) Detection of delirium by nurses among long-term care residents with dementia. BMC Nurs 7:4
Wiese M, Dew A, Stancliffe RJ, Howarth G, Balandin S (2013) 'If and when?': the beliefs and experiences of community living staff in supporting older people with intellectual disability to know about dying. J Intellect Disabil Res 57(10):980–992
Wiese M, Stancliffe RJ, Dew A, Balandin S, Howarth G (2014) What is talked about? Community living staff experiences of talking with older people with intellectual disability about dying and death. J Intellect Disabil Res 58(7):679–690
Wiese M, Stancliffe RJ, Read S, Jeltes G, Clayton JM (2015) Learning about dying, death, and end-of-life planning: current issues informing future actions. J Intellect Develop Disabil. doi:10.3109/13668250.2014.998183
Wood S, O'Bryan M (2012) In: Demakis GJ (ed) Civil capacities in clinical neuropsychology. Oxford University Press, New York, pp 185–205
Zuscak SJ, Peisah C, Ferguson A (2015) A collaborative approach to supporting communication in the assessment of decision-making capacity. Disabil Rehabil 12:1–8. epub ahead of print

Part III

Treatment and Services

Elderly Services, Community Care, and Health Economics of Service

17

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Abstract

The first half of this chapter describes how a Community Mental Health Team for Older People (CMHTOP) facilitates specialist assessment, diagnosis, treatment, and management of the over 65s with mental health problems. CMHTOP has two key characteristics: it is multidisciplinary and operates within an integrated care pathway involving statutory organizations, the voluntary sector and informal caregivers/family. This multidisciplinary and integrated approach is common in many high-income countries, as opposed to the single-discipline clinics (usually run by a psychiatrist) seen in low- and middle-income countries. A CMHTOP-based model improves decision-making, continuity of care, and diagnosis of comorbid problems and is more effective in reaching frail older people who have multiple health and social care needs.

The second half of this chapter describes how economic evaluations compare the costs and outcomes of different interventions and services to inform decisions about "best value for money" in the mental health care of older people. This is challenging not only because age-related health outcomes are naturally expected to worsen – or at best stay the same – rather than improve with time but also because care-related costs are spread widely and disproportionately across many different sectors and stakeholders. With dementia as a case in point, large costs are attributable to living

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_18

arrangements and informal care paid by social services and families during the severe stages of the illness, whereas the cost of therapies and drugs for mild to moderate dementia, incurred by health services, are relatively low.

Keywords

Community mental health • Elderly • Dementia • Depression • Economic evaluation • Cost-effectiveness • Multidisciplinary team • Integrated care

Contents

Introduction

Since 1997, the World Psychiatric Association (WPA) Old Age Psychiatry Section and the World Health Organization (WHO) have produced consensus statements and guidelines relevant to services for older people with mental health problems. Such services should be provided by professionals with relevant training, expertise, and competencies, working within an infrastructure that is designed to deal with the complex mix of social, psychological, and biological factors associated with mental illness and care for this population (Banerjee and Chan 2008; Draper et al. 2006). As discussed in ▶ Chaps. 1, "Challenges and Opportunities of Aging Populations Around the World," and ▶ 5, "(Neurobiology of) Dementia: Causes, Presentation, and Management," older people experience a range of mental health problems: depression and dementia are the most prevalent ones, but we should not lose sight of schizophrenia, mania, and anxiety disorders. Technological and medical advancements come at an increased cost for those paying for older people's mental health care. This is not only because services need to be updated with state-of-the-art equipment, new medicines, and trained specialist personnel but also because demand for these services increases rapidly and proportionately to the expanding older population worldwide, as discussed in ▶ Chap. 1, "Challenges and Opportunities of Aging Populations Around the World."

In principle, mental health care is a civil and human right for every person who must be offered equal and unlimited access to it. In reality, there are relentless

pressures on the "public purse" and many completing demands for spending on areas other than older people's mental health – such as children and young people's services, physical health, education, housing, and pensions. Governments establish ceiling thresholds for allocated resources across different sectors because funding is not infinite. They also define guaranteed protection floors for neglected sectors, such as mental health, so that people have fair and adequate access to interventions and services which they are entitled to and could potentially benefit from. Between ceiling thresholds and protection floors, decisions have to be made about value for money and affordability.

The first half of this chapter describes a model of state-funded community care that hinges on the *Community Mental Health Team for Older People* (CMHTOP) (Abendstern et al. 2012; Shah and Bhatkal 2005). This multidisciplinary team facilitates specialist assessment, diagnosis, treatment, and management of mental health problems in older people, as part of an integrated care pathway in liaison with other services and teams, such as primary care, inpatient services, and social care. The second half of this chapter describes the economics of mental health care for older people. Health economics is a social science that informs the allocation of scarce resources by conducting economic evaluations (Drummond et al. 2015; Phelps 2016); these compare the costs and outcomes across interventions or services to help those who pay – governments, insurance companies, and individuals – decide which option offers better value for money.

Community Mental Health Care for Older People

CMHTOPs are integrated multidisciplinary teams, usually based in secondary care, which are designed to facilitate assessment, diagnosis, treatment, and management of older people with mental disorders in a continuous and cohesive way (Shah and Ames 1994; Shah and Bhatkal 2005; Wilberforce et al. 2013). Such teams are in contrast to single-profession services, such an outpatient's clinic run by a psychiatrist that is not integrated within a wider system. This definition for CMHTOP is applicable internationally, although there are variations in its structure and function depending on the availability of human resources and other services in each locality.

The CMHTOP model originated from the innovative work of Professor Thomas Arie (Arie 1970). In 1969, Arie set up the Goodmayes psychogeriatric service in Northeast London, with the aim of achieving a high standard of psychiatric care for the older residents within the local hospital's catchment area. The second aim for Arie was to improve the recruitment of doctors into the specialty of psychogeriatrics by demonstrating that working with older adults can be exciting and rewarding. This service was innovative and perhaps the first of its kind. Within the first year, 276 patients were referred into this service and half of them were discharged by the end of the year. Of the original 350 occupied hospital beds, 40 beds had been emptied despite the increase in admissions and decrease in deaths. Not only did the service achieve its primary goal but it also enabled and fostered an integrated approach to working with older adults.

In high-income countries, like the UK, New Zealand, and Australia, community teams caring for older people with mental health problems are staffed by a range of professionals who complement each other, including psychiatrists, community psychiatric nurses (CPNs), social workers, occupational therapists, psychologists, physiotherapists, dieticians, chiropodists, and speech and language therapists (Shah and Ames 1994). In contrast, community mental health services for older people in low- and middle-income countries are nonexistent or are staffed by fewer disciplines (Prince et al. 2007). A multidisciplinary team can improve decision-making and provide greater continuity of care (Wilberforce et al. 2013). It can also achieve better reach of frail older people who have multiple health and social needs and who cannot access private care (O'Connor and Melding 2006). A multidisciplinary approach to diagnosing dementia does better in differentiating among subtypes of dementia and detecting comorbid psychiatric conditions such as depression (Wolfs et al. 2006).

Despite the added value of different professionals contributing to the mental health care of older people as an integrated team, there are issues around the design of such a team (Wilberforce et al. 2013). First, there are barriers to the integration of sessional (rather than full time) staff, like psychologists and social workers, because their loyalties are divided between different teams and services. Second, there are concerns about skills dilution and substitution because of the growing number of CMHTOP members without a professional registration who have less expertise – along with lower salaries – than clinical staff. More robust evaluations of the impact of CMHTOP design on patient outcomes and cost-effectiveness are needed (Abendstern et al. 2012).

Staff Roles Within CMHTOP

Psychiatrists

Psychiatrists working within a CMHTOP – whether senior, junior, and trainees – have several clinical responsibilities, including assessment and diagnosis of mental illness, assessment of risks, identification of the needs of patients and their carers, formulation of a management plan, evaluation and interpretation of the findings of special investigations (e.g., blood tests, urine tests, ECG, neuroimaging, EEG, and psychometry), and provision of pharmacological and psychological treatments. The role of the psychiatrist is also important in communicating with psychiatric inpatient and liaison services, geriatricians, general practitioners, and hospital managers. Senior psychiatrists also provide a leadership role within the CMHTOP, which involves the supervision and governance of the clinical team and its individual members.

Increasingly, consultant psychiatrists tend to be directly involved only with complex and treatment-resistant patients, but their role extends to advising other team members who are looking after the majority of patients. In Ontario, Canada, where there was a shortage of psychiatrists in CMHTOPs, at the very least each case was discussed with the psychiatrist in most teams (Ginsberg et al. 1998). Even

in vast geographical areas with low density of older people, such as South Australia, models can be developed to effectively use old age psychiatrists (Nowak 2012).

Community Psychiatric Nurses (CPNs)

CPNs have multiple roles and are often the backbone of CMHTOP. They often see patients in their own homes and care homes, in outpatient (including memory) clinics, and in general practice surgeries. They assess new patients and follow up existing ones, provide support for their caregivers/families, deliver psychological interventions like cognitive behavior therapy (CBT), administer depot antipsychotic medications, monitor treatment adherence and side effects, and coordinate all other aspects of patient care. CPNs are also the communication bridge between the patient and the CMHTOP. CPNs train staff in primary care and care homes in the identification, assessment, and management of mental health problems in older people. In some countries, like the UK, CPNs are also being trained for a new role as nurse prescribers, whereby they have autonomy to prescribe a limited number of psychotropic drugs. A study demonstrated the efficacy of a collaborative care intervention for older people with depression delivered by CPNs, who coordinated all aspects of care in liaison with primary care and old age services and facilitated a self-help program (Chew-Graham et al. 2007).

Social Workers

Social workers may be employed by social services in some countries (e.g., the UK) and by health services in others (e.g., State of Victoria in Australia). In both systems, social workers operate alongside other members of the CMHTOP within a collaborative and integrated model of care. Their role is to advise on housing, organization of community care packages for home-based care and "meals on wheels," organization of day centers and respite care, provision of technological aids (including alarms and telecare), financial issues, benefits entitlement in countries with a welfare system, and family work. In the UK, social workers also act as gatekeepers for placement in care homes, although much of their work is designed to try and manage the older person at home for as long as possible. Social workers can play an important role in promoting interventions to combat social isolation, which they perceive to be a major cause of depression in older adults (McCrea et al. 2005).

Occupational Therapists

The main task of occupational therapists (OTs) is to improve the older person's quality of life by assisting them to have optimum functioning in the context of any mental, physical, or social disability. OTs assess functional disabilities, provide assistive technologies to correct functional deficits, help in the assessment of those who may need placement in care homes, and run therapeutic group activities. The National Institute for Health and Care Excellence (NICE 2008), on behalf of England's Department of Health, has produced a public health guidance on occupational therapy interventions and physical activity interventions that promote mental well-being in older people. This guidance recommended initiatives to promote nutrition (e.g., healthy eating on a

budget), personal care (e.g., shopping, laundry, keeping warm), access to services and benefits, home and community safety, exercise programs of moderate intensity (e.g., dancing and swimming), and walking schemes. Updated evidence from the USA (Clark et al. 2012) was consistent with this guidance by showing that a community-based lifestyle-based intervention delivered by occupational therapists improved mental well-being among ethnically diverse older people.

Other Clinical Staff

A CMHTOP includes other professionals who can play an active and significant role with regard to patient care although they may not be part of the care-coordinating core team. Such professionals are *psychologists*, *physiotherapists*, *speech and language therapists*, *dieticians*, and *chiropodists*. Psychologists assess cognitive status, perform neuropsychometric tests, deliver psychological interventions and develop treatment programs to minimize cognitive deficits, and enhance preserved cognition. They also develop behavioral management programs for noncognitive symptoms of dementia and supervise their implementation by other members of the CMHTOP or care home staff or relatives (Pachana et al. 2006). Physiotherapists focus on improving older people's mobility, flexibility, stability, and function leading to greater independence; they also provide advice on avoiding injury. Speech and language therapists address any concerns related to swallowing and facilitate better communication with patients who may have altered language function because of physical disorder or cognitive impairment.

The role of the dietician is to provide an assessment of nutritional status and further support to patients who are underweight, suffering from dietary and nutritional problems, and those who need specific dietetic advice (e.g., those with high cholesterol or diabetes). This is particularly important in older mentally ill patients where both the poor dietary consequence of the illness and dietary requirement for dealing with risk factors is important. Chiropodists treat a wide variety of foot and lower limb abnormalities, and their services are vital to older people maintaining mobility and independence.

Support Workers and Nonclinical Staff

In England there has been a growth in recent years of support workers and nonclinical staff within multidisciplinary teams, who are directly involved in the care of older people with mental health problems under the supervision of clinicians (Wilberforce et al. 2013). This group of staff have previous experience in working in health care and receive training relevant about the specific population they work with and the local service's circumstances. This group of workers in CMHTOP are seen as less costly than clinicians, but little formal evaluation has been undertaken to establish whether lower salary costs provide good value for money in terms of improved patient outcomes and satisfaction.

Administrative Staff

Administrative support is a vital component of CMHTOP and includes secretarial time, equipment, and office space. Administrative staff are the first point of contact

for patients and carers and play a pivotal role in receiving referrals, setting up appointments, and maintaining communication between CMHTOP members and different agencies.

Referral and Assessment Processes

Closed Versus Open Referral Systems

Referral by letter, fax, or email is widely used. Telephone referrals are usually reserved for emergencies in the UK. In some countries, like India, there are self-referral walk-in clinics. There are two models of referral: open and closed. In the closed model, only another doctor, usually the general practitioner (GP), can refer to the CMHTOP. The advantage of this model is that the GP acts as a filter for physical disorders, delirium, social care problems independent of mental illness, or mental health problems that can be managed in primary care. Commissioning arrangements that are driven by primary care, as seen in the UK, or an oversubscription of specialist old age services encourage a closed referral system. The open referral system accepts referrals from other health-care staff working in the community or general practice, social workers, care home staff, police, voluntary sector agencies, and even relatives or self-referrals. The advantage of this system is that it is more responsive (Audit Commission 2000) as patients are referred directly by anyone concerned without unnecessary delay to consult the GP. Its disadvantages include potential referral of patients without a mental health problem or with delirium, referrals with an incomplete medical history, and referrals that the GP can manage. Examples of an open referral system include self-referrals to a community memory clinic in the Indian state of Kerala.

Assessments

During regular, scheduled clinical meetings, the CMHTOP discusses new referrals and then decides which team member is the most suitable to assess the patient. This decision is based on the relevant skills of the clinical staff, the patient's clinical presentation, and their potential risks. The first, and any follow-up assessments, of a newly referred older person can be conducted either at home or in specialist memory clinics that are set in psychiatric hospitals, general hospitals, day hospital premises, and in primary care. Assessments can also be conducted using videoconferencing/video telemetry when the clinicians are unable to visit the patient, or if the patient is unable to attend clinics, or if nursing homes are situated in rural locations and without their own old age psychiatry team. Memory clinics may be staffed by a variable combination of CMHTOP staff with the addition of neurologists and geriatricians. As an example, memory clinics in Australia have less than two full-time equivalent of clinical staff (doctors, nurses, psychologists, and allied health staff) and are open on average twice a week offering two new and three follow-up appointments in a half-day session (Woodward and Woodward 2009).

Pathways of Care

As a result of the assessment process described above, the CMHTOP decides whether the patient needs follow-up or whether advice to the patient, their carer, and the referrer will suffice. If follow-up is needed, the CMHTOP decides which team member should pursue this and in what setting: at home or in outpatient clinics, in day hospitals, by the crisis resolution and home treatment team, or as a hospital inpatient.

Home Follow-Up

Follow-up at home has many advantages, including popularity among older people, their caregivers, and general practitioners; seeing firsthand the home conditions of the older person, the older person is likely to feel more comfortable at home; the assessor can examine all the medications which may not be brought to the clinic; assess the person's eating habits and availability of food; assess any potential fire hazards; assess the needs of the carer; prevent or facilitate subsequent unnecessary referral for occupational therapy assessment; avoid a frail older person with poor mobility and sensory impairment the discomfort of attending a clinic, especially if the person or their family have no access to transport; avoid the stigma of visiting the psychiatric hospital; and improve engagement and consultation rates by preventing nonattendance at outpatient clinics. Initial home assessments, when compared to those in outpatient clinics, have been shown to identify a greater number of new or comorbid problems.

Crisis Resolution and Home Treatment Teams

Crisis resolution and home treatment teams provide intensive home-based care to older people with mental health problems. These can be nurse-led services, available during the day or through 24 h, with the view of reducing admission rates and supporting the caregivers in looking after their relative at home. Increasingly home treatment teams act as gatekeepers who reinforce alternatives to hospital admission. A systematic review (Toot et al. 2011) showed a lack of good quality evidence for the effectiveness of home treatment teams in supporting older people with mental illness to remain at home and subsequently reducing hospital admissions. Although the absence of evidence does not necessarily imply lack of effectiveness for home treatment teams, future controlled studies can provide empirical evidence to help decision-making about this type of service.

Day Hospitals

Day hospitals are health-care facilities, which patients can attend during the daytime and in which multidisciplinary assessment, treatment, and rehabilitation are available. Attendance may be daily for the whole week or for part of the week; some services are available at the weekend. The role of day hospital includes intensive multidisciplinary assessment and treatment for older people with complex mental health needs; gatekeeping for inpatient admissions; rehabilitation; time-limited interventions such as individual and group psychological interventions; education, information, and advice for carers; monitoring effects and side effects of medication; and support for care staff in other services to enable older patients to be managed at home.

Day hospitals can allow for intensive treatment while patients remain at home. Day hospitals have the same team design as in CMHTOP but require an ongoing review of staff and skills mix to ensure the best use of human resources. They may be located within the hospital or CMHTOP premises or in a non-health community venue. Innovative approaches in hosting day hospital include a travelling day hospital to cater for patients in rural areas with vast geographical distance and secondary satellite facilities in church halls and other venues, in addition to the main day hospital, to run groups closer to patients' homes. Most day hospitals will provide for older people with dementia and for functionally ill people on different days or on different sites. There is a risk that day hospitals may become more like a "day center" for socialization and day activity structure; although this can be helpful and even therapeutic for older people, it deviates from the clinical functions for which a day hospital team has been designed and resourced.

Inpatient Hospital Care

Hospital admissions may be necessary if it is no longer feasible or safe for the patient to remain in the community. Patients may be admitted into the medical wards of a general hospital if they have delirium with an underlying medical explanation, or a concomitant serious medical disorder, or catatonia of unclear origin, or a need for medical resuscitation after self-harm. Otherwise, patients may require admission directly to a psychiatric ward. The main aim of a psychiatric inpatient admission is to assess, treat, rehabilitate, and discharge the patient into the community. Some indications for the necessity of a psychiatric hospital admission are severity of the person's symptoms, risk to self or others, availability of support from mental health and social care services in the community, available family and friends, and certain treatments such as electroconvulsive therapy and clozapine titration. Other forms on inpatient admission include respite and long-term admission, although institutional continuing care is increasingly provided in care homes rather than hospitals.

CMHTOP are often involved in the hospital admission of an older patient and are likely to follow-up patients after they are discharged from hospital; therefore, close liaison work between inpatient units and CMHTOP is needed. Some services operate a "catchment area" model whereby some clinical staff from different disciplines work across inpatient and CMHTOP settings to maintain continuity of care and facilitate communication. Where this is not the case, models of close liaison between the two settings need to be developed and should be underpinned by a CMHTOP member, who performs the role of case manager, regularly attending inpatient ward rounds and other key meetings and reviewing the patient on the ward.

Liaison with Other Agencies

CMHTOP members maintain close links with geriatricians, general practitioners, neurologists, local social services, day centers, care homes, and relevant voluntary sector groups. These links help the provision of an integrated pathway of care and facilitate bidirectional training. CMHTOP in developed countries often rely on the voluntary sector to plug gaps in statutory service provision; this reliance is even greater in developing countries. Liaison with the voluntary sector include links with nonprofit

day centers, befriending services (where older people are linked with friendly volunteers), and informal support for carers. For example, in West London, a support service is available whereby a volunteer stays at home with the dementia sufferer to enable the carer to use that time for respite, shopping, and even doing household chores.

Apart from CMHTOPs liaising with other teams and services to enable patients and carers to make most efficient use of existing resources and expertise in the community and hospitals, CMHTs also add resources and expertise to other teams and services in the form of outreach activities. A national survey in the UK (Tucker et al. 2014) showed that 88% of CMHTOPs provided some form of outreach activity to care homes, social services, day centers, primary care, home care providers, and general hospitals. This included training, advice and consultations for the assessment, and management of mental illness in older people. Community psychiatric nurses and larger CMHTOPs were most likely to provide a structured outreach service, but the majority of liaison and outreach work was informal and unstructured, therefore more likely to be inconsistent.

Caregiver Support

Relatives, neighbors, and friends who provide unpaid support and care to older people with mental health problems can be described as informal caregivers. It is important that the CMHTOP members recognize the burden to caregivers and assess their needs and provide appropriate support. Carer-based interventions for dementia have been successfully evaluated (see meta-analysis by Brodaty et al. 2003) and include education about the older person's diagnosis and treatment, organization of carer support groups, training of carers in basic interventions, and access to financial advice and respite services.

Practical Considerations in Service Delivery and Evaluation

Transport in the Community

CMHTOP staff who visit patients at home or in other community settings away from their base may use hospital-provided transport, or personal vehicles, or public transport. Patients who visit CMHTOP staff at their premises, at outpatient clinics or day hospitals, may be able to walk there, use public transport, use their own vehicles, be driven by family or friends, use services like "bus-plus" or "dial-a-ride" (available in the UK), use taxis paid for by the service user or the CMHTOP, or use an ambulance service. The type of transport chosen by patients will depend on a range of factors including location of the facility to be visited, geographical nature of the locality (e.g., rural vs. urban), the availability of a particular form of transport, the availability of friends or relatives, and the presence of disabilities including cognitive impairment, reduced vision or hearing, or poor mobility.

Although ambulances are considered to be expensive, they have several advantages: the ambulance staff who are accompanying the patient usually have had some medical training; nurse or paramedics escorting patients out of the home are able to observe the home environment, therefore offering important collateral information;

patients with restricted mobility can travel comfortably. One important disadvantage is that ambulance transportation picks up several patients in one journey, so patients may have to wait for long periods of time to be collected and cannot travel at a time convenient for them. Taxis are a quick and convenient alternative to an ambulance. Taxis usually carry one patient and therefore provide the patient with flexibility to manage their time. On the flipside, repeated taxi rides can be expensive and taxi drivers have no medical or psychiatric training and are also unable to carry patients with significant mobility problems or other impairments.

Training and Professional Development of CMHTOP Staff

All CMHTOP staff, including nonclinical staff, should receive regular training that is specific and relevant to their role in the team. For many professional groups, there is a statutory requirement to keep their skills and knowledge up to date under the umbrella of *continuous professional development* (CPD). The team structure and budget should allow sufficient time and adequate access to relevant training. Any local connections with academic departments should be built upon to facilitate local training. A survey of 93 countries by the World Psychiatric Association reported that specific continuing professional development programs for old age psychiatry were only available in 50% of the surveyed countries and suggested the development of a global training program (Camus et al. 2003).

Quality Assurance

The activities of the CMHTOP, once it has been set up and is fully functional, should be subject to regular quality assurance monitoring through clinical audits, service evaluation, and feedback from service users, carers, and referrers. This monitoring can be internal or external. Internal audits and evaluations can be conducted by CMHTOP senior clinicians and service managers. External clinical audits and service evaluations may be conducted by governmental regulatory agencies; in the UK, such this role is performed by the Care Quality Commission (CQC) (http://www.cqc.org.uk) or the Royal College of Psychiatrists. Feedback from service users, carers, and service referrers should also be ascertained on a regular basis. The outcomes of internal and external scrutiny and service user feedback should be shared with CMHTOP staff and with those who manage and fund the service. Any improvement as the result of identified and implemented changes should be documented and benchmarked against local or national guidance.

Economics of Mental Health Care for Older People

Mental health problems in older people, especially dementia and depression, have a big economic impact on individuals, families, and societies. In 2010, depression across all ages was ranked the second leading cause of the global burden of disease (GBD) (Ferrari et al. 2013), and the cost of dementia is estimated at more than 1% of the global gross domestic product (GDP) (Wimo and Prince 2010). The recognition of mental illness internationally as a significant societal problem makes health

economics a useful tool to demonstrate that an investment into the identification, prevention, and care of mental illness is necessary and worthwhile, not only for clinical, social, and moral reasons but also for economic reasons.

Economics is a social science that seeks to analyze and describe production, distribution, and consumption of goods and services. Economists study how individuals, groups, and societies seek to satisfy wants and needs when the available resources are insufficient to satisfy *all* wants and needs. Health economics is the application of economic principles and methods to understand what drives our spending in health care, what benefits we get from this spending, and how our life and well-being may change if our pattern of spending changes (Phelps 2016). Economic evaluations are methods that inform decision-making in the allocation of available resources by estimating and presenting the relative costs and outcomes of different options (Drummond et al. 2015).

Cost in Health Economics

Defining "Cost"

Any activity involves a "cost" (for a useful glossary of different types of costs involved in health economics, see Shiell et al. 2002). In its most basic form, cost in health economics refers to the resources associated with an illness and the provision of care for it. There are generally three types of health-care cost: *direct cost*, *productivity loss or indirect cost*, and *intangible cost*. Direct cost refers to those resources whose consumption is wholly attributable to providing an intervention or service. Direct costs include resources provided by health care (inpatient, outpatient, day hospital, emergency room, community mental health center, general practitioner, community practice nurse, medication, psychological therapies), social care (social worker time, day-care center, meals on wheels, home care or support, care homes), and individuals and families (accommodation, out-of-pocket expenses for self-care and home adaptations, private hire of a nurse, unpaid home helper, health food and supplements). Indirect cost generally refers to loss of productivity (paid or unpaid) resulting from the morbidity or mortality of the patient and the caregiving activities of the family. Intangible cost refers to the pain and distress resulting from the illness and its treatment.

Commonly, cost is expressed in terms of money, but "cost" is not synonymous to "price." Cost refers to the amount of resources spent or foregone, whereas price is the monetary value of these resources, which is determined by the market, context of delivery, and many other factors (e.g., taxes, subsidies). To give a simple example, a patient may need to see a health professional once a week for an hour over 12 weeks. The resource may remain constant (12 h of professional time), but the price will vary depending on the background and grade of the professional (12 h will cost more for a senior doctor, less for a junior doctor, and even less for a nurse). Both direct and indirect costs are expressed in monetary terms, but intangible cost is typically more difficult to quantify in money, because this would require to attach a "price" or a "value" to someone's health state, pain, or distress. Still, health economists use

methods to do this in cost-utility and cost-benefit analyses, as described in section "Economic Evaluations."

Estimating Cost

There are steps in estimating costs in health economics: (a) measuring the amount of resources spent or foregone, which is called *resource utilization*, and (b) assigning a monetary value or price to those, which is called *unit cost*.

The most convenient method of data collection for resource utilization is via a questionnaire or structured interview, which quantifies and documents all aspects of care provision over a specific period of time at the various assessment points of a study (e.g., over the last 6 months, how many times did you visit the doctor?). Other methods of data collection for resource utilization are case notes and hospital/clinic records. At the initial stage of data collection, a list of relevant resources and potential units of utilization for these resources need to be identified, e.g., number of sessions of 10-min GP consultations, number of hourly sessions with a psychological therapist, number of days staying in hospital, number of hours spent per day looking after a relative, and number of medicine tablets.

The methods of data collection for resource utilization have to be adapted to the scope (perspective) of the economic analysis, the objectives and setting of the clinical study, and the particular care needs of the target population. For example, patients with severe or enduring mental illness, such as Alzheimer's disease or psychosis, often need a wider range of services (e.g., residential care, hospital transport, social services) than people with common mental health problems such as depression and anxiety.

A unit cost is expressed in money terms for each resource. The total cost of resources is estimated by multiplying the amount of a resource used by that resource's unit cost (amount of resource used $\times$ unit cost). Unit costs may be available through national databases (e.g., the salary of a doctor) – i.e., a top-down approach to cost estimation – but these may not always be available or relevant in the context of a study and often vary across different regions, time periods, or providers. Alternatively, unit costs can be collected alongside resource utilization by asking for information on the actual cost of the identified resources – i.e., a bottom-up approach.

There are several considerations when estimating resource utilization and cost values in economic studies:

(a) It is important not to double-count cost. For example, the time we spent caring for an older relative could have been used to study with a child or to produce a work report, but not both; therefore, we cannot count both the forgone study time and the forgone work report as the cost of caring for an older relative.
(b) When calculating the cost of an activity which is projected over a long time in the future, or which occurred several years in the past, the cost should be either discounted or inflated to the present value at an appropriate rate.
(c) A sensitivity analysis assesses how the cost may vary for different modes of delivery or patient groups or service contexts, by introducing alternative cost values to important resources (e.g., the grade of clinicians employed).

A sensitivity analysis is an important activity against uncertainty in an economic analysis, because it assesses how robust our conclusions are in the face of reasonable and expected variations to our key assumptions.

(d) Apart from clinical factors, resource utilization and assigned cost values are determined to a significant extent by two other factors: first, the socio-demographic and socioeconomic characteristics of the population (e.g., age, sex, education, and employment) and second, the accessibility, availability, and quality of the local health and social care system (structure, organization, and financing).

Outcomes in Health Economics

Defining Outcomes

Health economics is concerned as much with health outcomes as they are with cost. There are numerous ways of collecting data relevant to health outcomes:

- Patient-reported outcomes (e.g., global impression of improvement, functional status, health-related quality of life, symptoms)
- Caregiver-reported outcomes (e.g., dependency, functional status)
- Clinician-reported outcomes (e.g., global impressions, observations, tests of function)
- Physiological outcomes (e.g., FEV1, HbA1c, tumor size)

There are several types of outcomes that evaluate the effect of health-care interventions for patients and their carers, as described below:

- *Clinical outcomes*: Medical events that occur as a result of an illness or its treatment (e.g., stroke, disability, hospitalization)
- *Intermediary/surrogate outcomes*: Measurements of a patient's physical or bio-medical status used as a risk factor for, or to infer the degree of, illness (e.g., blood pressure, forced expiratory volume, plasma level of cholesterol, smoking).
- *Humanistic outcomes*: The impact of an illness or its treatment on the lives and well-being of patients and their families (e.g., satisfaction, quality of life)
- *Process outcomes*: Factors that influence patients' views in relation to their illness or its treatment (e.g., self-efficacy, perceptions of control, treatment expectations)

There is an important distinction between clinical outcomes and intermediary/surrogate outcomes which feeds into the selection of the most appropriate outcome for economic evaluations. For example, blood pressure is an intermediary outcome in the treatment of hypertension, while stroke or myocardial infarction are clinical outcomes (i.e., end results). Although for some illnesses there is a strong relationship between intermediate outcomes and end result (e.g., blood pressure and stroke, smoking and lung cancer), intermediaries for other illnesses may not be as well established or as relevant and informative as the end clinical outcome.

For example, the Mini-Mental State Examination (MMSE) is a measure of cognitive function and has been used as a clinical outcome for health economic evaluations in dementia intervention studies; however, it is not the decline in cognitive function itself that causes most problems in dementia care, but the need for institutionalization, because a patient's quality of life is positively correlated with staying in their own home. Having said this, a prolonged period of staying at home for an older person with significant cognitive impairment may increase the burden and distress for informal caregivers and therefore compromise the caregiver's quality of life. As a result, quality of life of both patients and caregivers is one of the most relevant and reliable outcomes for clinical trials and economic evaluations in older people's mental health care (Wimo et al. 2000).

Utility: A Common Currency for Outcomes Across Different Conditions and Interventions

A *utility* is a score which describes an individual's preference for a particular outcome or health state under conditions of uncertainty (Torrance 1986): the stronger the preference for a particular outcome/health state, the higher the utility score. Individuals have preferences for alternative health outcomes (e.g., they prefer health state A to health state B). The preferences can be measured on an ordinal scale or a cardinal scale. An ordinal scale is simply ranking outcomes in order of preference. A cardinal scale is a continuous numeric scale. In the most common version of health utilities, death is given a score of 0.0, perfect health is given a score of 1.0, and all other outcomes are scored relative to these two.

Utility measurement is a method of querying an individual in order to measure the strength of their preference for an outcome or health state and to represent this preference by a utility score. Two widely used methods for utility measurement are the standard gamble (SG) and the time trade-off (TTO) (Whitehead and Ali 2010). The SG is based directly on expected utility theory as first postulated by von Neumann and Morgenstern (1953) and is particularly designed for use with problems in which the outcomes are uncertain, like health problems. In all fields but health, the SG is the overwhelmingly preferred method to measure utilities. In health, the TTO was developed as an alternative. Unlike the SG, the TTO does not measure preferences under uncertainty; therefore, the preference scores from the TTO are technically values, not utilities. Still, the SG methods have now improved to the point where it is no longer difficult to administer for health. Both techniques are widely used.

In the SG, an individual expresses his or her preference by choosing between two alternatives. For example, an individual who prefers A to B to C would be asked to choose between one alternative in which outcome B would be received with certainty and a second alternative in which outcome A would be received with probability p and outcome C with probability $1- p$. The probability p would then be varied until the individual was indifferent between these three choices. The "indifference probability" is used to calculate the utility that the individual has for outcome B relative to the utilities for outcomes A and C.

In the TTO, an individual expresses his or her preference by choosing between two options. For example, an individual who prefers perfect health to outcome B

would be asked to choose between one option in which outcome B would be received with certainty for the remaining life expectancy t years and a second option in which perfect health would be received but for a shortened life expectancy x *years* (where $x<t$). The duration x would then be varied until the individual was indifferent between these two choices. The ratio x/t is the TTO value score for outcome B on a scale where immediate death is 0.0 and perfect health for the lifetime duration t is 1.0. Here is an example: You have 10 years left to live in your current health state. You can choose to live for less years in full health. How many years are you willing to sacrifice in order to live in full health compared to the 10 years in your current health state? If the answer is 5 years in full health as opposed to 10 years in current health, then the TTO score – utility for the current health state – is $5/10 = 0.5$.

Utility scores can be assigned to a health-related quality of life (HRQoL) measure, such as the EQ-5D, so are also known as HRQoL weights. The EQ-5D is the most widely used HRQoL measure in economic evaluations and has been validated in patients with dementia (Wolfs et al. 2007). It captures five dimensions of HRQoL (mobility; self-care; usual activities, e.g., work, study, housework, family, or leisure; pain/discomfort; anxiety/depression) with three levels each (no problems, some problems, severe problems); this yields 243 potential combinations of health states. Each combination has a utility score attached to it, between 1 for "perfect health" and 0 for "dead." Scores between 1 and 0 are on an interval scale (e.g., 0.2, 0.3) and states worse than death are given a negative value.

A health outcome measure which incorporates utility scores and is considered the cornerstone of economic evaluations is the *quality-adjusted life year* (QALY). QALYs express the impact of an illness or an intervention on both the quantity and quality of life. They are calculated by multiplying years added to life/years of survival in a specific health state by the utility score attached to this state. To give a basic example, if intervention A contributes to 5 years of survival in perfect health (i.e., utility score 1), then the gain over 5 years is $5 \times 1 = 5$ QALYs. If the same 5 years of life after an intervention B are spent in a health state with a 0.8 utility score, the total gain from B is $5 \times 0.8 = 4$ QALYs (without taking into account discounted values for each year). This shows that intervention A has a better outcome than intervention B because we gain one extra QALY.

Utility scores offer the possibility to use the same "currency," such as a QALY, to compare outcomes across different heath conditions and different interventions. Controversy exists as to "whose preferences" we should use when we assign different utility scores to a specific health state/illness: the preferences of the patients who have actually experienced an illness or those of a representative community sample? Generally, people experiencing an illness attach a lower utility score to that illness (or impaired health state) compared to the general population who may consider some health states "worse" than others, e.g., cancer over depression. Decision-makers for public health generally have to incorporate the utilities obtained from the general population rather than those from the affected patients.

Economic Evaluations

Scarcity of resources is a major barrier to improving mental health services for older people. Economic evaluations are a comparative analysis of costs and outcomes associated with different interventions or services to assist decision-making when choices have to be made about allocating health-care resources under conditions of scarcity and uncertainty (Drummond et al. 2015; Shiell et al. 2002). Economic evaluations are often built within clinical evaluations or trials, which compare the outcomes of a new intervention/service with the outcomes of a control (e.g., usual or standard care) over a specific period of time. This controlled study design is the "gold standard" of clinical and economic evaluations (especially if patient allocation is random), because it can demonstrate that any changes in the selected outcome measures are attributable to the intervention itself, rather than being due to chance or due to other confounding variables (e.g., spontaneous remission of symptoms over time, attention, or measurement effects).

The *economic scope, or perspective*, of an economic evaluation is important because it influences what costs and outcomes are to be measured; therefore, the perspective should be determined according to whether the intervention/service under study is expected to have a differential impact on a broad range of sectors and stakeholders. For example, residential care accounts for the largest proportion of dementia costs and informal care accounts for one-third, whereas health-care costs account for a relatively small proportion of the total dementia costs in the UK (McCrone 2008).

The perspective of an economic evaluation can be as narrow as a particular agency or government department (e.g., ministry of health) or can be broader to include the statutory/public sector as a whole (e.g., all health and social care services). If economic evaluations are performed from a restricted perspective, they may lead to cost-shifting: they may find an intervention cost-effective for a particular payer because it offloads costs and problems onto another part of the system. For this reason, it is recommended that economic evaluations adopt a broad societal perspective, which considers all costs and outcomes regardless of where they occur and who pays for them. In the case of dementia, this includes the estimated costs incurred by the health service that provides drugs, therapies and medical care, social services that provide residential facilities, and volunteers and families who provide a safe home and community care for older people without payment.

There are five types of economic evaluations that compare costs and outcomes between different interventions or services. All five types are similar in the way they measure costs, but they differ in the way they measure health outcomes and combine these with costs to reach decisions about value for money. These are:

- Cost-minimization analysis (CMA)
- Cost-consequences analysis (CCA)
- Cost-effectiveness analysis (CEA)
- Cost-utility analysis (CUA)
- Cost-benefit analysis (CBA)

Cost-Minimization Analysis (CMA)

Cost-minimization analysis (CMA) accepts that two interventions or services have similar outcomes (in terms of effectiveness and safety) but different costs. The value and use of CMA are limited because the lack of a statistically significant difference in the outcomes between two different interventions or services does not mean that these are equivalent (Briggs and O'Brien 2001). There are some uses of CMA when comparing "me-too" drugs (or "follow-on" drugs) (diMasi and Paquette 2004) that have the same mechanism of action with existing drugs and potentially different costs; still, the evidence on price competition from me-too drugs suggests that they confer little or no cost saving to those who pay for them (Hollis 2004).

An example of a CMA relevant to the care of older people with mental health problems is a UK study which compared psychiatric assessments conducted at the patient's homes versus at a clinic situated in a hospital (Aquilina and Anderson 2002). Home-based assessments were marginally (£2) cheaper than those at the hospital-based clinic over 4 years, but costs fluctuated depending on local variables: for the clinic, costs varied with the grade of the doctor doing the assessments and the patients' nonattendance rates, whereas for home visits, costs varied with time spent travelling to the patient's home.

Cost-Consequence Analysis (CCA)

A cost-consequence analysis (CCA) considers all the health and non-health impacts and costs of different interventions or services across different sectors; it then lists or tabulates these in a disaggregated form for each intervention/service. The costs can include direct costs (e.g., for drugs, therapies, social services, and transportation), indirect costs (e.g., productivity loss due to time off work and criminal justice expenditure), and intangible costs (e.g., impaired quality of life and distress of living with pain). CCA can also be useful for complex clinical or public health interventions which have a wide range of health and non-health benefits that are difficult to measure in a common unit like a QALY (NICE 2013). Still, decisions based on a CCA run the risk of "cherry-picking" positive impacts in favor of a specific intervention and do not provide a generalizable and objective measure of cost-effectiveness.

Interestingly, CCA does not combine the costs and outcomes of the interventions under consideration nor does it indicate their relative importance; instead, it leaves their appraisal to the decision-maker (e.g., service users, insurance companies, governments). A CCA is based on the premise that decision-makers have the knowledge and experience to make value judgments for the trade-offs between different interventions when they have a comprehensive presentation of the costs and impacts of each intervention. This can be useful because the appraisal of these interventions is not restricted to a predetermined viewpoint, so decision-makers can review them from various perspectives, including those of sectors other than health care, such as criminal justice (Brazier et al. 2007).

A case study of CCA in relation to a rehabilitation program for patients with Parkinson's disease (Gage et al. 2006) provided a descriptive summary of all direct and overheard costs for the health service as well as the costs of hospital-provided patient transport. Consequences from the perspectives of patients and carers (e.g.,mobility, disability, psychological well-being, health-related quality of life, satisfaction) and of other service providers (e.g., social care) were measured immediately after the rehabilitation program at 6 weeks and then at 4 months follow-up. The case study identified overheads and transport as the main costs for the program, whereas its consequences included improved immediate – but not long-term – outcomes for patients, high satisfaction for patients, no benefits for carers, and increased demand for social services.

Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analysis (CEA) compares two or more interventions/services on costs and health outcomes measured in their natural units (e.g., symptom-free days, depression score). Their relative costs and outcomes are summarized into one number known as the *incremental cost-effectiveness ratio* (ICER), which is their difference in cost (incremental cost) divided by their differences in outcome (incremental effect), as in the formula below:

$$\mathrm{ICER} = \Delta C/\Delta E = (C_A - C_B)/(E_A - E_B).$$

where
Δ = difference
C = costs
E = effects
A, B = interventions/services compared

A CEA relating to older people with depression was conducted as part of a randomized controlled trial (RCT) comparing cognitive behavior therapy (CBT) versus a nonspecific control (talking) versus treatment as usual (Holman et al. 2011). The Beck Depression Inventory II (BDI-II), a self-reported questionnaire scored 0–63 with higher scores denoting more severe depression, was the main outcome measure at 10 months follow-up. Direct treatment costs were compared with reductions in depression scores. CBT was significantly more costly and more effective than its two comparators. CBT's incremental cost was £120 per point reduction in the BDI score (approximately 1.6% improvement in depression), with a 90% probability of being cost-effective if payers were willing to pay up to £270 per BDI point reduction.

Cost-Utility Analysis (CUA)

Cost-Utility Analysis (CUA) is a specific type of CEA in which the primary outcome is measured in units of utility or preference, often as a quality-adjusted life year (QALY). As described in section Utility: A Common Currency for Outcomes Across Different Conditions and Interventions, QALYs are based on individual preferences for different health states. CUA is considered the "gold standard" of economic evaluations because it allows comparisons across different interventions and

different conditions. In the same way as in CEA, the incremental cost-effectiveness ratio (ICER) of an intervention A compared to an alternative B is calculated by dividing their differences in cost (incremental cost) by their differences in QALYs (incremental effect). The ICER of A compared to B is calculated as:

$$\text{ICER} = (\text{cost } A - \text{cost } B)/(\text{QALY of } A - \text{QALY of } B).$$

If the cost of intervention A is $50,000 and the cost of B is $40,000, and if the QALYs of A are 5 and the QALYs of B are 4, then the ICER of A is ($50, 000 – $40, 000)/(5 – 4) = $10 , 000/1 QALY. So, we gain an extra QALY with intervention A at a cost of $10,000.

An example of CUA in older people's mental health services comes from a Dutch RCT (Wolfs et al. 2009) which compared an integrated multidisciplinary diagnostic facility with usual care, using the EQ-5D at baseline and at 6 and 12 months follow-up for 230 patients with suspected dementia or other cognitive impairment. Usual care was provided by the GP who either made a direct diagnosis or referred the patient to a specialist service. The conclusion was that the new service model of a multidisciplinary diagnostic facility was more cost-effective based on its incremental cost of €1,267 per QALY. The largest difference in costs, in favor of the new service, was due to a longer home stay (so there were fewer admissions to nursing homes and shorter stay in them during the period of the study) if patients were referred to the new service instead of being diagnosed and managed as per usual care.

Cost-Benefit Analysis

Cost-benefit analysis (CBA) compares the net costs of an intervention or service with its benefits, but both the net costs and benefits are expressed in monetary units to produce a "net benefit." The net benefit is estimated by deducting the actual costs from the monetary value of the benefits. The advantage of CBA, like CUA, is that it allows comparison of interventions and services with entirely different measures of outcomes, because the comparisons are based on a monetary value. Furthermore, it provides a definitive, self-contained decision rule for evaluating single interventions: if the net benefit of the intervention is positive, the intervention is likely to be worthwhile for those who pay.

CBA is not favored in health and social care because of ethical concerns related to placing a monetary value on human well-being (or lack of well-being because of illness) and to the subjectivity of assigning such values by asking those who do not directly experience the illness. *Willingness to pay* (WTP), the common method used for assigning values to health benefits by asking people how much they would be prepared to pay for specific interventions or services to yield specific outcomes, has been criticized for giving greater weight to the preferences of the wealthy, because inevitably one's willingness to pay is linked to one's ability to pay.

An example of CBA in dementia comes from a small Canadian study (Wu et al. 2003) in which CBA was based on the responses of a cohort of 28 caregivers who were asked to state the maximum they would be willing to pay for treatment

(compared to no treatment) to delay disease progression and to treat the behavioral symptoms of dementia in their relatives. WTP for the treatment of mild to moderate dementia was higher than the actual cost of cholinesterase inhibitors, even when the adverse effects of the drugs were taken into consideration, indicating a net benefit for these. Not surprisingly, the caregivers' yearly income significantly predicted WTP for cholinesterase inhibitors.

Cost of Illness (COI)

It is worth noting here that another type of a widely used economic analysis, called *cost of illness* (COI), is often not discussed within the remit of economic evaluations because it does not compare or consider outcomes between different interventions or services. COI studies are important in making an economic case for investing not only in a specific population but also in the "right" type of interventions or services for this population. As a case in point, two systematic reviews (Quentin et al. 2010; Schaller et al. 2015) of COI studies for dementia found that stage of illness and type of care setting are important determinants of illness cost. The cost of dementia more than doubles from mild to severe stages and is driven not by medical expenses but by accommodation costs; these are incurred by informal carers if the patient lives at home or in privately paid nursing homes or are incurred by social services if the patient lives in a state-funded institution. On the basis of dementia's COI studies, interventions and service models need to delay the onset of the severe stages of the illness and prolong the stage of independent living.

Summary

As discussed throughout the chapter, an economic evaluation is the process of comparing costs and outcomes across different interventions or services to determine which option offers the best value for money. Table 1 below gives an overview of how the five types of economic evaluations differ in terms of outcomes and their synthesis with costs. Under each type of economic evaluation, there is an example relevant to older people's mental health care.

Conclusion

The first half of this chapter gave an overview of a community care model for older people with mental health problems. This model hinges on a multidisciplinary team, the CMHTOP, who has the competencies and expertise to assess and coordinate specialist care in an integrated pathway involving other statutory and voluntary services and informal carers. Although this is the preferred model in many developed countries, one size does not fit all. Staff skill mix and service delivery may vary according to the population size of older people, the geographical spread and the urban or rural nature of a service's catchment area, and the dominant cultural and religious norms in the population.

Table 1 Types of economic evaluations in older people's mental health care

Analysis	Expression of outcomes	Synthesis of costs and outcomes	Examples relevant to older people's mental health
Cost-minimization analysis (CMA)	Not applicable – outcomes are assumed similar and are not included in the economic analysis	Not applicable – only costs are compared	Cohort study: home- vs. hospital-based psychiatric assessment of older adults (Aquilina and Anderson 2002)
Cost-consequences analysis (CCA)	Several outcomes in their natural units	Not applicable – costs and outcomes are not combined but presented in separate tables for qualitative comparison	Case study: rehabilitation program for Parkinson's disease (Gage et al. 2006)
Cost-effectiveness analysis (CEA)	One primary outcome: condition-specific score in its natural unit (e.g., points on a depression scale or improvement in cognitive functioning)	Incremental cost-effectiveness ratio (ICER): cost per unit of improvement (e.g., on depression or cognitive functioning scores) calculated by dividing the difference in costs by the difference in changes in the outcome of interest	Randomized controlled trial: cognitive behavior therapy (CBT) vs. talking control vs. treat as usual for depression in older adults (Holman et al. 2011)
Cost-utility analysis (CUA)	One primary outcome: "Utility" (e.g., QALYs or DALYs)	Incremental cost-effectiveness ratio (ICER): cost per quality-adjusted life year (QALY) calculated by dividing the difference in costs by the difference in quality-adjusted life years (QALYs)	Randomized controlled trial: integrated multidisciplinary diagnostic facility vs. GP-based usual care for the diagnosis and management of dementia (Wolfs 2009)
Cost-benefit analysis (CBA)	"Money" (e.g., the monetary value that people attach to a unit of improvement (e.g., days free of depression)	Net cost	Single-group observational study: carers' willingness to pay for treatment (compared to no treatment) to delay disease progression and to treat the behavioral symptoms of dementia in their relatives (Wu et al. 2003)

The second half of this chapter described how economic evaluations can help those who pay for the mental health care of older people choose between different interventions and services by comparing the outcomes and costs of these. With dementia as a case in point, costs are largely attributable to living arrangements

and informal care for severe dementia, whereas the cost of therapies and drugs for mild to moderate dementia is relatively low. New interventions and service models need to focus on (and consider as their primary outcome) prolonging the stage of independent living for those with mild or moderate dementia and reducing the costs of residential care for those with severe dementia, by supporting community care and facilitating informal and voluntary caregiving.

The feasibility of adopting a CMHTOP-based model depends on whether there is available funding for developing a service infrastructure and for training health-care staff from different disciplines. Still, the two key components of the model – a community-based multidisciplinary team and an integrated care pathway – can be used for developing older people's mental health services that suit local circumstances within existing resource constraints. In line with the adage "nothing ventured, nothing gained," some level of investment is needed in the present, in order to introduce new interventions and transform services that are likely to yield better outcomes and save costs in the future for individuals, their families, and the health and social care sectors affected by age-related mental health problems.

Cross-References

► Challenges and Opportunities of Aging Populations Around the World
► Epidemiology of Mental Disorders (Including Cross-Cultural Comparisons)

References

Abendstern M, Harrington V, Brand C, Tucker S, Wilberforce M, Challis D (2012) Variations in structures, processes and outcomes of community mental health teams for older people: a systematic review of the literature. Ageing Ment Health 16:861–873

Aquilina C, Anderson D (2002) Domiciliary clinics II: a cost minimisation analysis. Int J Geriatr Psychiatry 17(10):945–949

Arie T (1970) The first year of the Goodmayes psychiatric service for old people. Lancet 296 (7684):1179–1182

Audit Commission (2000) Forget me not: mental health services for older people. Audit Commission, London

Banerjee S, Chan J (2008) Organisation of old age psychiatry services. Psychiatry 7:49–54

Brazier J, Ratcliffe J, Salomon J, Tsuchiya A (2007) Measuring and valuing health benefits for economic evaluation. Oxford University Press, Oxford

Briggs AH, O'Brien BJ (2001) The death of cost-minimization analysis? Health Econ 10:179–184

Brodaty H, Green A, Koschera A (2003) Meta-analysis of psychosocial interventions for caregivers of people with dementia. J Am Geriatr Soc 51:657–664

Camus V, Katona C, de Mendonça Lima CA, Abdel-Hakam AM, Graham N, Baldwin R, Tataru N, Chiu E, World Psychiatric Association section on old age psychiatry (2003) Teaching and training in old age psychiatry: a general survey of the World Psychiatric Association member societies. Int J Geriatr Psychiatry 18(8):694–699

Chew-Graham CA, Lovell K, Roberts C, Baldwin R, Morley M, Burns A, Richards D, Burroughs H (2007) A randomised controlled trial to test the feasibility of a collaborative care model for the management of depression in older people. Br J Gen Pract 57:364–370

Clark F, Jackson J, Carlson M et al (2012) Effectiveness of a lifestyle intervention in promoting the wellbeing of independently living older people: results of the well elderly 2 randomised controlled trial. J Epidemiol Community Health 66:782–790

diMasi J, Paquette C (2004) The economics of follow-on drug research and development trends in entry rates and the timing of development. Pharmacoeconomics 22(Suppl. 2):1–14

Draper B, Brodaty H, Low L (2006) A tiered model of psychogeriatric service delivery: an evidence-based approach. Int J Geriatr Psychiatry 21:645–653

Drummond MF, Sculpher MJ, Calxton K, Stoddart GL, Torrance GW (2015) Methods for the economic evaluation of health care programmes, 4th edn. Oxford University Press, Oxford

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G et al (2013) Burden of depressive disorders by country, sex, age, and year: findings from the Global Burden of Disease Study 2010. PLoS Med 10(11):e1001547. doi:10.1371/journal.pmed.1001547

Gage H, Kaye J, Owen C, Trend P, Wade D (2006) Evaluating rehabilitation using cost-consequences analysis: an example in Parkinson's disease. Clin Rehabil 20(3):232–238

Ginsberg L, Hamilton P, Madora P, Robichaud L, White J (1998) Geriatric psychiatry outreach practices in province of Ontario: the role of psychiatrist. Can J Psychiatr 43:386–390

Hollis A (2004) "Me-too drugs– is there a problem?" WHO Report. Available from http://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf?ua=1. Accessed 28 June 2016

Holman AJ, Serfaty MA, Leurent BE, King MB (2011) Cost-effectiveness of cognitive behaviour therapy versus talking and usual care for depressed older people in primary care. BMC Health Serv Res 11:33. doi:10.1186/1472-6963-11-33

McCrea N, Murray J, Banerjee S, Huxley P, Bhugra D, Tylee A, MacDonald A (2005) 'They are all depressed, aren't they?' A qualitative study of social care workers and depression in older adults. Ageing Ment Health 9:508–516

McCrone P (2008) Paying the price: the cost of mental health care in England to 2026. King's Fund, London

National Institute for Health and Care Excellence (NICE) (2008) Public health guideline 16 – mental wellbeing in over 65s: occupational therapy and physical activity interventions. NICE, London. Available from: https://www.nice.org.uk/guidance/ph16/resources/mental-wellbeing-in-over-65s-occupational-therapy-and-physical-activity-interventions-1996179900613 Accessed 28 June 2016

National Institute for Health and Care Excellence (NICE) (2013) How NICE measures value for money in relation to public health interventions: NICE advice [LGB10] nice.org.uk/guidance/lgb10. Available from: https://www.nice.org.uk/Media/Default/guidance/LGB10-Briefing-20150126.pdf

Nowak S (2012) South Australia's older persons mental health services' model of service: a country perspective. Int Psychogeriatr 24(5):848–849

O'Connor D, Melding P (2006) A survey of publicly funded old age psychiatry services in Australia and New Zealand. Austr N Z J Psychiatry 40:368–373

Pachana N, Helmes E, Koder D (2006) Guidelines for the provision of psychological services for older adults. Austr Psychol 41:15–22

Phelps CE (2016) Health economics, 5th edn. Routledge, New York

Prince M, Livingston G, Katona C (2007) Mental health care for the elderly in low-income countries: a health systems approach. World Psychiatry 6(1):5–13

Quentin W, Riedel-Heller SG, Luppa M, Rudolph A, König HH (2010) Cost-of-illness studies of dementia: a systematic review focusing on stage dependency of costs. Acta Psychiatr Scand 121(4):243–259

Schaller S, Mauskopf J, Kriza C, Wahlster P, Kolominsky-Rabas PL (2015) The main cost drivers in dementia: a systematic review. Int J Geriatr Psychiatry 30(2):111–129

Shah AK, Ames D (1994) Planning and developing psychogeriatric services. Int Rev Psychiatry 6:15–27

Shah AK, Bhatkal S (2005) Core service components – acute care. In: Draper B, Brodaty H, Melding P (eds) Psychogeriatric service delivery – an international perspective. Oxford University Press, Oxford, pp 193–212

Shiell A, Donaldson C, Mitton C, Currie G (2002) Health economic evaluation. J Epidemiol Community Health 56:85–88

Toot S, Devine M, Orrell M (2011) The effectiveness of crises resolution/home treatment teams for older people with mental health problems: a systematic review and scoping exercise. Int J Geriatr Psychiatry 26:1221–1230

Torrance GW (1986) Measurement of health state utilities for economic appraisal. J Health Econ 5:1–30

Tucker S, Wilberforce M, Brand C, Abendstem M, Challis D (2014) All things to all people? The provision of outreach by community mental health teams for older people in England: findings from a national survey. Int J Geriatr Psychiatry 29:489–496

von Neumann J, Morgenstern O (1953) Theory of games and economic behavior. Princeton University Press, Princeton

Whitehead SJ, Ali S (2010) Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 96:5–21

Wilberforce M, Tucker S, Abendstern M, Brand C, Challis D (2013) Membership and management: structures of inter-professional working in community mental health teams for older people in England. Int Psychogeriatr 25:1458–1492

Wimo A, Prince M (2010) World Alzheimer Report 2010: The Global Economic Impact of Dementia. Alzheimer's Disease International, London

Wimo A, Karlsson G, Winblad B (2000) Health economic aspects of dementia. In: O'Brien J, Ames D, Burns A (eds) Dementia, 2nd edn. Arnold, London, pp 207–216

Wolfs CA, Dirksen CD, Severens JL, Verhey FR (2006) The added value of a multidisciplinary approach in diagnosing dementia: a review. Int J Geriatr Psychiatry 21(3):223–232

Wolfs CA, Dirksen CD, Kessels A, Willems DC, Verhey FR, Severens JL (2007) Performance of the EQ-5D and the EQ-5D+C in elderly patients with cognitive impairments. Health Qual Life Outcomes 5(1):33

Wolfs CA, Dirksen CD, Kessels A, Severens JL, Verhey FR (2009) Economic evaluation of an integrated diagnostic approach for psychogeriatric patients: results of a randomized controlled trial. Arch Gen Psychiatry 66(3):313–323

Woodward MC, Woodward E (2009) A national survey of memory clinics. Int Psychogeriatr 21:696–702

Wu G, Lanctot KL, Herrmann N, Moosa S, Oh PI (2003) The cost-benefit of cholinesterase inhibitors in mild to moderate dementia: a willingness-to-pay approach. CNS Drugs 17(14):1045–1057

Pharmacotherapy for Mood and Anxiety Disorders

18

Trevor R. Norman

Abstract

Mood and anxiety disorders are common in the elderly. They are associated with significant morbidity and mortality. Unrecognized psychiatric conditions may have a significant negative effect on treatment outcomes for somatic disorders. Psychopharmacological treatment strategies should aim to provide not only symptomatic response and remission of symptoms but also full functional recovery. While medications are the mainstay for moderate to severe conditions, the use of adjunctive psychotherapy should also be considered. The selective serotonin reuptake inhibitors have become the first-line pharmacological treatment of depression and anxiety for the elderly. Alternative options (benzodiazepines, other antidepressants, and buspirone), while effective, have drawbacks associated with their use which makes them unsuitable as first-line choices. Clinical use of the selective serotonin reuptake inhibitors requires careful consideration of the mental status of the individual patient, their physical health (robust good health for age or frailty), and the presence of somatic illness. The choice of medication and initial dose will be guided by the interaction of these factors. Careful assessment of response to and monitoring of side effects of medication is essential to ensure optimal outcomes.

Keywords

Depression • GAD • Elderly • Antidepressants • Anxiety • Benzodiazepines • Pregabalin • Tricyclics • Monoamine oxidase inhibitors • SSRIs • SNRIs • Agomelatine • Vortioxetine

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_19

Contents

Introduction

It has been estimated that between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22% (WHO 2015). Within the same time frame, about 80% of these older people will be living in low- and middle-income countries. The United Nations has identified the decline in fertility rates as the primary determinant of population aging. In developed countries the decline in fertility is below the population replacement rate, while in the less developed countries, fertility rates are predicted to fall below population replacement around 2050 (United Nations 2002). This lowered fertility rate coupled with an increasing life expectancy at birth (the UN estimates an increase of more than 20 years in the past five decades (United Nations 2002) implies that the elderly will increasingly consume healthcare services, including mental healthcare delivery. Much of this burden is likely to be due to high-prevalence mental disorders in later life, particularly the mood and anxiety disorders, as well as dementia.

Although the elderly currently represent a minor proportion of the population, they account for a disproportionate number of medication prescriptions. Older surveys suggested that while the elderly constituted 12% of the population, they accounted for 33% of expenditure on prescription medicines (Judge and Caird

1978). This is perhaps not surprising as aging is associated with a greater likelihood of developing a condition (or conditions) which will require ongoing medication. Polypharmacy is relatively common as a consequence of this situation. Indeed it has been estimated that one in six elderly people take three or more medications a day (Judge and Caird 1978). Later surveys suggest that the elderly take two to five prescription medications regularly while polypharmacy occurs in 20–50% of patients (Kennerfalk et al. 2002; Pizzuti et al. 2006).

The use of medications in the elderly is associated with a number of common problems including ineffectiveness, adverse drug effects, overdosage, underdosage, and drug-drug interactions due to the use of multiple medications (Herrlinger and Klotz 2001; Mallet et al. 2007**)**. Polypharmacy and age-related changes in pharmacodynamics and pharmacokinetics increase the risk of adverse effects. Furthermore, adverse drug reactions are often more serious in the elderly (Doucet and Queneau 2005; Cresswell et al. 2007) and are a frequent cause of admission to hospital. The potential for a prescribing cascade occurs when adverse effects of an originally prescribed drug are interpreted as a symptom of a new disorder and a further drug is prescribed to treat it. This new, unnecessary agent may cause additional side effects which are misinterpreted as another disorder and treated unnecessarily. For example, the use of an antipsychotic medication leads to Parkinson like symptoms which are then treated as a new disorder.

Further distinction needs to be drawn between "fit elderly" and "frail elderly" (Ahmed et al. 2007). The later subpopulation of patients represents a group for whom multiple disease states rather than age per se primarily account for alterations in drug responses (Woodhouse and O'Mahony 1997; Hubbard et al. 2008). Differences in response of the elderly, especially those over 75 years, from younger patients are an important cause of morbidity and mortality. Psychotropic medications are frequently prescribed to the elderly in both ambulatory care and in nursing homes. Prescribing in the elderly must take into account the principles of good clinical practice. Treatment must be tailored to fit each elderly individual's unique comorbidities where these exist. Table 1 outlines a number of issues to be given consideration before prescribing a medication for an elderly patient.

Metabolic, Pharmacokinetic, and Pharmacodynamic Changes in the Elderly

It is well recognized that aging brings with it alterations in physiological parameters that can affect both drug handling (pharmacokinetic) and responses to medication (pharmacodynamics). These changes have been described in detail in the past (Benedetti et al. 2007; Hilmer et al. 2007; Hutchison and O'Brien 2007; Kinirons and O'Mahony 2004; McLean and Le Couteur 2004; Schwartz 2007; Wauthier et al. 2007; Klotz 2009) and are not reiterated in detail here. Several factors, outlined in Table 2, contribute to alterations in drug kinetic differences between elderly and young subjects. Although such differences are well recognized, there is, in general and for

Table 1 Prescribing principles for the elderly

Is drug therapy required at all?	Accurate diagnosis and assessment of severity
Which drug is appropriate?	Accurate diagnosis; depression and anxiety are often symptoms not disorders; underlying organic causes evaluated?
Is the dosage correct?	Smaller doses are often required. Start low go slow
What are the undesirable effects?	Potential for postural hypotension and anticholinergic effects should be considered
Is the choice of preparation correct?	Some sub-lingual preparations are available for patients with difficulty swallowing
Can the patient living at home manage self-administration?	Simple, clear instructions for drug regimens; compliance decreases with increase in number of medications
Is the drug correctly packaged and labeled?	Use of large print for eyesight difficulties; containers easily opened due to arthritis
When can the drug therapy be ceased?	Withdrawal of medications no longer indicated; tapered withdrawal for most psychotropics

Table 2 Age-related changes potentially affecting pharmacokinetics of medications

Organ system	Physiology change with aging	Major effect	Pharmacokinetic effect
GI tract	↓Gastric secretion	Decreased transport efficiency	Onset of action may be delayed
	↓GI motility		Unlikely to be of concern on repeated administration
	↓GI blood flow		
	↑Gastric pH		
Kidney	Decreased renal blood flow	Decreased GFR	Decreased clearance
			Increased plasma elimination half-life
Liver	↓Enzyme induction	Decreased availability of drugs to the liver	Reduced hepatic clearance of drugs
	↓Hepatic mass		Increased plasma half-life
	↓Hepatic blood flow		Increased potential for drug interactions
	↓Activity in enzyme activity		
Plasma	Generally decreased proteins		Higher concentrations of free drug
Muscle	More fat, less muscle	Altered distribution	Increased Vd
			Increased elimination half-life

GFR glomerular filtration rate, *GI* gastrointestinal, *Vd* volume of distribution

psychotropic medications specifically, a lack of well-designed clinical studies to evaluate single- and repeated-dose pharmacokinetic studies in elderly populations. Evaluations of pharmacokinetic and pharmacodynamic responses to psychotropic medications rarely include elderly patients with coexisting physical disorders.

Absorption

Changes in the gastrointestinal (GI) tract with aging may affect how some drugs are absorbed. Both GI motility and GI blood flow are generally reduced with aging. Gastric acid secretion may also be reduced leading to an elevation in gastric pH. Reduced absorption may result from increased gastric pH and reduced gastric blood flow, whereas reduced motility may result in greater drug absorption. The use of antacids and proton pump inhibitors will also contribute to changes in the GI tract (Kapadia et al. 2010). Although these age-related changes in absorption may affect the onset of action of a drug following single doses, repeated administration is less likely to be affected in a clinically significant way.

Distribution

A number of factors influence the theoretical volume of distribution of a drug, including protein binding (only unbound drug is distributed), water or lipid solubility (highly lipid-soluble drugs have greater volumes of distribution), pH, and molecular size. The decline in muscle mass and increase in the proportion of body fat with aging will significantly affect drug distribution in the body. In general lipophilic agents have increased volumes of distribution in the elderly. Diazepam, which is highly fat soluble, is a case in point. Aging is associated with a reduction in total body water with a consequential effect on the volume of distribution for drugs which are water soluble.

Age-related changes in plasma protein binding are not regarded as of clinical relevance (Benet and Hoener 2002). Although mean serum albumin concentrations have been shown to decline progressively with age (Greenblatt 1979), α1-acid glycoprotein tends to increase with age (Butler and Begg 2008). Such changes have been attributed more to pathophysiology or disease states than to aging per se (Benet and Hoener 2002). Nevertheless, reductions in protein binding can result in an increased free drug concentrations which may affect pharmacological responses (Hutchison and O'Brien 2007; Mangoni and Jackson 2004**;** Greenblatt et al. 2002).

The multidrug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (*ABCB1*) gene product, P-glycoprotein (P-gp), is an efflux pump that is present in excretory organs as well as the blood-brain barrier (Taylor 2002). Potentially drug disposition might be affected by P-gp expression and activity (Lin and Yamazaki 2003). With respect to the effects of aging, there is a paucity of data on the importance of P-gp for drug distribution (Klotz 2009). Such studies which have been conducted show either no or minimal effects (Toornvliet et al. 2006).

Metabolism

Before excretion most drugs undergo biotransformation to more polar metabolites by cytochrome P450 (CYP)-dependent phase I reactions and/or phase II pathways, such as glucuronidation, acetylation, or sulfation. This drug metabolism mainly takes place in the liver (Klotz 2009). Liver size/mass (~20–30%) and hepatic blood flow

(~20–50%) decrease with age which might result in alteration of the elimination of high-clearance drugs. Hepatocyte volume remains unchanged between 20 and 95 years, while there are no age-related changes in routine clinical tests of liver function (Le Couteur et al. 2005; Herrlinger and Klotz 2001). Studies in vivo assessing the capacity of specific cytochrome enzymes in elderly versus young subjects or population kinetic studies have generally failed to demonstrate clinically significant changes in healthy elderly subjects (Klotz 2009). Nevertheless, for hepatically cleared drugs dosing is usually recommended to be reduced in elderly patients. Although adjustments are somewhat arbitrary, doses should be titrated to therapeutic outcome or adverse effects.

Elimination

Renal excretion is the primary route of elimination for most psychotropic medications. The apparent plasma half-life of elimination of drugs is increased as renal function declines. Although there are significant changes in kidney mass and the number of glomeruli decreases by about 20–30% with aging, it has been estimated that about a third of elderly patients have no decline in renal function (Klotz 2009). Indeed a small subpopulation of elderly renal function, based on creatinine clearance, may actually increase (Lindeman et al. 1985; Froissart and Rossert 2005). Changes in renal function with aging are more likely to arise due to concomitant disease states than aging *per se* (Fliser et al. 1997). Nevertheless there are some psychotropic medications for which renal elimination is important. Lithium is a case in point being subject to renal clearance only, and therefore alterations in renal function can result in inadvertent over- or underdosing if this is not taken into account.

Overview

In summary, the altered pharmacokinetics observed in most elderly patients can be attributed to physiological changes with aging. Table 2 summarizes important physiological changes with aging and their likely effects on pharmacokinetic parameters. What is perhaps best to bear in mind is not that the kinetics are different from younger patients but that there is a much greater variability in kinetic parameters seen in elderly patients than in younger patients. Furthermore concomitant disease states are likely to influence kinetics more than aging per se. Nevertheless, the dosing strategy of "start low, go slow" represents a balance between the kinetic and dynamic alterations in medication responses in the elderly.

Depression in the Elderly

While in the community-dwelling elderly population depressive symptoms are relatively common (15% according to the Epidemiological Catchment Area study (Blazer and Hughes 1987)), a much smaller subset meets full criteria for major

depressive disorder, perhaps 1–2%. In nursing homes the prevalence of depression may be much higher, up to 25% in one study (Samuels and Katz 1995). Estimates of prevalence clearly are influenced by the setting of the survey as well as the presence of chronic medical illness associated with depressive symptoms (Mock et al. 2010). Depression in the elderly is associated with significant morbidity and disability, as well as increased risk of mortality. The presentation of depression in older people is often regarded as atypical. Older people are less likely to report feelings of sadness or identify with the term "depression." Commonly patients present with complaints of anxiety, somatic symptoms, and memory loss. Hospitalized depressed patients frequently have psychotic symptoms (mood-congruent delusional beliefs with themes of persecution, nihilism, and guilt). Response and remission with treatment are often lower in the elderly with higher relapse rates as a consequence of suicidal ideation and attempts (Driscoll et al. 2007). Rates of suicide are high in the elderly, particularly elderly men, with some specific risk factors identified (divorced or single, widowers). Acts of deliberate self-harm in older patients should be managed as a "failed suicide" however trivial the attempt, as most incidents are performed with high suicidal intent (Osgood 1991).

Treatment of Depression

The mainstay of treatment for depression of moderate to severe intensity has been the use of pharmacotherapy. The efficacy and tolerability of the first-generation antidepressants (tricyclics and monoamine oxidase inhibitors), as well as the second-generation antidepressants (selective serotonin reuptake inhibitors), in older people have a reasonably robust database of controlled clinical evaluations in specific elderly populations. The so-called "third-generation" antidepressants with variable modes of action are not as well evaluated in elderly populations. The very elderly (older than 85 years) are underrepresented in clinical trials (Giron et al. 2005). Similarly, patients who reside in nursing homes and who have dementia and medical comorbidities are also generally excluded from clinical trials. This population has high rates of depression (three to five times higher than community-dwelling elderly) that is often under-recognized and undertreated, resulting in a lack of clinical evidence guiding treatment (Giron et al. 2005).

Most available tricyclic antidepressants have been evaluated in specific populations of elderly patients. Thus evidence of varied degrees of reliability suggests that amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, maprotiline, and nortriptyline are effective in relieving the symptoms of depression. It is beyond the scope of this chapter to reproduce the evidence for each of the studies associated with the clinical evaluation of these agents, but a comprehensive compendium of studies is available (Alexopoulos et al. 2005).The majority of studies are observational or evaluations based on comparison with another agent (or psychotherapy). Placebo-controlled comparisons are relatively few, probably due to ethical concerns in this population. Nevertheless, a review of 12 placebo-controlled evaluations involving tricyclic antidepressants over a mean 7-week

treatment period reported that both imipramine and nortriptyline were superior to placebo in 11 of the studies examined (Taylor and Doraiswamy 2004). The authors identified small sample sizes and lack of inclusion of common comorbid conditions as shortcomings of the extant database. Cross-trial comparisons were also difficult due to large placebo response rates and lack of controlled head-to-head comparisons. A later meta-analysis (Kok et al. 2012) also found tricyclics to be superior to placebo for response rates ($\geq$50% decrease on Hamilton Depression Rating Scale (HDRS) or Montgomery Depression rating Scale (MADRS) or a Clinical Global Impression (CGI) score of 1 or 2) but not for remission of symptoms. Since most studies did not report remission rates, this finding is unreliable due to a small sample size. The number needed to treat (NNT) from this analysis was 4.2. Alexopoulos' compilation of studies suggests that no one tricyclic antidepressant has an established superiority over any other tricyclic, at least in the group comparisons. Choice of medication from this class is likely to be influenced by the side effects of the medication and the particular needs of an individual patient, i.e., which side effects are best avoided due to concomitant medical illness or other characteristics of the patient. Secondary amine tricyclics, particularly desipramine and nortriptyline, are claimed to have some advantages for the elderly due to their less complex metabolism and milder side effects. By far the greatest set of published data in geriatric patients is for nortriptyline. In contrast the use of tertiary amine tricyclics is not recommended in late-life depression by an expert consensus statement (Alexopoulos et al. 2001). It is claimed that there is a greater likelihood of side effects and dose-limiting toxicity with these agents. While all of the medications generally have response rates equivalent to those seen in younger patients (around 60%; Wilson et al. 2001), the majority of studies do not have published data on remission rates for depression. Current management guidelines for depression suggest that remission of symptoms, rather than response, is the most desirable outcome and the targeted goal of treatment (Keller 2003). The few studies for which remission data is available suggest that the tricyclics achieve acceptable rates of remission in the longer term. Thus, a remission rate of 78% was noted during maintenance therapy for recurrent major depression in patients treated with a combination of interpersonal psychotherapy and nortriptyline (Reynolds et al. 1996). Following stabilization 15.5% of patients relapsed. Imipramine and doxepin were associated with a 45% remission rate in patients aged 55 years or older in a 26-week study (Jarvik et al. 1982).

A Cochrane Review examined the efficacy of antidepressant classes in the elderly and compared the withdrawal rates between classes of agent (Mottram et al. 2006). There were no differences in efficacy between classes of antidepressants, but there was a higher withdrawal rate associated with tricyclics due to side effect experiences. Two side effects of particular concern with elderly patients using tricyclics are the well-recognized issues of orthostatic hypotension and conduction alterations (Sloman et al. 1983). These effects are generally dose (and plasma concentration) dependent but cardiac arrhythmias are often unpredictable, while orthostatic hypotension can lead to falls with hip fractures. Partly for these reasons, a recent American Geriatric Society Beers Criteria Update Expert Panel has recommended that tricyclic antidepressants taken either alone or

in combination should be avoided (American Geriatrics Society 2015 Beers Criteria Update Expert Panel 2015).

Monoamine oxidase inhibitors were among the first antidepressants available, yet surprisingly few controlled studies have been performed in elderly groups. Both phenelzine, a nonselective inhibitor of monoamine oxidase (MAO), and moclobemide, a selective MAO-A inhibitor, have been evaluated in double-blind, placebo-controlled trials as noted in Table 3. The single trial of phenelzine showed that it was more effective than placebo and at least as effective as nortriptyline, based on the decline in the HDRS from baseline (Georgotas et al. 1986, 1987). No data was available on response or remission rates in this study. Moclobemide has been evaluated in two placebo-controlled trials. In one large trial, over 600 elderly patients with either depression or dementia were assigned to treatment with moclobemide or placebo (Roth et al. 1996). While it was reported that moclobemide was superior to placebo for depressive symptoms in both groups, few details of the response were available. In the second study, remission rates, defined as a HDRS score <10 at end point, for moclobemide were 23% compared to 33% for nortriptyline and 11% for placebo (Nair et al. 1995). The intent to treat analysis found no differences between moclobemide and placebo and marginal significance for nortriptyline. The study is compromised by a high dropout rate (~50% of treated patients in all groups) and relatively short treatment duration. Comparative or open-label studies with MAOIs in the elderly generally support their efficacy in geriatric depression. Nevertheless they are less likely to be used due to side effects, particularly postural hypotension in the elderly, and the necessity for dietary restrictions.

Recommended first-line treatment of depression in the elderly is a course of one of the selective serotonin reuptake inhibitor (SSRI) medications (Mulsant et al. 2001). These agents are regarded as having a more favorable side effect profile than other classes of antidepressants, a generally safer drug-drug interaction potential and therefore better tolerated at appropriate doses (Rajji et al. 2008). Clinical trials in the elderly have demonstrated that SSRIs are superior to placebo for the treatment of depression (Roose and Schatzberg 2005). A detailed review of the efficacy of SSRIs in elderly patients is published elsewhere (Mukai and Tampi 2009). This review concluded that SSRIs were at least as effective as tricyclics and that they were better tolerated in elderly patients. The meta-analysis of Kok et al. (2012), on the other hand, suggested that remission rates for SSRIs compared to placebo were not significantly different. For response rates however, there was a statistically significant difference from placebo and the NNT was 10 (Kok et al. 2012). The perception of the efficacy of SSRIs may be altered when studies in the very old age group are considered. For example, citalopram failed to separate from placebo in a group of patients aged >80 years (Roose et al. 2004).

Dual reuptake inhibitors provide an alternative approach for the treatment of depression in the elderly. Both venlafaxine and duloxetine have been evaluated in placebo-controlled evaluations in elderly populations. There does not appear to have been any placebo-controlled evaluations of desvenlafaxine in a specifically designed trial in an elderly group. Duloxetine has the best evidence for efficacy: both published studies suggested a statistically significant benefit of the drug at 60 mg/day

Table 3 Placebo-controlled studies of MAOIs in elderly depression

	Sample size	Mean age (yrs)	Dose mg/day	Length of randomized treatment	Primary efficacy variables	Efficacy	REF
Moclobemide							
Moclobemide	25	67	400	6 weeks	HDRS	23%	Nair et al. (1995)
Nortriptyline	27	71	75			33%	
Placebo	25	71				11% (Remission HDRS <10)	
Moclobemide	694	73.6	400	7 weeks	HDRS	MOCLO > PBO on HDRS at end point	Roth et al. (1996)
Placebo							
Phenelzine							
Phenelzine	22	>55	45	7 weeks	HDRS	PHEN = NORT > PBO on HDRS at end point	Georgotas et al. (1987)
Nortriptyline	25		75			PHEN 61.1%, NORT 61.9%; PBO 13.3% responders HDRS <10	
Placebo	28						

(Nelson et al. 2005; Raskin et al. 2007). Venlafaxine showed antidepressant efficacy in open and comparative trials, but three placebo-controlled evaluations were negative studies (Mock et al. 2010). This may have been due to the choice of formulation, immediate release versus extended release. The immediate release formulation is associated with poorer tolerability than the extended release resulting in more dropouts due to side effects and lower statistical power to detect significant differences (Mock et al. 2010).

Recent developments in depression pharmacotherapy have seen the introduction of several new medications: agomelatine, vilazodone, and vortioxetine. Both vortioxetine and agomelatine have been evaluated in limited studies in an elderly population with positive results compared to placebo. Vortioxetine (5 mg/day) was superior to placebo in elderly patients treated for 8 weeks (Katona et al. 2012). Response was achieved by 53.2% of vortioxetine patients and 35.2% of placebo patients. Remission rates were 29.2% and 19.3% for vortioxetine and placebo, respectively. Somewhat similar results were achieved with agomelatine (25–50 mg/day) over 8 weeks compared to placebo (Heun et al. 2013). Response rates were 59.5% and 38.6% for agomelatine and placebo, respectively. Remission rates were not statistically significantly different between drug and placebo. Both agomelatine and vortioxetine are generally well tolerated in the elderly at the doses used in these studies with relatively benign side effect profiles. In addition the putative beneficial effects on sleep (agomelatine) and cognition (vortioxetine) might prove advantageous for these two agents in treating elderly depressed patients. Further evaluations of these agents are required.

Expert consensus guidelines currently recommend only a limited number of antidepressants for geriatric depression. These recommendations are summarized in Table 4 along with dose ranges and particular side effect issues related to use in elderly populations.

While there is a reasonable body of evidence suggesting that antidepressants are effective in elderly depressed populations, the studies are mostly of short treatment duration. Efficacy of pharmacotherapy in continuation and maintenance therapy is less robust. Late-life depression is generally considered as a recurring disorder (Alexopoulos 2005). In the absence of continuation treatment, recurrence rates are around 50% within 4–6 months (Rajji et al. 2008). Recurrence occurred in 90% of elderly patients with major depression within 3 years of remission when maintained on placebo (Reynolds et al. 1999). Lower recurrence was observed in patients maintained on nortriptyline or interpersonal psychotherapy (IPT). A similar observation was made in patients treated with paroxetine and IPT (Reynolds et al. 2006). Recurrence rates over 2 years were 32% in those maintained on paroxetine compared to 58% in those for whom the drug was discontinued. The benefits of longer-term antidepressant treatment on mortality were supported by the PROSPECT study which showed that in practices which implemented depression care management (including antidepressants), mortality was lower over a 5-year period than in patients treated with usual care (Gallo et al. 2007).

The literature would support the necessity for 4–6 months of continuation pharmacotherapy to consolidate remission and achieve recovery. For maintenance treatment, antidepressants are recommended to be used at the same doses as for the

Table 4 Antidepressants for the treatment of late-life depression

Antidepressant	Initial daily dose	Dose ranges	Major side effects
Selective serotonin reuptake inhibitors			
Citalopram	10 mg	20–40 mg/day	Anxiety, dose-dependent QT prolongation
Escitalopram	5 mg	10–20 mg/day	Dose-dependent QT prolongation
Sertraline	25 mg	50–100 mg	Dyspepsia, tremor, weight loss
Serotonin-noradrenaline reuptake inhibitors			
Duloxetine	30 mg	60–120 mg/day	Constipation decreased appetite, fatigue, hyperhidrosis, diarrhea
Desvenlafaxine	50 mg	50–100 mg/day	Hyperhidrosis, dizziness, insomnia, constipation, decreased appetite, fatigue, vomiting, sexual dysfunction
Venlafaxine	37.5 mg	75–225 mg/day	Abnormal dreams, anorexia, dizziness, nervousness, hyperhidrosis, tremor, sexual dysfunction
Tricyclic antidepressants			
Desipramine	25 mg	75–100 mg at night	Abdominal cramps, nausea, vomiting, asthenia, insomnia, weakness, headache, lethargy, agitation
Nortriptyline	25 mg	50–75 mg at night	Sedation, weight gain, lowered seizure threshold, fatigue
Noradrenergic/specific serotonergic antidepressants			
Mirtazapine	7.5 mg at night	15–30 mg at night	Dry mouth, sedation, arthralgia, somnolence, increased appetite, weight gain, dizziness, constipation
Monoamine oxidase inhibitors			
Moclobemide	75 mg bid	300–600 mg bid	Sleep disturbance, anxiety, restlessness, tremor, vomiting, hypotension
Newer antidepressants			
Agomelatine	25 mg at night	25–50 mg at night	Increases ALT and/or AST, headache
Vortioxetine	5 mg	5 mg/day	Nausea, diarrhea, dry mouth, headache, hyperhidrosis

acute treatment phase. For a single severe episode of depression, drug treatment should continue for at least 1 year, while in patients with three or more lifetime episodes, maintenance treatment is recommended to continue for longer than 3 years (Alexopoulos 2005). The value of maintenance pharmacotherapy appears to be greater in older patients with more severe forms of depression. In psychotic depression patients who achieve remission after treatment with an antidepressant and an antipsychotic, the general consensus is that the antipsychotic drug be continued for 6 months. For patients in whom electroconvulsive therapy is effective, continuation or maintenance therapy should consist of an antidepressant not yet tried by the patient and a mood stabilizer. Continuation or maintenance electroconvulsive therapy is another option (Alexopoulos 2005).

Clearly, further studies for the management of depression in older patients are needed in order to develop reliable and practical guidelines as well as to evaluate thoroughly the efficacy of newer agents in the elderly. Studies of the "old-old" as well as those that include comorbid medical illnesses and cognitive impairment are also required.

Anxiety in the Elderly

The prevalence of anxiety disorders among older adults (10–20%) surpasses that of other old age conditions such as dementias (8%) and major depressive disorder (1–3%) (Reiger et al. 1988). Although anxiety disorders are the most common psychiatric disorder through the life span, they are often difficult to diagnose or missed entirely (Cassidy and Rector 2008). The vast majority of presentations (~90%) are accounted for by either generalized anxiety disorder (GAD) or a specific phobia (Krasucki et al. 1999). Obsessive-compulsive (OCD), post-traumatic stress (PTSD), and panic disorders account for the remaining 10% of the anxiety disorders of the elderly (Cassidy and Rector 2008). More recently a survey among aged care residents found the overall rate of anxiety disorders ranged from 3.2% to 20% (Creighton et al. 2016). Generalized anxiety disorder and specific phobias were the most common disorders, while clinically significant anxiety symptoms were more frequent than threshold disorders.

Data on risk factors for the development of an anxiety disorder in old age are limited. Nevertheless a review of the literature has suggested that the following factors increase the likelihood of developing an anxiety disorder in late age: (a) being female; (b) having several chronic medical conditions; (c) being single, divorced, or separated (compared to being married); (d) lower education; (e) impaired subjective health; (f) stressful life events; (g) physical limitations in daily activities; (h) adverse events in childhood; and (i) neuroticism (Wolitzky-Taylor et al. 2010).

A recent survey of longitudinal studies of anxiety disorders in the elderly identified their chronicity (Sami and Nilforooshan 2015). Furthermore, the disorders are associated with a high relapse rate with up to 39–52% relapse in 3–6 years. There was a substantial conversion to depression and anxiety-depression over their natural course. Remission rates in depressive anxiety were shown to be lower than pure depression in 3- and 6-year follow-up (Schoevers et al. 2005; Steffens and McQuoid 2005) indicating anxiety-depression had a worse prognosis than depression or anxiety alone. A further significant finding was that anxiety disorders in community settings are undertreated.

Treatment of Anxiety Disorders

Controlled clinical evaluation of pharmacological treatments for anxiety disorders in late life is sparse with guidelines based on extrapolation of evaluations in younger age groups (Krasucki et al. 1999).

Benzodiazepines are more effective than placebo in the studies which have been conducted in elderly populations. In outpatients with a primary diagnosis of anxiety neurosis, oxazepam was superior to placebo over a 4-week study period (Koepke et al. 1982). The drug was well tolerated. Similarly ketazolam (15 mg/day) was superior to placebo over a 15-day treatment period for generalized anxiety disorder (Bresolin et al. 1988). Response to treatment was achieved by 83% of the ketazolam-treated patients and 43% of the placebo patients ($P < 0.01$). The partial benzodiazepine agonist abecarnil was evaluated in outpatients with anxiety over a 6-week period (Small and Bystritsky 1997). Abecarnil (3.0–7.0 mg/day) was superior to placebo in reducing anxiety at weeks 2–4 and 6. A higher dose of the drug (7.5–17.5 mg/day) although effective was not well tolerated. The efficacy of **alpidem** (25–50 mg t.i.d.), administered for 3 weeks in anxious elderly patients (65–80 years), was significantly ($p < 0.01$) superior to placebo (Frattola et al. 1992). Psychomotor and mnemonic performances were not impaired by alpidem. Benzodiazepines are still widely prescribed for anxiety disorders despite a small database of placebo-controlled evaluations and their association with well-known serious problems for the elderly: hip fracture, impaired cognitive and psychomotor function, dependence, and withdrawal (Cassidy and Rector 2008). In a survey of mental health utilization by 55–85-year-olds, 25.3% of those with anxiety disorders were prescribed benzodiazepines, whereas 3.8% reported being prescribed antidepressants (de Beurs et al. 1999). Benzodiazepine use is not a favorable prognostic factor – patients who require benzodiazepines are significantly less likely to remit than those who do not take benzodiazepines (Steffens and McQuoid 2005). Risks to the elderly from long-term use of benzodiazepines suggest that their use should be limited to the short term. As late-life GAD is a chronic condition, benzodiazepines do not appear to be an appropriate option for its treatment (Lenze et al. 2003).

The high level of comorbidity of GAD and depression and the observation that late-onset generalized anxiety is frequently secondary to depression suggest that antidepressant medication should be the treatment of choice for many older adults who present with GAD. Limited evaluations in older populations have shown antidepressants to be effective for the treatment not only of GAD but of panic disorder as well (Wolitzky-Taylor et al. 2010). Citalopram, sertraline, and venlafaxine ER have all demonstrated efficacy for reducing anxiety among elderly patients. Compared to CBT or a waitlist control, sertraline had a greater effect on symptoms for older patients with GAD, panic disorder, agoraphobia, and social anxiety disorder(Schuurmans et al. 2006). Pooled data from five placebo-controlled trials evaluating the efficacy of venlafaxine ER for GAD in younger and older adults found similar response rates between the two groups (66% older versus 67% younger) (Katz et al. 2002).

Buspirone, a 5HT1A partial agonist, is an alternative option for the treatment of anxiety in the elderly. It has demonstrated efficacy over placebo and comparable efficacy to benzodiazepines in younger populations. However, its usefulness in treating elderly populations is unclear since it has a slow onset of action and is reported to be less effective for those previously treated with a benzodiazepine (Flint 2005). The safety and efficacy of pregabalin were evaluated in the treatment of generalized

anxiety disorder in people 65 years and older in a double-blind, randomized, placebo-controlled, 8-week trial (Montgomery et al. 2008). Flexible doses of 150–600 mg/day pregabalin were associated with a greater reduction in anxiety ratings than placebo. Discontinuations due to adverse events were similar for pregabalin and placebo. Pregabalin was a safe and effective treatment of GAD in older patients.

Other medication options for late-life anxiety include mirtazapine and atypical antipsychotics, but there are no studies in specific elderly anxious populations.

A meta-analysis of studies in GAD reported that elderly patients benefited from pharmacotherapy but that the benefits were no greater than with psychotherapy (Goncalves and Byrne 2012). There is a growing body of evidence that cognitive behavioral therapy (CBT) is the most appropriate treatment for anxiety disorders in the elderly (Barrowclough et al. 2001). Benzodiazepine use has been shown to decline with CBT reducing the risk of falls and fall-related deaths in this age group. Enhanced models of CBT for older individuals, modified to better meet the needs of older adults, have been shown to be more effective than standard CBT in an individual or group format (Mohlman et al. 2003). The use of CBT in the elderly is not discussed further here.

Pharmacotherapy Side Effects of Concern in the Elderly

Treatment of psychiatric disorders in the elderly with medication involves risks of adverse reactions and side effects. Benzodiazepines are well known for their psychomotor and cognitive impairing effects as well as the withdrawal syndrome as discussed above. In addition benzodiazepines and hypnotic agents are respiratory depressants. Behavioral disinhibition may also occur with benzodiazepines, which makes them less suitable for controlling agitation and aggressive outbursts in elderly demented patients. The general consensus is that benzodiazepines should be avoided in elderly patients wherever possible. The side effects of concern with these agents are therefore not discussed further. Since antidepressants are more likely to be prescribed, there are some significant issues for their use in elderly patients.

The selection of a particular antidepressant can be influenced by the mundane issues of pharmacokinetic and pharmacodynamic considerations. Both paroxetine and fluoxetine are effective in the elderly, but are not good first-line choices due to the long half-life of elimination of fluoxetine and the significant anticholinergic effects associated with the use of paroxetine. The anticholinergic effects of TCA antidepressants preclude their use in patients with preexisting glaucoma, urinary retention, and hypertrophy of the prostate or cognitive impairment. Furthermore, their cardiovascular effects and toxicity on overdose suggest a contraindication in patients with a recent history of myocardial infarction, cardiac conduction defects, and orthostatic hypotension. The necessity for dietary restrictions, due to interaction with tyramine in certain foods, as well as their orthostatic effects limits the usefulness of monoamine oxidase inhibitors in the elderly (Alamo et al. 2014).

Mortality by All Causes

The risk of all-cause mortality with antidepressant use is increased in the elderly (Gallo et al. 2007). Poorer self-care and noncompliance with medications used in the treatment of conditions such as diabetes and heart disease are associated with comorbid depression (Alamo et al. 2014). This may also contribute to greater mortality. The association between antidepressant treatment and risk of adverse outcomes was examined in a cohort study of people aged 65 with depression in over 500 general practices in the UK (Coupland et al. 2011). SSRIs (54.7%), TCAs (31.6%), MAOIs (0.2%), and other antidepressants (13.5%) were prescribed. The adjusted hazard ratio for all-cause mortality was highest for the group of other antidepressants.

Hyponatremia and Inappropriate ADH Secretion

Excessive secretion of antidiuretic hormone (ADH) can be caused by antidepressants, notably SSRIs and venlafaxine leading to hyponatremia (De Picker et al. 2014). Hyponatremia is associated with significant morbidity, such as lethargy, headache, confusion, convulsions, and coma, and can occasionally cause death. The estimated prevalence of hyponatremia in elderly patients receiving SSRIs ranges from 12% to 25% (Alamo et al. 2014). A more recent systematic review supported the predominant involvement of SSRIs and SNRIs as well as mirtazapine in case reports and clinical studies evaluating hyponatremia in older adults (Viramontes et al. 2016).

Bleeding Risks Related to Antidepressant Drugs

Excessive bleeding is of concern for patients receiving SSRIs and SNRIs including elderly patients. SSRI use is associated with roughly doubled odds of upper gastrointestinal (GI) bleeding; bleeding at other sites has been less commonly described (Andrade et al. 2010). Concomitant use of NSAIDs, anticoagulants, and antiplatelet agents increases the risk of SSRI-associated GI bleeding. On the other hand, the risk is decreased by concurrent use of proton pump inhibitors.

More recently antidepressant use has been associated with a higher cerebral micro-bleed incidence than nonuse (Akoudad et al. 2016). When stratified by affinity for the serotonin transporter, intermediate serotonin affinity antidepressant use was associated with an increased risk of developing micro-bleeds. Both SSRIs and non-SSRI antidepressant use were associated with increased micro-bleed incidence.

Cardiovascular Risks Related to Antidepressant Drugs

Antidepressant-related cardiovascular adverse effects are well known, especially as related to TCA overdoses (Sloman et al. 1983). The tricyclic pharmacological effects of muscarinic blockade, noradrenaline reuptake inhibition, and quinidine-like effects

are thought to be responsible for their cardiovascular effects. In addition TCAs affect the electric conduction of the heart such that they tend to slow conduction; prolong PR, QRS, and QT intervals; as well as induce heart block and arrhythmias in the elderly. An increased relative risk of 2.2 for myocardial infarction was associated with antidepressant use compared to nonuse in a cohort study (Cohen et al. 2000). Adjusting for age, gender, baseline heart disease, diabetes, hypertension, hyperlipidemia, anxiety, and cancer, users of TCAs had a higher relative risk than users of SSRIs. The difference was attributed to the inhibitory effect of SSRIs on platelet aggregation. SSRIs are recommended in patients with cardiovascular disease, while sertraline has been found to be safe in patients with a history of acute myocardial infarction or unstable angina (Alamo et al. 2014). Nevertheless, SSRIs are not without attendant cardiovascular risks in the elderly. A widely used surrogate marker of drug cardiotoxicity is prolongation of the QTc interval (Roden 2004). Both citalopram and its congener, escitalopram, have been associated with a dose-dependent increase in the QTc interval (Cooke and Waring 2013). This prompted a warning from the US FDA that citalopram should not be used in doses exceeding 20 mg/day for patients with hepatic impairment, older than 60 years, for CYP2C19 poor metabolizers, or for those taking concomitant CYP2C19 inhibitors (US Food and Drug Administration).

Orthostatic hypotension is also of concern in the elderly as it is associated with an increased risk of falls and fractures (Alamo et al. 2014). This is in part due to the blockade of α1-adrenergic receptors by TCAs and MAOIs. Drugs with noradrenergic reuptake effects are associated with tachycardia and slightly raised blood pressure or even hypertension at higher doses. The SNRI antidepressants duloxetine and venlafaxine are particularly implicated.

Risk of Antidepressant Overdose

Rates of suicide are generally higher in the elderly, particularly in the population 85 years and older (Osgood 1991). Although antidepressants may reduce the overall suicide rate, they are frequently used in overdose in a suicide attempt. The relative toxicity of antidepressants was determined in an observational study of prescriptions, poisoning deaths, and nonfatal self-poisoning episodes in England and Wales (Hawton et al. 2010). Of the TCAs, dothiepin and doxepin had the greatest toxicity based on overdose deaths both relative to prescriptions and nonfatal self-poisonings. Venlafaxine appeared to be less toxic than the TCAs but more toxic than the SSRIs and mirtazapine. Of the five SSRIs examined, citalopram was more toxic than the other four.

Although considered safer than TCAs on overdose, SSRIs may result in a serotonin syndrome, particularly when combined with another serotonergic agent. Additionally, early in treatment SSRIs may be associated with a paradoxical increase in anxiety and suicidal ideation. Patients should be monitored closely in the early stages of treatment for the emergence of akathisia which has been associated with an increased suicide behavior.

Risk Due to Anticholinergic Effects

Negative effects on the physical health and quality of life of elderly patients may be due to side effects experienced because of the antimuscarinic effects of some antidepressants, especially TCA and paroxetine. Peripheral effects of dry mouth, blurred vision, urinary hesitancy, and constipation are well known. In the central nervous system, confusion and delirium may occur in elderly patients due to cholinergic blockade. In those with an underlying dementia, this risk is exacerbated.

Sexual Dysfunction

Depression and pharmacological treatments of depression are associated with sexual dysfunction in both men and women. Sexual dysfunction is frequently cited as a reason for noncompliance with or a discontinuation of treatment (Clayton et al. 2014). Decreased quality of life is also associated with sexual dysfunction. SSRIs and SNRIs inhibit desire, cause erectile dysfunction, decrease vaginal lubrication, as well as impair orgasm (Conaglen and Conaglen 2013). Variable effects depending on the putative mechanism of action are seen with TCAs. All inhibit sexual desire and orgasm, but clomipramine, a more selective serotonergic agent, causes orgasmic difficulties, whereas nortriptyline causes more erectile dysfunction with less effect on orgasm. MAOIs are also associated with sexual dysfunction, although moclobemide was reported to increase sexual desire. Variable negative effects on all aspects of sexual function are associated with other antidepressants such as venlafaxine and mirtazapine. Initial reports suggest that both agomelatine and vortioxetine do not have significant sexual adverse effects in the elderly (Katona et al. 2012). However, evaluation of the sexual effects of these agents requires further investigation.

Risk of Osteoporosis

The use of antidepressants at therapeutic doses is associated with decreased bone mineral density (BMD) and increased fall and fracture risk (Bruyere and Reginster 2014). A cohort study in elderly women on SSRIs reported greater bone loss at the hip, which was class specific as TCAs did not appear to have this effect (Cizza et al. 2009). Identification of the serotonin transporter on osteoblasts suggests that a direct effect on bone mass is biologically plausible. The risk of fractures might differ among different antidepressants. A dose-dependent increase in fracture risk was associated with most SSRIs. TCAs with the greatest sedating effects, e.g., amitriptyline and clomipramine, were associated with fractures, whereas imipramine and nortriptyline were not. The clinical evidence suggests that antidepressants in general should be considered among agents which are risk factors for osteoporotic bone fractures.

Withdrawal Syndrome

Discontinuation or withdrawal syndromes for antidepressants and benzodiazepines are well recognized.

It has been estimated that between 15% and 44% of chronic benzodiazepine users experience withdrawal symptoms after ceasing medication (Lugoboni and Quagli 2014). The withdrawal syndrome is characterized by a number of emergent symptoms, particularly anxiety and depressed mood, but may also include perceptual changes, paranoia, and seizures in the most severe cases. Seizures are more likely to be associated with the prolonged use of high doses (>50 mg equivalents of diazepam). The use of short half-life benzodiazepines (alprazolam in particular is associated with withdrawal syndrome) and abrupt cessation of medication is more likely to produce a withdrawal syndrome. Management of benzodiazepine withdrawal involves an individually devised tapering of the drug combined with switching to an equivalent dose of a long half-life drug (usually diazepam) before commencement of tapering. Other medications such as antiepileptics or pregabalin might be useful but have not been evaluated in sufficient clinical studies for firm recommendations. Occasionally management of withdrawal syndrome may require hospitalization, and the use of supportive psychotherapy is always appropriate.

SSRIs, like TCAs and MAOIs, are associated with a well-recognized syndrome following discontinuation or dose reduction (Olver et al. 1999). Commonly the withdrawal syndrome is characterized by flu-like symptoms. Rarely extrapyramidal syndromes and mania/hypomania can occur (Haddad and Anderson 2007). Common features of withdrawal are an abrupt onset within days of cessation of the drug, a relatively short duration when untreated and rapid resolution on reinstatement of the antidepressant. Withdrawal symptoms can be attenuated or prevented by using an individualized tapering schedule at the end of treatment. Noncompliance with medication during treatment might also be associated with withdrawal symptoms potentially confused as relapse of the underlying condition. Usually symptoms are of mild intensity and short lived. Severe symptoms may require symptomatic treatment or reinstatement of the antidepressant. There are some differences between medications with respect to withdrawal. For example, paroxetine appears to have the highest and fluoxetine the lowest incidence of withdrawal symptoms. Other SSRIs are associated with an intermediate incidence. SNRIs are also associated with a withdrawal syndrome similar in presentation to that of the other antidepressants. Venlafaxine has been most often associated with a withdrawal phenomenon.

Drug-Drug Interactions: Pharmacotherapy in Elderly

Older age is associated with a greater likelihood of somatic illness to which patients with psychiatric disorders are not immune. Thus polypharmacy is likely to be the rule rather than the exception. Such polypharmacy leads to the potential for drug-drug interactions at both the pharmacokinetic and pharmacodynamic level. The medications which are used to treat psychiatric conditions are, for the most part,

Table 5 Benzodiazepine drug interactions

Drug	Clinical effects
Antacids	Decreased absorption single doses; doubtful relevance repeated dosing
Anticholinergic agents	As above
Cimetidine	Inhibition of metabolism; possible increased side effects
Alcohol, CNS depressants	Lower tolerance to alcohol; additive effects on psychomotor performance
Succinylcholine	Prolonged muscular blockade
Disulfiram	Inhibition of metabolism; increased clinical effects
Rifampicin	Increased metabolism; decreased clinical efficacy
L-DOPA	Exacerbation of Parkinsonian symptoms[a]
Digoxin	Increased plasma digoxin concentrations[a]
Lithium	Hypothermia[a]
Phenytoin	Changes in phenytoin concentration; dubious clinical significance

[a]Based on case reports alone

extensively metabolized by liver enzymes (P450 system), while some are well-recognized inhibitors of individual cytochrome enzymes. Phase II conjugative metabolism is a related metabolic system which has been implicated in drug-drug interaction. The family of uridine 5-diphosphate glucuronosyltransferases (UGTs) is the most prominent of these enzymes. P-glycoprotein (P-gp) an ATP-dependent, extruding transporter resides in the plasma membrane of the gut where it is an important regulator of absorption. P-gp is also present at the blood-brain barrier, where it is an important gateway for preventing various substances accessing the CNS. An extensive discussion of interactions is not provided here, but a few are highlighted since they are likely to be important in considering the choice of medication for depression and anxiety treatments in the presence of comorbidity. More extensive reviews are available in the published literature (e.g., Spina and Scordo 2002).

Some interactions observed with benzodiazepines are summarized in Table 5. The most important clinical interaction is that with alcohol and other CNS depressants, where psychomotor performance might be impaired leading to falls and fractures (*vide supra*) with the attendant risk of mortality due to medical complications.

TCAs and MAOIs are associated with significant interactions with other agents of which the most relevant for the elderly are likely to be with drugs used to treat cardiovascular disorders (Spina and Scordo 2002). The effectiveness of older antihypertensive agents (guanethidine, debrisoquine, bethanidine, bretylium, clonidine, methyldopa) is often reduced by TCAs due to competitive antagonism at similar receptor sites. Calcium channel blockers may affect the metabolism of some TCAs. Both MAOIs and TCAs are mild to moderate inhibitors of some of the P450 enzymes, while TCAs are inhibitors of P-gp. The combination of TCA and MAOI has sometimes proven fatal possibly due to the development of a serotonin syndrome.

Table 6 Effect of antidepressants on cytochrome P450 enzymes

	Cytochrome enzyme inhibition				
Drug	2D6	1A2	2D6	2C9	2D6
Tricyclics					
Amitriptyline	+	++	0	+	+++
Clomipramine	+	++	0	+	+++
Desipramine	+	0	0	0	+
Doxepin	+	+	0	+	+++
Dothiepin	+	+	0	+	+++
Nortriptyline	+	0	0	0	+
SSRIs					
Citalopram	++	0	0	0	0
Escitalopram	++	0	0	0	0
Fluoxetine	+++	0	+	++	+++
Fluvoxamine	+	+++	++	+++	+++
Paroxetine	+++	0	0	0	0
Sertraline		0	0	0	0
SNRIs					
Desvenlafaxine	++	0	0	0	0
Duloxetine	++	0	0	0	0
Venlafaxine	+	0	0	0	0
Recent Agents					
Agomelatine	0	0	0	0	0
Vortioxetine	0	0	0	0	0

Adapted from Gilman (2007)
+ Unlikely to be of clinical significance
++ May be clinically significant depending interacting agents
+++ Large clinical effect possible with some other agents

The effect of SSRIs on cytochrome P450 enzymes is more extensively investigated than for TCAs or MAOIs. Table 6 shows the effect of the different SSRIs on the various cytochrome subtypes. Despite the opportunities for a multiplicity of potential interaction events, the data on clinically significant interactions with these agents is sparse (DeVane 2006). However as pointed out a "lack of evidence does not equate to evidence of absence." Among the SSRIs escitalopram and sertraline have the lowest risk for interactions with other agents metabolized by the cytochrome system. Pharmacodynamic interactions are somewhat less predictable, and vigilance in prescribing, particularly in elderly patients on multiple medications, is always warranted.

Conclusions

Assessment of psychiatric disorders in the elderly requires that potentially contributing factors such as primary medical causes, medications, and dementia should be identified as potential confounders of diagnosis. As with all prescribing the risk and

benefits of the use of medications needs to be judiciously assessed taking into account the patients' physical as well as their mental health.

SSRIs are broad-spectrum agents effective in both depression and anxiety. Furthermore, they are generally well tolerated, have a good safety profile on overdose, and are relatively free of drug-drug interactions. They have become the preferred first-line treatment of depression and anxiety in the elderly. Nevertheless there are some nuances in their clinical application which needs to take into account the differences in their side effects, safety on longer-term administration, and potential for drug-drug interactions.

TCAs and MAOIs are probably less suited to use in the elderly due to their generally lower tolerability and lower cardiovascular safety. Other antidepressant agents including the SNRIs and mirtazapine also have side effect and longer-term safety issues which would make them second-line treatment in the elderly. The newer agents such as agomelatine, vortioxetine, and vilazodone appear, from limited clinical evaluations, to have efficacy in the short-term treatment of depression in the elderly with relatively benign side effect profiles. However there is still much to learn about the use of these drugs in specific elderly populations.

Benzodiazepines must be prescribed judiciously to the elderly due to increased risk of falls, cognitive impairment, and the withdrawal syndrome.

Cross-References

- ▶ Anxiety in Late Life
- ▶ Depression in Late Life: Etiology, Presentation, and Management
- ▶ Elderly Suicide and Suicide Prevention
- ▶ Physical Comorbidities and Mood Disorders in Older Adults
- ▶ Psychological Interventions for Older Adults: Evidence-Based Treatments for Depression, Anxiety, and Carer Stress

References

Ahmed N, Mandel R, Fain MJ (2007) Frailty: an emerging geriatric syndrome. Am J Med 120:748–753

Akoudad S, Aarts N, Noordam R, Ikram MA, Tiemeier H, Hofman A, Stricker BH, Vernooij MW, Visser LE (2016) Antidepressant use is associated with an increased risk of developing microbleeds. Stroke 47:251–254

Alamo C, Lopez-Munoz F, Garcia-Garcia P, Garcia-Ramos S (2014) Risk–benefit analysis of antidepressant drug treatment in the elderly. Psychogeriatrics 14:261–268

Alexopoulos GS (2005) Depression in the elderly. Lancet 365:1961–1970

Alexopoulos GS, Katz IR, Reynolds CF, Carpenter D, Docherty JP (2001) The expert consensus guideline series: pharmacotherapy of depressive disorders in older patients. Postgrad Med Special Report 1–86

Alexopoulos GS, Lerner DM, Salzman C (2005) Treatment of depression with tricyclic antidepressants, monoamine oxidase inhibitors and psychostimulants. In: Salzman C (ed) Clinical geriatric psychiatry, 4th edn. Lippincott, Williams and Wilkins, Philadelphia, pp 233–303

American Geriatrics Society 2015 Beers Criteria Update Expert Panel (2015) American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 63:2227–2246

Andrade C, Sandarsh S, Chethan KB, Nagesh KS (2010) Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry 71:1565–1575

Barrowclough C, King P, Colville J et al (2001) A randomized trial of the effectiveness of cognitive-behavioral therapy and supportive counselling for anxiety symptoms in older adults. J Consult Psychol 69:756–762

Benedetti MS, Whomsley R, Canning M (2007) Drug metabolism in the paediatric population and in the elderly. Drug Discov Today 12:599–610

Benet LZ, Hoener BA (2002) Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 71:115–121

Blazer D, Hughes DC (1987) The epidemiology of depression in an elderly community population. Gerontologist 27:281–287

Bresolin N, Monza G, Scarpini E et al (1988) Treatment of anxiety with ketazolam in elderly patients. Clin Ther 10:536–542

Bruyere O, Reginster J-Y. Osteoporosis in patients taking selective serotonin reuptake inhibitors: a focus on fracture outcome. Endocrine DOI 10.1007/s12020-014-0357-0, August 2014.

Butler JM, Begg EJ (2008) Free drug metabolic clearance in elderly people. Clin Pharmacokinet 47:297–321

Cassidy K-L, Rector NA (2008) The silent geriatric giant: anxiety disorders in late life. Geriatr Aging 11:150–156

Cizza G, Primma S, Csako G (2009) Depression as a risk factor for osteoporosis. Trends Endocrinol Metab 20:367–373

Clayton AH, Croft HA, Handiwala L (2014) Antidepressants and sexual dysfunction: mechanisms and clinical implications. Postgrad Med 126:91–99

Cohen HW, Gibson G, Alderman MH (2000) Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 108:2–8

Conaglen HM, Conaglen JV (2013) Drug-induced sexual dysfunction in men and women. Aust Prescr 36:42–45

Cooke MJ, Waring WS (2013) Citalopram and cardiac toxicity. Eur J Clin Pharmacol 69:755–760

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:d4451

Creighton AS, Davison TE, Kissane DW (2016) The prevalence of anxiety among older adults in nursing homes and other residential aged care facilities: a systematic review. Int J Geriatr Psychiatry 31:555–566

Cresswell KM, Fernando BF, McKinstry B, Sheikh A (2007) Adverse drug events in the elderly. Br Med Bull 83:259–274

de Beurs E, Beekman ATF, van Balkom AJLM et al (1999) Consequences of anxiety in older persons: its effect on disability, well-being and use of health services. Psychol Med 29:583–593

De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG (2014) Antidepressants and the risk of hyponatremia: a class-by-class review of literature. Psychosomatics 55:536–547

DeVane CL (2006) Antidepressant–drug interactions are potentially but rarely clinically significant. Neuropsychopharmacol 31:1594–1604

Doucet J, Queneau P (2005) Adverse drug reactions in the elderly. Bull Acad Natl Med 189:1693–1707. discussion, 1708–1709

Driscoll HC, Karp JF, Dew MA, Reynolds CF (2007) Getting better, getting well: understanding and managing partial and non-response to pharmacological treatment of non-psychotic major depression in old age. Drugs Aging 24:801–814

Flint AJ (2005) Generalised anxiety disorder in elderly patients: epidemiology, diagnosis and treatment options. Drugs Aging 22:101–114

Fliser D, Franek E, Ritz E (1997) Renal function in the elderly – is the dogma of an inexorable decline of renal function correct? Nephrol Dial Transplant 12:1553–1555
Frattola L, Piolti R, Bassi S, Albizzati MG et al (1992) Effects of alpidem in anxious elderly outpatients: a double-blind, placebo controlled trial. Clin Neuropharmacol 15:477–487
Froissart M, Rossert J (2005) How to improve estimation of renal function in the elderly. Rev Prat 55:2223–2229
Gallo JJ, Bogner HR, Morales KH, Post EP, Lin JY, Bruce ML (2007) The effect of a primary care practice-based depression intervention on mortality in older adults: a randomized trial. Ann Intern Med 146:689–698
Georgotas A, McCue RE, Hapworth W, Friedman E, Kim OM, Welkowitz J, Chang I, Cooper TB (1986) Comparative efficacy and safety of MAOIs versus TCAs in treating depression in the elderly. Biol Psychiatry 21:1155–1166
Georgotas A, McCue RE, Friedman E, Cooper TB (1987) Response of depressive symptoms to nortriptyline, phenelzine and placebo. Br J Psychiat 151:102–106
Gillman PK (2007) Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol 151:737–748
Giron MS, Fastbom J, Winblad B (2005) Clinical trials of potential antidepressants: to what extent are the elderly represented: a review. Int J Geriatr Psychiatry 20:201–217
Goncalves DC, Byrne GJ (2012) Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. J Anxiety Disord 26:1–11
Greenblatt DJ (1979) Reduced serum albumin concentration in the elderly: a report from the Boston Collaborative Drug Surveillance Program. J Am Geriatr Soc 27:20–22
Greenblatt DJ, von Moltke LL, Harmatz JS et al (2002) Pharmacokinetics, pharmacodynamics, and drug disposition. In: Davis KL, Charney D, Coyle JT et al (eds) Neuropsychopharmacology: the fifth generation of progress, 5th edn. Lippincott Williams & Wilkins, Philadelphia, pp 507–524
Haddad PM, Anderson IM (2007) Recognising and managing antidepressant discontinuation symptoms. Adv Psychiatr Treat 13:447–457
Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, Kapur N (2010) Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 196:354–358
Herrlinger C, Klotz A (2001) Drug metabolism and drug interactions in the elderly. Best Pract Res Clin Gastroenterol 15:897–918
Heun R, Ahokas A, Boyer P, Giménez-Montesinos N, Pontes-Soares F, Olivier V (2013) The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo-controlled study. J Clin Psychiatry 74:587–594
Hilmer SN, McLachlan AJ, Le Couteur DG (2007) Clinical pharmacology in the geriatric patient. Fundam Clin Pharmacol 21:217–230
Hubbard RE, O'Mahony MS, Calver BL, Woodhouse KW (2008) Plasma esterases and inflammation in ageing and frailty. Eur J Clin Pharmacol 64:895–900
Hutchison LC, O'Brien CE (2007) Changes in pharmacokinetics and pharmacodynamics in the elderly patient. J Pharm Pract 20:4–12
Jarvik L, Mintz J, Steuer J, Gerner R (1982) Treating geriatric depression: a 26-week interim analysis. J Am Geriatr Soc 30:713–717
Judge TG, Caird FI (1978) Drug treatment of the elderly patient. Pitman Medical Publishing Tunbridge Wells, UK, p P7
Kapadia A, Wynn D, Salzman B (2010) Potential adverse effects of proton pump inhibitors in the elderly. Clin Geriatr 18:24–31
Katona C, Hansen T, Olsen CK (2012) A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety ofLu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol 27:215–223
Katz IR, Reynolds CF, Alexopoulos GS et al (2002) Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc 50:18–25

Keller MB (2003) Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 289:3152–3160
Kennerfalk A, Ruigómez A, Wallander MA, Wilhelmsen L, Johansson S (2002) Geriatric drug therapy and healthcare utilization in the United Kingdom. Ann Pharmacother 36:797–803
Kinirons MT, O'Mahony MS (2004) Drug metabolism and ageing. Br J Clin Pharmacol 57:540–544
Klotz U (2009) Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 41:67–76
Koepke HH, Gold RL, Linden ME, Lion JR, Rickels K (1982) Multicentre controlled study of oxazepam in anxious elderly outpatients. Psychosomatics 23:641–645
Kok RM, Nolen WM, Heeren TJ (2012) Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. J Affect Dis 141:103–115
Krasucki C, Howard R, Mann A (1999) Anxiety and its treatment in the elderly. Int Psychogeriatr 11:25–45
Le Couteur DG, Fraser R, Hilmer S, Rivory LP, McLean AJ (2005) The hepatic sinusoid in aging and cirrhosis: effects on hepatic substrate disposition and drug clearance. Clin Pharmacokinet 44:187–200
Lenze EJ, Pollock BG, Shear K,MD, Mulsant BH, Bharucha A, Reynolds CF (2003) Treatment considerations for anxiety in the elderly. CNS Spectr 12(Suppl 3):6–13
Lin JH, Yamazaki M (2003) Role of P-glycoprotein in pharmacokinetics. Clinical implications. Clin Pharmacokinet 42:59–98
Lindeman RD, Tobin J, Shock NW (1985) Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 33:278–285
Lugoboni F, Quagli G (2014) Exploring the dark side of the moon: the treatment of benzodiazepine tolerance. Br J Clin Pharmacol 77:239–241
Mallet L, Spinewine A, Huang A (2007) Prescribing in elderly people. 2. The challenge of managing drug interactions in elderly people. Lancet 370:185–191
Mangoni AA, Jackson SH (2004) Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 57:6–14
McLean AJ, Le Couteur DG (2004) Aging biology and geriatric clinical pharmacology. Pharmacol Rev 56:163–184
Mock P, Norman TR, Olver JS (2010) Contemporary therapies for depression in older people. J Pharm Pract Res 40:58–64
Mohlman J, Gorenstein EE, Kleber M et al (2003) Standard and enhanced cognitive-behaviour therapy for late-life generalized anxiety disorder: two pilot investigations. Am J Geriatr Psychiatry 11:24–32
Montgomery S, Chatamra K, Pauer L, Whalen E, Baldinetti F (2008) Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder. Br J Psychiatry 193:389–394
Mottram P, Wilson K, Strobl J (2006) Antidepressants for depressed elderly. Cochrane Database Syst Rev 1:CD003491
Mukai Y, Tampi RR (2009) Treatment of Depression in the Elderly: A Review of the Recent Literature on the Efficacy of Single- Versus Dual-Action Antidepressants. Clin Therap 31:945–961
Mulsant BH, Alexopoulos GS, Reynolds CF, PROSPECT Study Group (2001) Pharmacological treatment of depression in older primary care patients: the PROSPECT algorithm. Int J Geriatr Psychiatry 16:585–592
Nair NPV, Amin M, Holm P, Katona C, Klitgaard C, NgYing Kin NMK, Kragh-Sorensen P, Kiihn H, Leek CA, Stage KB (1995) Moclobemide and nortriptyline in elderly depressed patients: a randomized, multicentre trial against placebo. J Affect Disord 33:1–9
Nelson JC, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Kennedy JS (2005) Duloxetine for the treatment of major depressive disorder in older patients. Am J Geriatr Psychiatry 13:227–235

Olver JS, Burrows GD, Norman TR (1999) Discontinuation syndromes with SSRIs: are there clinically relevant differences? CNS Drugs 12:171–177
Osgood NJ (1991) Prevention of suicide in the elderly. J Geriatr Psychiatry 24:293–305
Pizzuti R, Caffari B, Binkin N, Argento G (2006) Prescription drugs and the elderly: results of the Argento study. Ig Sanita Publ 62:11–26
Rajji TK, Mulsant BH, Lotrich FE, Lokker C, Reynolds CF (2008) Use of antidepressants in late-life depression. Drugs Aging 25:841–853
Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ et al (2007) Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry 164:900–909
Reiger DA, Boyd JH, Burke JD et al (1988) One month prevalence of mental disorders in the US – based on five epidemiologic catchment area sites. Arch Gen Psychiatry 45:977–986
Reynolds CF, Frank E, Kupfer DJ, Thase ME, Perel JM, Mazumdar S, Houck PR (1996) Treatment outcome in recurrent major depression: a post hoc comparison of elderly ("Young Old") and midlife patients. Am J Psychiatry 153:1288–1292
Reynolds CF, Frank E, Perel JM 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
Reynolds CF, Dew MA, Pollock BG et al (2006) Maintenance treatment of major depression in old age. N Engl J Med 354:1130–1138
Roden DM (2004) Drug induced prolongation of the QT interval. N Engl J Med 350:1013–1022
Roose SP, Schatzberg AF (2005) The efficacy of antidepressants in the treatment of late-life depression. J Clin Psychopharmacol 25:S1–S7
Roose SP, Sackeim HA, Krishnan KR et al (2004) Old-Old Depression Study Group. Antidepressant pharmacotherapy in the treatment of depression in the very old: a randomized, placebo controlled trial. Am J Psychiatry 161:2050–2059
Roth M, Mountjoy CQ, Amrien R (1996) Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. Br J Psychiatry 168:149–157
Sami MB, Nilforooshan R (2015) The natural course of anxiety disorders in the elderly: a systematic review of longitudinal trials. Int Psychogeriater 27:1061–1069
Samuels SC, Katz IB (1995) Depression in the nursing home. Psychiatr Ann 25:419–424
Schoevers RA, Deeg DJ, van Tilburg W, Beekman AT (2005) Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. Am J Geriatr Psychiatry 13:31–39
Schuurmans J, Comijs H, Emmelkamp PMG et al (2006) A randomized, controlled trial of the effectiveness of cognitive- behavioral therapy and Sertraline versus a Waitlist Control group for anxiety disorders in older adults. Am J Geriatr Psychiatry 14:255–263
Schwartz JB (2007) The current state of knowledge on age, sex, and their interactions on clinical pharmacology. Clin Pharmacol Ther 82:87–96
Sloman JG, Norman TR, Burrows GD (1983) Clinical studies of antidepressant cardiotoxicity. In: Burrows GD, Norman TR, Davies BM (eds) Drugs in psychiatry, vol. 1., antidepressants. Elsevier Biomedical Press, Amsterdam, pp 173–186
Small GW, Bystritsky A (1997) Double-blind, placebo-controlled trial of two doses of abecarnil for geriatric anxiety. J Clin Psychiatry 58:24–29
Spina E, Scordo MG (2002) Clinically significant drug interactions with antidepressants in the elderly. Drugs Aging 19:299–320
Steffens DC, McQuoid DR (2005) Impact of symptoms of generalized anxiety disorder on the course of late-life depression. Am J Geriatr Psychiatr 13:40–47
Taylor EM (2002) The impact of efflux transporters in the brain on the development of drugs for CNS disorders. Clin Pharmacokinet 41:81–92
Taylor WD, Doraiswamy PM (2004) A systematic review of antidepressant placebo-controlled trials for geriatric depression: limitations of current data and directions for the future. Neuropsychopharmacol 29:2285–2299

Toornvliet R, van Berckel BNM, Luurtsema G, Lubberink M, Geldorf AA, Bosch TM, Oerlemans R, Lammertsma AA, Franssen EJF (2006) Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[11C] verapamil and positron emission tomography. Clin Pharmacol Ther 79:540–548

U.S. Food and Drug Administration. FDA drug safety communication: revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. http://www.fda.gov/drugs/drugsafety/ucm297391.htm

United Nations Department of Economic and Social Affairs, Population Division (2002) http://www.un.org/esa/population/publications/worldageing19502050/

Viramontes TS, Truong H, Linnebur SA (2016) Antidepressant-induced hyponatremia in older adults. Consult Pharm 31:139–150

Wauthier V, Verbeeck RK, Calderon PB (2007) The effect of ageing on cytochrome P450 enzymes: consequences for drug biotransformation in the elderly. Curr Med Chem 14:745–757

WHO (2015) http://www.who.int/mediacentre/factsheets/fs404/en

Wilson K, Mottram P, Sivanranthan A, Nightingale A (2001) Anti-depressants versus placebo for the depressed elderly (Cochrane Review). Cochrane Database Syst Rev 2:CD000561

Wolitzky-Taylor KB, Castriotta N, Lenze EJ, Stanley MA, Craske MG (2010) Anxiety disorders in older adults: a comprehensive review. Depress Anxiety 27:190–211

Woodhouse KW, O'Mahony MS (1997) Frailty and ageing. Age Ageing 26:245–246

Pharmacotherapy of Dementia

19

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Abstract

Alzheimer's disease (AD), the most common form of dementia, is a progressive and debilitating condition that causes deterioration in cognition and function, as well as disturbances in behavior. Currently available treatments for AD (donepezil, rivastigmine, galantamine, and memantine) are symptomatic and do not prevent the progression of the disease. These therapies demonstrate modest but consistent benefit for cognition, global status, functional ability, and behavioral disturbances or neuropsychiatric symptoms. The search for disease-modifying interventions has focused largely on compounds targeting the amyloid-β pathway. Current efforts are also geared toward other disease hallmarks such as tau pathology, neuroinflammation, and mitochondrial dysfunction. Given the negative results of disease-modifying drug candidates for mild-to-moderate AD patients, a large number of trials are focusing on the early or prodromal stages of the disease. Neuropsychiatric

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_20

symptoms, including apathy, depression, agitation and aggression, sleeping disorders and insomnia, and psychotic symptoms, are prevalent in dementia and have a negative impact on both quality of life and caregiver burden. Pharmacological management of specific neuropsychiatric symptoms is also a focus of clinical trials. Given that AD patients are frailer and have more comorbid illnesses, the prescription of psychotropic medications, particularly those of questionable benefit, should be done with careful consideration. In this chapter, we critically examine evidence of the safety and efficacy of currently approved drugs and emerging pharmacotherapies in AD.

Keywords

Alzheimer's disease • Pharmacotherapy • Clinical trials • Cognition • Neuropsychiatric symptoms

Contents

Introduction

Alzheimer's disease (**AD**), the most common form of dementia, accounts for between 40% and 75% of dementia cases (World Health Organization 2012). Alzheimer's Disease International estimated that in 2015, 46.8 million people worldwide were living with dementia with the prevalence expected to reach 74.7 million by 2030 (Alzheimer's Disease International 2015). Furthermore, the total economic burden in 2015 was estimated at $818 billion USD and is projected to be $2 trillion USD by 2030 (Alzheimer's Disease International 2015). This progressive and fatal neurodegenerative disorder is steadily leading to a public health crisis in developed as well as developing countries around the world. The expression of

symptoms is heterogeneous; progressive decline in cognition (most prominently memory and attention) and behavioral disturbances or neuropsychiatric symptoms (**NPS**) is a characteristic manifestation of the illness. Within the dementia population, the prevalence of NPS is estimated to be between 60% and 90% (McKeith and Cummings 2005).

Thus far, clinical research in AD has resulted in the regulatory approval of four pharmacotherapies in most countries, including three cholinesterase inhibitors (**ChEIs**) and an N-methyl-d-aspartate (**NMDA**) receptor antagonist. These drugs consistently demonstrate small but statistically significant effects on primary cognitive and functional outcomes with additional small benefit for behavioral symptoms. These symptomatic treatments have shown to improve cognition or functional ability for a limited period of time, rather than halting or reversing the advancement of the disease. Research and development within the last decade have focused on the discovery of disease-modifying drugs, including compounds to reduce amyloid burden, hyperphosphorylated tau, and neuroinflammation. Scientists and clinicians in the field have also begun to increase efforts toward investigating treatments for common NPS, most notably, apathy, agitation, and aggression. Effective management of these behavioral disturbances, in addition to cognitive symptoms, may work to increase quality of life for patients as well as reduce caregiver burden.

Approved Therapies

Currently approved pharmacological treatments for the symptomatic management of AD include ChEIs (donepezil, rivastigmine, and galantamine) and the NMDA antagonist, memantine. Though ChEIs are approved for the management of mild-to-moderate AD, donepezil, the rivastigmine transdermal patch, and memantine are also approved for the treatment of severe AD. Tacrine-huperzine A, a moss extract with properties similar to the ChEIs, was the first cholinergic drug to be approved for AD. Ginkgo biloba, an herbal supplement thought to have antioxidant and anti-inflammatory properties, may have some benefit for AD (Janssen et al. 2010). Currently, ginkgo biloba has only been approved for the treatment of dementia and other memory-related impairments in Germany.

Cholinesterase Inhibitors

Through inhibiting acetylcholinesterase, ChEIs enhance cholinergic neurotransmission by reducing the conversion of acetylcholine into acetate and choline. In 1993, the FDA approved tacrine-huperzine A, the first ChEI for the symptomatic management of mild-to-moderate AD. Though tacrine was reported to be associated with reduced cognitive deterioration and improved global function, it was also associated with prominent adverse events **(AEs)**. Due to these safety concerns in addition to the evidence of its limited efficacy, tacrine has largely been discontinued. As such,

Table 1 Bayesian network analysis of efficacy and tolerability of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease

Outcome	Efficacy/tolerability hierarchy	Comparison with placebo
Cognition	Galantamine > rivastigmine > donepezil	Significant benefit in all ChEIs compared to placebo
Global change	Donepezil > rivastigmine > galantamine	Significant benefit in donepezil and rivastigmine compared to placebo
Neuropsychiatric symptoms	Galantamine > donepezil > rivastigmine	No ChEIs clinically significant compared to placebo
Risk of adverse events	Donepezil < galantamine < rivastigmine patch < rivastigmine	No significant increased risk with donepezil compared to placebo
		Significant increased risk in other ChEIs compared to placebo
Risk of nausea	Rivastigmine patch < donepezil < galantamine < rivastigmine	Significant increased risk in all ChEIs compared to placebo
Risk of vomiting	Donepezil < rivastigmine patch < galantamine < rivastigmine	Significant increased risk in all ChEIs compared to placebo
Risk of diarrhea	Galantamine < rivastigmine < rivastigmine patch < donepezil	No significant increased risk with galantamine compared to placebo
		Significant increased risk in other ChEIs compared to placebo
Risk of dizziness	Rivastigmine patch < galantamine < donepezil < rivastigmine	No significant increased risk with rivastigmine patch compared to placebo
		Significant increased risk in other ChEIs compared to placebo

ChEIs cholinesterase inhibitors

second-generation ChEIs (donepezil, rivastigmine, and galantamine) are the currently recommended treatment for AD (Thompson et al. 2004).

In a Bayesian network meta-analysis of 21 studies, the efficacy and tolerability of ChEIs in the treatment of mild-to-moderate AD were investigated (Kobayashi et al. 2015). The results are summarized in Table 1. Compared to placebo, all ChEIs were associated with clinically significant cognitive improvement. The reported hierarchy was galantamine > rivastigmine > donepezil. With respect to global change, both donepezil and rivastigmine were associated with clinically significant improvement compared to placebo, with donepezil demonstrating better efficacy. None of these ChEIs were associated with clinically significant benefits on NPS when compared to placebo. With regard to absolute changes in tests of cognition, a meta-analysis of 13 double-blind randomized controlled trials (**RCTs**) reported that 6–12 months of ChEI treatment in patients in the mild-to-severe stages of dementia produced a mean improvement of 2.37 points (95% CI –2.73 to −2.02) on the Alzheimer's Disease Assessment Scale-cognitive subscale (**ADAS-cog**) and a mean improvement of 1.37 points (95% CI 1.13 to 1.61) on the Mini-Mental State Exam (**MMSE**) (Birks 2006). Though cognitive improvement was statistically significant compared to baseline scores, a 3-point difference on the ADAS-cog over 6 months, and a 2–4-

point on the MMSE over 1.5 years, is generally considered to be clinically significant, questioning the clinical meaningfulness of ChEIs for cognitive outcomes.

The Bayesian network meta-analysis also compared tolerability data among the ChEIs. Tolerability was assessed as study withdrawals due to AEs, nausea, vomiting, diarrhea, and dizziness. All ChEIs, except donepezil, were associated with a significantly greater risk of AEs when compared to placebo. All ChEIs were significantly associated with the risk of nausea and vomiting when compared to placebo. With respect to diarrhea, galantamine was the only ChEIs not associated with increased risk compared to placebo. All ChEIs except rivastigmine were significantly associated with the risk of dizziness when compared to placebo. However, there are limitations to this network analysis that must be considered when interpreting results. There were few studies included when investigating NPS ($N = 6$), which may have led to the wide effect sizes reported. Tolerability was only assessed in studies which reported at least one efficacy outcome due to the inclusion criteria of the meta-analysis. As such, additional studies which also included safety outcomes were not reported. Finally, the trials included allowed for flexible drug doses, though the investigators tried to address this limitation by estimating and categorizing the dosages used in each trial.

It is difficult to report on other clinical outcomes such as activities of daily living (**ADL**) and time to institutionalization as most studies investigating the efficacy of ChEIs in mild-to-moderate AD were under 1 year in duration. However two 1-year RCTs reported that compared to placebo, donepezil improved cognition, global status, and ADLs and was associated with a 38% reduction in the risk of functional decline at 1 year (Mohs et al. 2001; Winblad et al. 2001). A larger trial (AD2000), which investigated long-term outcomes, including time to nursing home placement and the progression of disability in mild-to-moderate AD, reported no significant benefit of donepezil versus placebo over 3 years (Kaiser et al. 2005). However, that trial was plagued by power problems and large numbers of dropouts, limiting the interpretation of results.

Though the ChEIs have been associated with improvements in cognition, behavior, and ADLs, these benefits are modest and are associated with central and peripheral side effects. These include gastrointestinal, cardiorespiratory, and neuromuscular AEs, as well as increased dizziness, headaches, parkinsonian symptoms, and sleep disturbances (Thompson et al. 2004). As AD patients are older and frailer, have more comorbid illnesses, and take more concomitant medications, it is important to consider the side effect profile of AD medications.

The efficacy and tolerability of ChEIs have also been investigated in those with mild cognitive impairment (**MCI**). Patients diagnosed with MCI have an increased risk of developing AD, with 5–10% of individuals diagnosed with MCI expected to progress to dementia per year. However, to date, there is no evidence supporting the use of ChEIs in the symptomatic management of MCI (Fitzpatrick-Lewis et al. 2015). Furthermore, in this patient population, ChEIs were associated with a greater risk of gastrointestinal-related AEs, such as nausea, diarrhea, and vomiting when compared to placebo (Tricco et al. 2013).

Discontinuation Studies

Approximately 96% of patients receiving ChEI treatment experience drug-related AEs. Despite this high incidence, one in three patients receiving a ChEI remains on one until death (Herrmann et al. 2007). Additionally, ChEI use may contribute to unnecessary polypharmacy in the AD population, which may increase the risk of drug-related AEs, drug-drug and drug-disease interactions, functional impairment, institutionalization, and mortality. As such, clinical practice guidelines (**CPGs**) encourage clinicians to consider ChEI discontinuation should tolerability issues arise or if there is no longer a clinical benefit.

In a meta-analysis of five ChEI discontinuation RCTs, discontinuation was associated with cognitive deterioration and an increased occurrence and severity of NPS (O'Regan et al. 2015). However, those studies were completed in non-institutionalized patients, and only one was completed in patients with moderate-to-severe AD. Recently, one RCT in institutionalized patients with moderate-to-severe AD reported that ChEI discontinuation did not have a significant effect on cognition, function, NPS, or global ratings. The presence of baseline hallucinations and delusions may predict clinical deterioration in patients who have discontinued their ChEI (Herrmann et al. 2016).

Since ChEI discontinuation studies have varying durations of follow-up, it is difficult to draw conclusions regarding the long-term impact of ChEI discontinuation. To date, one study had a duration of 6 weeks (Gaudig et al. 2011), one with 8 weeks (Herrmann et al. 2016), two with a duration of 3 months (Holmes et al. 2004; Johannsen et al. 2006), one with 12 months (Jones et al. 2009), and one with 24 months (Scarpini et al. 2011). In three studies that had study durations longer than 6 weeks, cognitive decline was greatest during the first 6 weeks following ChEI discontinuation (O'Regan et al. 2015). Nevertheless, while physicians should closely monitor patients for 6 weeks following ChEI discontinuation to assess cognition and NPS, it should be recognized that evidence of long-term impact is lacking.

Memantine

Memantine, used for the treatment of moderate-to-severe AD, functions by reducing glutamate-induced excitotoxicity, a neurochemical mechanism distinct from the ChEIs. Clinical studies investigating the efficacy and tolerability of memantine have reported that compared to placebo, memantine has been associated with improvements in measures of global function, cognition, and behavior (Matsunaga et al. 2015b). Memantine has also been reported to have greater tolerability than ChEIs as it is not associated with the gastrointestinal AEs that frequently accompany ChEIs. However, memantine has only been approved for the moderate-to-severe stages of AD as it has shown limited efficacy in the milder stages (Schneider et al. 2011).

A meta-analysis of nine studies ($N = 2433$ patients with AD) reported that when compared to placebo, memantine monotherapy improved cognition, NPS, ADL,

global function, and stage of dementia. The effect sizes were small (−0.09 to −0.27), so clinical benefit may be limited. Nevertheless, this meta-analysis also reported that memantine had a relatively safe side effect profile. Specifically, rates of AEs, SAEs, insomnia, anxiety, depression, falls, influenza-like symptoms/upper respiratory infections, dizziness, headache, UTIs, peripheral edema, constipation, rhinitis, and death were similar when compared to placebo (Matsunaga et al. 2015b). In another meta-analysis (Livingston and Katona 2004) investigating the benefits of memantine, it was reported that the numbers needed to treat (**NNTs**) for improvement on global outcomes were three (**CGI-C**) and six (**CIBIC**), seven for cognitive outcome, and four and eight for ADLs. With respect to numbers needed to harm (**NNH**), there were no significant differences between memantine and placebo. These results suggest that memantine may be effective in the symptomatic management of AD.

Despite the previous meta-analysis reports that memantine may be efficacious and tolerable in patients with moderate-to-severe AD, memantine is not approved for use in patients with mild AD. In a meta-analysis of three trials which included patients with mild and moderate AD, it was reported that when compared to placebo, memantine did not have a significant effect on cognition, global change, ADL, or NPS (Schneider et al. 2011).

Combination therapy of memantine and ChEIs has been suggested as a treatment for patients with moderate-to-severe AD as it has shown benefits for cognition and NPS. A meta-analysis of seven studies ($N = 2182$ patients) reported that combination therapy had significant benefits for NPS, ADL, and global change. With respect to cognition, combination therapy had a significant benefit in patients with moderate-to-severe AD, which was not observed in patients with mild-to-moderate AD. There were no significant differences in combination therapy versus ChEI monotherapy with respect to tolerability measures such as the proportion of study discontinuations and the incidence of AEs, SAEs, agitation/aggression, confusion, anxiety/asthenia/depression, falls, influence-like symptoms/upper respiratory infection, dizziness, UTI, diarrhea, and GI symptoms (Matsunaga et al. 2015a).

Emerging Therapies

Currently approved pharmacotherapies offer modest symptomatic relief and do not specifically target the proposed underlying pathophysiology associated with AD. Observations of protein aggregate formation in the brains of AD patients have led to the amyloid cascade hypothesis, which has been the primary focus of research in the field. Additionally, efforts have also been geared toward development of interventions targeting other disease hallmarks such as tau pathology, neuroinflammation, and mitochondrial dysfunction. Despite continuing efforts, these disease-modifying approaches have thus far been unsuccessful in RCTs. Currently, late-stage trials continue to investigate drugs that modulate amyloid, tau, and other alternative

pathways, with many shifting to the early stages of the disease (see Table 2). Additionally, there have been continuing efforts to investigate the efficacy of symptomatic therapies, with several drugs in the later stages of development (Table 3).

Table 2 Disease-modifying drugs in late-stage clinical trials

Drug, trial	Mechanism	Participants	Primary outcome	Duration
E2609 (phase 2, NCT02322021)	BACE1 inhibitor	700 MCI/ prodromal AD or mild-to-moderate AD	ADCOMS	18 months (completion by 2018)
AZD3293 or LY3314814, AMARANTH (phase 2/3, NCT02245737)	BACE1 inhibitor	2202 MCI due to AD or mild AD	CDR-SB	2 years (completion by 2021)
Verubecestat, APECS (phase 3, NCT01953601), EPOCH (phase 2/3, NCT01739348)	BACE1 and BACE2 inhibitor	APECS: 1500 MCI due to AD EPOCH: 1960 mild-to-moderate AD	APECS: CDR-SB EPOCH: ADAS-cog, ADCS-ADL	APECS: 2 years (completion by 2021) EPOCH: 18 months (completion by 2019)
Bryostatin-1 (phase 2, NCT02431468)	α-Secretase modulator	150 moderate-to-severe AD	SIB	7 months (completion by 2017)
Carvedilol (phase 4, NCT01354444)	Aβ aggregation inhibitor	50 mild AD	HVLT	6 months (completion by 2016
Solanezumab, EXPEDITION 3 (phase 3, NCT01900665)	Anti-Aβ monoclonal antibody	2100 mild AD	ADAS-cog	18 months (completion by 2018)
Gantenerumab (phase 3, NCT01224106, NCT02051608)	Anti-Aβ monoclonal antibody	NCT01224106: 799 prodromal AD NCT02051608: 389 mild AD	CDR-SB ADAS-cog ADCS-ADL	2 years (completion by 2018)
Aducanumab, EMERGE (phase 3, NCT02484547), ENGAGE (phase 3, NCT02477800)	Anti-Aβ monoclonal antibody	1700 MCI due to AD or mild AD	CDR-SB	18 months (completion by 2022)
BAN2401 (phase 2, NCT01767311)	Anti-Aβ monoclonal antibody	800 MCI due to AD or mild AD	ADCOMS	18 months (completion by 2018)
Crenezumab, CREAD (phase 3, NCT02670083)	Anti-Aβ monoclonal antibody	750 MCI/ prodromal AD or mild AD	CDR-SB	2 years (completion by 2021)

(*continued*)

Table 2 (continued)

Drug, trial	Mechanism	Participants	Primary outcome	Duration
IVIg and albumin, AMBAR (phase 2/3, NCT01561053)	Anti-Aβ polyclonal antibody	350 mild-to-moderate AD	ADAS-cog ADCS-ADL	14 months (completion by 2016)
TRx0237 (phase 3, NCT01689246, NCT01689233)	Tau aggregation inhibitor	1533 mild-to-moderate AD	ADAS-cog ADCS-ADL	18 months (completion by 2016)
Azeliragon, STEADFAST (phase 3, NCT02080364)	RAGE inhibitor, inflammation modulator	800 mild AD	ADAS-cog CDR-SB	18 months (completion by 2018)
Masitinib (phase 3, NCT01872598)	Selective tyrosine-kinase inhibitor, inflammation modulator	396 mild-to-moderate AD	ADAS-cog	6 months (completion by 2016)
Nilvadipine, NILVAD (phase 3, NCT02017340)	Calcium channel blocker	500 mild-to-moderate AD	ADAS-cog	18 months (completion by 2017)
Insulin, SNIFF (phase 2/3, NCT01767909)	Glucose metabolism regulator	240 MCI or mild AD	ADAS-cog	18 months (completion by 2017)

BACE β-secretase, *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *ADCOMS* Alzheimer's Disease Composite Score, *CDR-SB* Clinical Dementia Rating, *ADAS-cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *ADCS-ADL* Alzheimer's Disease Cooperative Study-Activities of Daily Living, *SIB* Severe Impairment Battery, *HVLT* Hopkins Verbal Learning Test, *RAGE* receptor for advanced glycation end products

Amyloid-Targeted Treatments

Under non-disease conditions, the transmembrane protein APP is cleaved by α-secretase to form soluble peptides (**sAPPα**). The amyloid cascade hypothesis posits that insoluble, neurotoxic Aβ plaques are generated through the cleavage of APP via β- and γ-secretase. Thus, drugs within the pipeline include modulators and inhibitors of β- and γ-secretase as well as antibodies against amyloid-β (**Aβ**).

Reducing Aβ Production Production of Aβ can be reduced through inhibition of β-secretase or β-site APP-cleaving enzyme 1 (**BACE1**). Rosiglitazone, an agonist of peroxisome proliferator-activated receptor γ (**PPARγ**), can downregulate β-secretase and APP expression. A 24-week double-blind RCT (REFLECT-1) of APOE ε4-negative AD patients did not show efficacy with rosiglitazone monotherapy on measures of cognition and global function (Clarke et al. 2011). Another PPARγ agonist, pioglitazone, with potentially greater ability to cross the blood-brain barrier is currently being investigated in a phase 3 trial of cognitively healthy elderly at risk of developing MCI due to AD (TOMORROW, NCT01931566) with an extension

Table 3 Symptomatic drugs in late-stage development

Drug, trial	Mechanism	Participants	Primary outcome	Duration
Idalopirdine, STARSHINE (phase 3, NCT001955161), STARBEAM (phase 3, NCT02006641), STARBRIGHT (phase 3, NCT02006654)	5-HT6 receptor antagonist, enhance cholinergic, glutamatergic, norepinephrine, dopamine neurotransmission	STARSHINE: 930 mild-to-moderate AD	ADAS-cog	STARSHINE: 24 weeks (completion by 2016)
		STARBEAM: 840 mild-to-moderate AD		STARBEAM: 24 weeks (completion by 2017)
		STARBRIGHT: 720 mild-to-moderate AD		STARBRIGHT: 24 weeks (completion by 2017)
SUVN-502 (phase 2, NCT02580305)	5-HT6 receptor antagonist	537 mild-to-moderate AD	ADAS-cog	24 weeks (completion by 2017)
DAOIB (phase 2, NCT02239003, NCT02103673)	NMDA receptor regulator, enhance glutamatergic neurotransmission	NCT02239003: 50 MCI	ADAS-cog	NCT02239003: 6 months (completion by 2016)
		NCT02103673: 90 mild, moderate, severe AD		NCT02103673: 6 weeks (completion by 2016)

5-HT serotonin, *ADAS-cog* Alzheimer's Disease Assessment Scale-cognitive subscale

study planned for completers who have a diagnosis of MCI at termination (NCT02284906). Several companies are pursuing development of inhibitors of BACE1 and its homolog BACE2 in phase 2 and 3 trials. E2609 (NCT02322021), AZD3293 or LY3314814 (AMARANTH, NCT02245737), and verubecestat (APECS, NCT01953601) are currently being explored in prodromal AD and MCI patients. E2609 and a separate trial with verubecestat (EPOCH, NCT01739348) are recruiting participants in the mild-to-moderate stage of the disease.

The final step in the production of Aβ involves the action of γ-secretase on β-secretase-processed APP. One important challenge in developing γ-secretase inhibitors to block amyloidogenesis is restricting the affinity of γ-secretase for Notch receptors, a key component of neural signaling and cell development pathways. Thus far, the only γ-secretase inhibitor to reach phase 3 clinical investigation was semagacestat (IDENTITY trials). That study was discontinued before completion due to preliminary findings of worsening cognition, daily function, and higher occurrences of adverse events in the active treatment group compared with placebo (Doody et al. 2013). Early-stage phase 2 RCTs to determine the safety and tolerability of γ-secretase modulators with low selectivity for Notch have been completed, though results have not been published (NIC5-15: NCT00470418, EVP-0962: NCT01661673).

α-Secretase, the competing enzyme of β-secretase for APP, results in sAPPα, a soluble protein with lower propensity to aggregate, and some studies suggest it may have neuroprotective memory-enhancing and antiapoptotic properties. Upregulation of this pathway may be an alternative mode of restricting Aβ expression and plaque formation. Bryostatin-1, a potent activator of protein kinase C that can stimulate the α-secretase transduction pathway, is currently in phase 2 clinical trial of moderate-to-severe AD patients (NCT02431468).

Decreasing Aβ Aggregation Drugs that bind Aβ monomers in order to suppress the aggregation or reduce the stability of senile plaque constituents have also been examined. The only late-phase trial of a therapy with anti-aggregation activity, tramiprosate, did not find significant benefit for overall cognition (Aisen et al. 2011). However, exploratory analyses have suggested benefit for domains of cognition, including memory, language, and praxis skills (Saumier et al. 2009). A pilot phase 4 RCT of carvedilol, a nonselective β-adrenoceptor blocker which also prevents accumulation of Aβ oligomers, is currently recruiting patients (NCT01354444).

Facilitating Aβ Clearance Removal of toxic aggregated Aβ deposits via immune response is a focused target of research to reduce amyloid plaques, with several large late-stage trials currently underway. A phase 3 RCT did not find efficacy of bapineuzumab for cognition in APOE ε4 carriers and non-carriers with AD (Salloway et al. 2014). However, amyloid PET imaging showed reduced Aβ levels in the active treatment group compared with placebo. Similarly, phase 3 trials of solanezumab (EXPEDITION 1 and 2) showed no improvement on standard measures of cognition and activities of daily living (Doody et al. 2014). However, subgroup analyses of mild AD patients revealed a trend for improvement on cognition. Thus, another phase 3 trial focusing on mild AD patients was registered and set to be completed in 2018 (NCT01900665). Other monoclonal antibodies which have entered phase 2 and 3 trials in early stage AD include gantenerumab (NCT01224106; NCT02051608), aducanumab (EMERGE, NCT02484547; ENGAGE, NCT02477800), BAN2401 (NCT01767311), and crenezumab (CREAD, NCT02670083).

An alternative mode of obtaining passive immunotherapy is through the use of intravenous immunoglobulin (**IVIg**), nonspecific polyclonal antibodies acquired from human donors. A phase 3 trial found no significant benefit of IVIg (10%) for cognition and function in mild-to-moderate AD patients (NCT00818662, results published on ClinicalTrials.gov). Currently, infusion of albumin combined with IVIg is being investigated in a phase 2/3 trial of mild-to-moderate AD patients (NCT01561053).

Tau-Targeted Treatments

Inhibition of tau hyperphosphorylation and promotion of filament disassembly are also viable strategies for AD disease-modifying therapies. Hyperphosphorylation of

tau, a cytoplasmic protein that interacts with tubulin to stabilize axonal microtubules, causes detachment from microtubules leading to formation of neurofibrillary tangles. Inhibitors of GSK-3, a protein kinase that mediates phosphorylation, such as valproate (VALID study) (Tariot et al. 2009), lithium (Hampel et al. 2009), and tideglusib (ARGO study) (Lovestone et al. 2015), have not demonstrated efficacy for cognition in late-stage clinical trials. Currently, two phase 3 RCTs are testing a formulation of the tau antiaggregant methylene blue, leuco-methylthioninium chloride (LMTX, TRx0237), in mild-to-moderate AD patients (NCT01689246, NCT01689233). Additionally, exenatide (NCT01255163) and liraglutide (ELAD, NCT01843075), approved diabetes drugs with inhibitory actions on tau phosphorylation, are in phase 2 trials evaluating safety and tolerability in mild AD. Cognition and function are also included as secondary outcome measures.

Other Approaches

Modulating Neuroinflammation Given the failure of amyloid- and tau-based therapies to endure past late-stage clinical development, research efforts have turned toward targeting other disease hallmarks. Though these processes are not specific for dementia, they have been shown to contribute to neurotoxicity and neuronal loss. The presence of activated microglia and pro-inflammatory factors such as cytokines and cyclooxygenase (**COX**)-2 enzymes has been associated with plaques and tangles found in AD (Swardfager et al. 2010). However, clinical trials investigating the disease-modifying potential of nonsteroidal anti-inflammatory drugs, including rofecoxib (Reines et al. 2004), indomethacin (de Jong et al. 2008), and tarenflurbil (Green et al. 2009), have been unsuccessful. Currently, two drug candidates with neuroinflammatory-modulating effects are being investigated in phase 3 trials: azeliragon, an inhibitor of receptor for advanced glycation end products (STEADFAST, NCT02080364), and masitinib, a selective tyrosine-kinase inhibitor (NCT01872598).

Enhancing Mitochondrial Function Mitochondrial dysfunction at the early stages and during the progression of AD can occur, leading to apoptosis and damage at synaptic sites. Thus, researchers have also pursued strategies aimed at improving metabolic function and reducing oxidative stress. One such compound is latrepirdine, an antihistamine with additional mechanistic actions on acetylcholinesterase, butyrylcholinesterase, and NMDA signaling, as well as mitochondrial function. Phase 3 trials (CONNECTION, CONCERT) have not demonstrated efficacy in the mild-to-moderate AD population (Chau et al. 2015).

Another disease-modifying approach was based on observations of lower AD incidence associated with ingestion of omega-3 polyunsaturated fatty acids and cholesterol-lowering medications. However, no improvements in cognition were found in RCTs of docosahexaenoic and eicosapentaenoic acid (Freund-Levi et al. 2006; Quinn et al. 2010). Though the mechanism remains unclear, statins used for reducing serum cholesterol have been shown to possess anti-Aβ, anti-inflammatory,

and antioxidant properties. Late-stage clinical trials of atorvastatin (LEADe study) (Feldman et al. 2010) and simvastatin (CLASP study) (Sano et al. 2011) in mild-to-moderate AD did not yield positive results on cognitive measures. A phase 4 trial (SIMaMCI, NCT00842920) plans to evaluate the efficacy of simvastatin in MCI patients. Drugs approved for other indications are also being investigated. The calcium channel blocker, nilvadipine, through its antihypertensive action, may enhance brain circulation and, as a result, facilitate clearance of amyloid from the central nervous system (NILVAD, NCT02017340). Given that therapies with β-secretase inhibitory action (discussed above) are used principally to regulate glucose metabolism and that insulin resistance has been postulated as an underlying mechanism of AD pathogenesis, there is a rationale for the use of diabetes medications for AD. A phase 2/3 trial of an intranasally administered insulin formulation is currently recruiting MCI and mild AD patients (SNIFF, NCT01767909).

Symptomatic Treatments

Symptomatic therapies to treat the cognitive symptoms of AD often specifically target the neurotransmitter systems. Many pharmaceutical companies are pursuing the development of drug candidates to target acetylcholine (**ACh**), serotonin (**5-HT**), and glutamate signaling (see Table 3). Overall, trials of symptomatic cognitive-enhancing agents have a shorter duration than disease-modifying treatments. There is preclinical evidence to suggest modulation of the 5-HT6 receptor can improve attention and cognition. Three large parallel phase 3 trials are currently investigating the efficacy and safety of idalopirdine, a 5-HT6 receptor antagonist, in mild-to-moderate AD patients (STARSHINE, NCT001955161; STARBEAM, NCT02006641; STARBRIGHT, NCT02006654). A phase 2a RCT of another 5-HT6 receptor antagonist, SUVN-502, is also currently underway (NCT02580305). Other approaches to enhancing cholinergic neurotransmission are also being investigated. Agonists of the α-7 nicotinic ACh receptor (**α-7 nAChR**) have been shown to augment the positive effects of sub-efficacious doses of ChEIs on memory and attention. Two 26-week phase 3 trials of an α-7 nAChR agonist, encenicline, were initiated based on promising results from the phase 2 trial (NCT01969136; NCT01969123). In 2015, the trials were suspended due to reports of gastrointestinal side effects. Given that moderate-to-severe AD is an indication of memantine, drug candidates with glutamatergic mechanisms of action are also currently being investigated. Two small trials of an NMDA enhancer, DAOIB, are currently recruiting AD (NCT02103673) and MCI patients (NCT02239003).

The disappointing results in phase 3 RCTs highlighted above should not provide grounds for dismissal of disease-modifying approaches to pharmacotherapies for dementia. It is likely that disease-modifying therapies will require many years of administration before differences can be observed on standard tests of cognition and function. Thus, the importance of continuing to develop better symptomatic medications should not be overlooked. A combination of symptomatic and disease-modifying therapies may provide the most beneficial course of therapy. Recently,

there has been a shift toward research on prodromal or presymptomatic AD. It is likely that disease-modifying treatments would be most effective if administered for a long period of time, starting in the early or prodromal stages of the disease trajectory. Additionally, continuing efforts to manage the NPS associated with dementia may provide added benefit for cognition as well as function.

Management of NPS

NPS have been reported to occur in 98% of patients, with apathy (75%), depression (60%), and agitation/aggression (55%) among some of the most frequent symptoms (Garcia-Alberca et al. 2008). Sleeping disorders (36%) and hallucinations (20%) are also commonly present in AD (Garcia-Alberca et al. 2008) and can have a negative impact on both quality of life and caregiver burden (Khoo et al. 2013). The high prevalence of these symptoms in AD patients points to the necessity of treatment for NPS in dementia. First-line treatments involve non-pharmacological interventions such as person-centered care, behavior modification techniques, structured social interaction, exercise, aromatherapy, music therapy, etc. However, more refractory cases may require pharmacological management. Current and emerging pharmacotherapies for NPS in dementia are listed in Table 4.

Pharmacotherapies for Apathy

Apathy is defined as a disorder of motivation, distinct from depression, which includes reduced goal-directed behavior, goal-directed cognitive activity and

Table 4 Pharmacotherapies for frequent NPS in dementia

NPS	Primary pharmacotherapy	Emerging and alternative pharmacotherapies
Apathy	Antidepressants	Methylphenidate (NCT02346201) Repetitive transcranial magnetic stimulation (NCT02190084)
Depression	Antidepressants	Acetaminophen and buprenorphine (NCT02267057)
		Transcranial direct current stimulation (NCT02351388)
Agitation or aggression	Antipsychotics	Dextromethorphan/quinidine (NCT01584440, NCT02442765, NCT02442778)
		Dronabinol (NCT02351882)
		Lithium (NCT02129348)
		Nabilone (NCT02792257)
Sleep disturbances or insomnia	Melatonin	Mirtazapine (NCT01867775)
		Quetiapine (NCT00232570),
		Suvorexant (NCT02750306)
Psychotic symptoms	Antipsychotics	Donepezil (NCT00190021)
		Lithium (NCT02129348)

NPS neuropsychiatric symptoms

emotions, as well as increased functional impairments. As such, pharmacological treatments that target apathy may improve the quality of life of those living with AD and their caregivers.

Pharmacological, postmortem, and imaging studies suggest that apathy in patients with AD may be due to pathological changes to the cholinergic, dopaminergic, serotoninergic, noradrenergic, and GABAergic neurotransmitter systems. Though multiple placebo-controlled RCTs have investigated ChEIs and memantine in the treatment of apathy in AD, apathy was studied as a secondary outcome measure (Waldemar et al. 2011). A recent placebo-controlled RCT investigating modafinil in the treatment of apathy in patients with mild-to-moderate AD reported that in the treatment group, there was no significant improvement in apathy or global function over 8 weeks (Frakey et al. 2012). Additionally, two off-label case studies with modafinil (Camargos and Quintas 2011; Padala et al. 2007) and one RCT with nefiracetam (Robinson et al. 2009) in patients without a formal AD diagnosis suggest that these alternative pharmacological interventions may be effective in treating apathy, warranting the need for additional study.

Methylphenidate for the treatment of apathy has also been investigated in patients with vascular dementia (Galynker et al. 1997) and AD (Padala et al. 2010), in nursing home patients with dementia (Maletta and Winegarden 1993), and in patients with mixed diagnoses, in a series of individual crossover, double-blind, randomized "N of 1" trials (Jansen et al. 2001). One small crossover RCT (Herrmann et al. 2008) and one open-label trial (Padala et al. 2010) in outpatients with mild-to-moderate AD reported that methylphenidate was effective in the treatment of apathy. These results were supported by a recent multicenter, phase 2, double-blind, placebo-controlled RCT investigating the treatment of methylphenidate for apathy in patients with mild-to-moderate AD (ADMET study) (Rosenberg et al. 2013). Based on the findings from ADMET, a ten-center phase 3 trial of methylphenidate for apathy was initiated and is currently in the patient recruitment stage (ADMET 2, NCT02346201).

Pharmacotherapies for Depression

Depression is distinct from apathy and can include feelings of depressed mood, loss of interest or pleasure, fatigue, guilt/worthlessness, diminished concentration, suicidality, as well as changes in appetite and sleep. Furthermore, evidence suggests that apathy and depression have different underlying pathophysiological processes. Whereas apathetic behaviors are closely linked with the cholinergic system and the anterior cingulate frontal-subcortical circuit, depression in AD is hypothesized to be related to dopaminergic and serotonergic deficits as well as the dysregulation of frontal-striatal and subcortical limbic circuits.

Selective serotonin reuptake inhibitors (**SSRIs**) are the first-line pharmacotherapy for depression in dementia and are supported by positive findings from numerous RCTs. In those studies, patients were given either citalopram, clomipramine, moclobemide, or sertraline (Lyketsos et al. 2003; Nyth and Gottfries 1990; Petracca

et al. 1996; Roth et al. 1996). One meta-analysis also reported that antidepressant treatment was more efficacious compared to placebo for depression in AD (Thompson et al. 2007). However, it should be noted that there are also studies which have reported negative findings. One of the largest trials investigating depression in dementia with sertraline and mirtazapine over the course of 13 weeks found no significant difference in depressive symptoms following antidepressant usage or placebo with all groups experiencing equally large improvements (Banerjee et al. 2013). A recent multicenter, double-blind, placebo-controlled trial also found no difference in efficacy with sertraline compared to placebo for depression in AD. In addition, two meta-analyses examining antidepressants for treating depression in dementia have come to the same conclusion (Bains et al. 2002; Nelson and Devanand 2011).

As a result of those inconclusive findings, alternative therapies are currently being explored. The Transcranial Direct Current Stimulation (**tDCS**) for Depression in Alzheimer's Disease Patient - Preliminary Research (ADAPT) study is investigating the safety and efficacy of tDCS, a noninvasive brain stimulation technique, for the treatment of depression among patients with AD over the course of 3 weeks with sessions occurring 5 days a week (NCT02351388). Another ongoing RCT aims to determine whether pain treatment can reduce symptoms of depression in patients with dementia (NCT02267057). As undiagnosed pain may present itself as depression in patients with dementia, acetaminophen and buprenorphine will be compared to placebo over the course of 13 weeks.

Pharmacotherapies for Agitation and Aggression

Agitation refers to excessive motor activity associated with irritability, pacing, and wandering, whereas aggression consists of verbal or physical actions that can be overt and potentially harmful. Both behaviors have a significant negative impact on daily functioning, quality of life, disease progression, as well as caregiver burden (Khoo et al. 2013). Multiple pathophysiological mechanisms may underlie agitation and aggression in dementia, including dysregulation of the dopaminergic, serotonergic, noradrenergic, and GABAergic systems.

Current clinical practice guidelines have endorsed the cautious use of antipsychotics for the management of severe agitation and aggression. Atypical antipsychotics, particularly risperidone, were shown to have the best evidence for short-term efficacy (6–12 weeks) (Schneider et al. 2006). In this meta-analysis, the authors reported a significant decrease in aggressive behaviors with risperidone treatment using the Behavioral Pathology in Alzheimer's Disease rating scale. Although this change demonstrated statistical significance, it indicated only modest clinically meaningful benefit when risperidone was administered at the 2 mg dose. Antipsychotics are also associated with an increase in serious adverse events including extrapyramidal symptoms, cerebrovascular events, and mortality (Schneider et al. 2006). As a result,

the FDA issued a black box warning of excess mortality associated with the use of antipsychotics in elderly individuals with dementia (Singh and Nayak 2015). Several recent clinical studies have also reported increased mortality in elderly patients associated with psychotropic drug use (Ma et al. 2014). These adverse events were more marked with longer-term use, with one RCT reporting 59% mortality compared to 30% in the placebo group following 36 months of treatment (Ballard et al. 2009). As a result, some researchers have suggested that these adverse effects offset the potential advantages (Corbett et al. 2014).

Other medications have been investigated for the treatment of agitation and aggression in dementia. These pharmacological agents including memantine, ChEIs, antidepressants, anticonvulsants, and cannabinoids have also been used in patients with dementia with some studies reporting a reduction in agitation and aggression. Combined treatment with memantine and ChEIs was found to be effective in slowing cognitive impairment as well as in reducing agitation and aggression in patients with AD (Gareri et al. 2014). The selective serotonin reuptake inhibitor (SSRI), citalopram, was also found to be efficacious in the reduction of agitation/aggression, irritability, anxiety, and delusions after 9 weeks of treatment (Porsteinsson et al. 2014). Of the antiepileptic drugs, carbamazepine has the best evidence to support its use; however, the evidence base remains relatively small (Gallagher and Herrmann 2014). Emerging literature has also suggested that cannabinoids such as dronabinol and nabilone may improve agitation/aggression (Liu et al. 2015), but larger studies need to be conducted in order to establish efficacy in patients with AD. Currently, nabilone is being investigated for the management of agitation in AD in a 14-week crossover RCT (NCT02351882). Another pilot study administering dronabinol is exploring its use as an adjunctive treatment for agitation in AD (NCT02792257). As lithium has been shown to have mood-stabilizing effects, it is currently being investigated in a 12-week clinical trial for the treatment of agitation and psychosis in patients with dementia (NCT02129348). Dextromethorphan/quinidine (DM/Q) is a NMDA receptor antagonist and currently indicated for the treatment of pseudobulbar affect. Several RCTs are also studying the effects of DM/Q in agitated patients with AD (NCT0244276, NCT02442778, NCT02446132).

Careful identification of individual target symptoms, medical history, and concomitant medications are essential considerations when choosing alternative treatments. A recent study conducted across 11 nursing homes reported a 17% reduction in antipsychotic usage following educational intervention among staff and clinicians (Gordon et al. 2016), suggesting that antipsychotics may likely be overprescribed, especially in long-term care facilities. Several guiding principles have been suggested by North American medical associations (Reus et al. 2016), with one of the key recommendations being to limit or refrain from using antipsychotics to treat NPS. Antipsychotics should be considered if neither psychosocial interventions nor alternative pharmacological treatments are effective, but should also be cautiously weighed against the associated risks and are not recommended for long-term use in patients with dementia.

Pharmacotherapies for Sleeping Disorders and Insomnia

Sleep disturbances, including reduced nighttime sleep, sleep fragmentation, nighttime wandering, and daytime sleepiness, are common in patients with AD. Furthermore, these symptoms are related to increased caregiver burden, associated with other NPS, and can significantly reduce patients' quality of life and functional abilities (Khoo et al. 2013). Evidence has suggested that areas of the brain involved in the neural networks that control sleep function (i.e., the anterior hypothalamus, reticular activating system, suprachiasmatic nucleus, and pineal gland) may be impaired in individuals with dementia.

There is a wide range of pharmacological interventions used to treat sleep disorders in dementia, with the majority of RCTs investigating the effects of melatonin. Melatonin is synthesized in pineal cells, with its production and release regulated by the light-dark cycle. As evidence has shown that melatonin levels are diminished in AD patients compared to healthy controls, administration of melatonin is believed to improve sleep behaviors (Skene et al. 1990). However, evidence-based literature has reported conflicting results. One meta-analysis of RCTs administering melatonin for sleep disorders in dementia concluded that melatonin therapy may be effective in improving sleep efficiency and prolonging total sleep time (Xu et al. 2015). In contrast, a Cochrane review found no evidence that melatonin, either immediate or slow release, improved any major sleep outcome in patients with dementia (McCleery et al. 2014).

Alternative medications have also been investigated, including hypnotics and antidepressants. Benzodiazepines and non-benzodiazepine hypnotics such as zolpidem and zaleplon are frequently prescribed as short-term sleep aids to the general population but should be cautiously considered in patients with AD due to increased incidences of sedation, confusion, anterograde amnesia, daytime sleepiness, and rebound insomnia (Cipriani et al. 2015). It is recommended that benzodiazepines only be used for short-term insomnia management (Wilt et al. 2016). Antidepressant mediations, such as trazodone, have also been used for sleep disturbances in patients with comorbid depression and anxiety. Compared to placebo, trazodone was shown to significantly improve nocturnal sleep time and sleep efficiency following 2 weeks of daily treatment in 30 AD patients with sleep disturbances (Camargos et al. 2014). More RCTs are needed to establish definitive conclusions and to evaluate the risks and benefits regarding the use of trazodone for sleep disturbances in AD. Clinical trials for the treatment of sleep disorders in dementia are currently investigating the use of quetiapine (NCT00232570), mirtazapine (NCT01867775), and suvorexant, an orexin receptor antagonist (NCT02750306).

Pharmacotherapies for Psychotic Symptoms

Psychotic symptoms, comprised of hallucinations and delusions, are associated with additional NPS, functional impairment, and mortality. Common delusions in AD patients include delusions of persecution, theft, infidelity, abandonment, and false

beliefs (e.g., such as one's home is not one's home, deceased individuals are still living, a family member is someone else, and that images on the television are actually present in the house). Hallucinations in AD can occur in any sensory modality but are commonly visual hallucinations that may include seeing things not seen by others (i.e., people, animals, light). Although the exact etiology is unknown, neuroimaging studies suggest that AD patients with psychotic symptoms demonstrate greater reduced gray matter volume, regional blood flow, and regional glucose metabolism compared to those without psychosis.

Current pharmacotherapies for psychotic symptoms in AD include antipsychotics such as haloperidol, risperidone, olanzapine, and aripiprazole. Evidence has shown that haloperidol has mild-to-moderate efficacy relative to placebo in AD patients with psychosis (Devanand et al. 2011). Treatment with escitalopram or risperidone has also been shown to improve behavioral and psychotic symptoms in patients with AD (Barak et al. 2011). Clinical studies also support the use of olanzapine for the management of psychosis in dementia (De Deyn et al. 2004). However, as previously described, there are significant adverse events associated with the use of antipsychotic medications in dementia (Schneider et al. 2006). The use of high dosages of haloperidol has been shown to double the mortality risk compared with the use of low dosages (Huybrechts et al. 2012). Unfortunately, several studies have demonstrated that discontinuation of haloperidol and risperidone is associated with an increased risk of relapse (Devanand et al. 2011, 2012). Thus, there is a need for alternative and safer pharmacotherapies for the treatment of psychotic symptoms in dementia.

There is currently an ongoing 12-week clinical trial investigating the use of lithium for the management of psychosis and agitation patients with AD (NCT02129348). As lithium has been shown to have positive effects on mood and is often used as an add-on treatment to antipsychotics in patients with schizophrenia (Leucht et al. 2015), it may be able to modulate psychotic symptoms in dementia as well. Additionally, lithium has been found to have neuroprotective effects on the brain, specifically increasing gray matter volume (Lyoo et al. 2010). This suggests that lithium may be able to improve psychotic symptoms by restoring the loss of gray matter volume seen in patients with AD. The ChEI, donepezil, has also been investigated for the treatment of psychotic symptoms in dementia patients (NCT00190021). A 4-week clinical trial of donepezil as an add-on treatment showed a greater improvement in mental state with significant differences in Positive and Negative Symptom Scale scores between those who received donepezil and those who did not receive the adjunctive treatment. More studies with larger sample sizes are needed in order to establish the efficacy of donepezil for the management of psychotic symptoms in dementia.

Evaluating Benefit of Medications

Therapeutic recommendations with regard to the elderly, particularly those with mental illnesses, should be taken with careful consideration utilizing the most up-to-date evidence. Nursing home patients with advanced dementia receive

approximately 5–15 medications per day which give rise to concerns such as polypharmacy, drug-drug and drug-disease interactions, and economic burden. As such there is an increasing need to determine the medical appropriateness of pharmacological treatments which may include the consideration of a patient's remaining life expectancy, goals of care, and potential benefits of medications (Tjia et al. 2010).

In a cross-sectional study of medication use in 5406 nursing home patients with advanced dementia, the use of medications with questionable benefit and the mean 90-day expenditures associated with these medications per resident was studied (Tjia et al. 2014). The authors reported that 54% of patients received at least one medication of questionable benefit, with ChEIs (36.4%) and memantine (25.2%) being the most commonly prescribed. They also reported that the mean 90-day expenditure for medications of questionable benefit per patient was $816 US dollars, which accounted for approximately 35% of the total 90-day expenditures for those patients.

Prescribers are encouraged to prioritize reviewing medications and deprescribing medications of questionable benefit as this may reduce drug-related AEs and improve quality of life in patients with advanced dementia. However, there are few discontinuation studies available to assist clinicians in deprescribing medications to advanced AD patients.

The 2015 American Geriatrics Society Beers Criteria outline a list of medications of questionable benefit which should be avoided in the elderly population and recommend dose adjustments based on an individual's kidney function and drug-drug interactions associated with harms in older adults (By the American Geriatrics Society Beers Criteria Update Expert 2015). The Screening Tool of Older Persons' potentially inappropriate Prescriptions (**STOPP**) and Screening Tool to Alert doctors to Right Treatment (**START**) criteria assist researchers and healthcare personnel identify potentially inappropriate medications and potential prescribing omissions which should be considered when treating the elderly (Hill-Taylor et al. 2013). However, these tools are not without their limitations. Elderly patients with AD, and specifically in the advanced stages, are underrepresented in clinical studies investigating the safety and efficacy of potentially harmful medications, which may contribute to an underestimation of drug-related AEs. Additionally, the criteria in both tools may not account for frail patients in palliative or hospice care, in which the benefits and risks associated with certain medications differ from the general older population.

Conclusions

Given the complex interactions between demographics, polypharmacy, and comorbidities, it is important to identify effective and safe therapies for AD patients. Collaborative efforts from clinicians, regulatory authorities, researchers, and pharmaceutical companies are critical in the evolution of these pharmacotherapies. It is becoming increasingly apparent from the lack of success of disease-modifying

therapies that earlier interventions may result in more positive clinical outcomes. Thus, guidelines for revised diagnostic criteria of AD have given further emphasis on the preclinical stage of the disease and incorporate biomarker information (DeKosky et al. 2011). Pharmacotherapies may be more effective at the pre-symptomatic stage, when pathological events have yet to produce irreversible cognitive deficits. Care for dementia patients should be an integrated evidence-based approach, focusing on the behavioral, psychosocial, and physical, as well as the cognitive and functional, aspects. With 17 candidates for disease-modifying and 3 for symptomatic treatments currently in phase 2 trials or beyond, the potential for improved pharmacotherapy in the next 10 years remains possible.

Cross-References

- ▶ Biomarkers of Alzheimer's Disease
- ▶ Dementia and Bioethics
- ▶ Dementia and Caregiving
- ▶ (Neurobiology of) Dementia: Causes, Presentation, and Management
- ▶ Pharmacotherapy for Mood and Anxiety Disorders
- ▶ Prevention of Alzheimer's Disease and Alzheimer's Dementia

References

Aisen PS, Gauthier S, Ferris S, Saumier D, Haine D, Garceau D, Duong A, Suhy J, Oh J, Lau WC, Sampalis J (2011) Tramiprosate in mild-to-moderate Alzheimer's disease – a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase Study). Arch Med Sci 7:102–111

Alzheimer's Disease International (2015) World Alzheimer report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International, London

Bains J, Birks J, Dening T (2002) Antidepressants for treating depression in dementia. Cochrane Database Syst Rev 4:CD003944

Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R, Investigators D-A (2009) The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol 8:151–157

Banerjee S, Hellier J, Romeo R, Dewey M, Knapp M, Ballard C, Baldwin R, Bentham P, Fox C, Holmes C, Katona C, Lawton C, Lindesay J, Livingston G, McCrae N, Moniz-Cook E, Murray J, Nurock S, Orrell M, O'Brien J, Poppe M, Thomas A, Walwyn R, Wilson K, Burns A (2013) Study of the use of antidepressants for depression in dementia: the HTA-SADD trial – a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health Technol Assess 17:1–166

Barak Y, Plopski I, Tadger S, Paleacu D (2011) Escitalopram versus risperidone for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: a randomized double-blind pilot study. Int Psychogeriatr 23:1515–1519

Birks J (2006) Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 1: CD005593

By the American Geriatrics Society Beers Criteria Update Expert P (2015) American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 63:2227–2246

Camargos EF, Quintas JL (2011) Apathy syndrome treated successfully with modafinil. BMJ Case Rep 2011. doi:10.1136/bcr.08.2011.4652, Published Nov 15

Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nobrega OT (2014) Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. Am J Geriatr Psychiatry 22:1565–1574

Chau SA, Herrmann N, Ruthirakuhan MT, Chen JJ, Lanctot KL (2015) Latrepirdine for Alzheimer's disease. Cochrane Database Syst Rev 4:CD009524

Cipriani G, Lucetti C, Danti S, Nuti A (2015) Sleep disturbances and dementia. Psychogeriatrics 15:65–74

Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS (2011) Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res 70:73–97

Corbett A, Burns A, Ballard C (2014) Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. BMJ 349:g6420

De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL, Breier A (2004) Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 19:115–126

de Jong D, Jansen R, Hoefnagels W, Jellesma-Eggenkamp M, Verbeek M, Borm G, Kremer B (2008) No effect of one-year treatment with indomethacin on Alzheimer's disease progression: a randomized controlled trial. PLoS One 3:e1475

DeKosky ST, Carrillo MC, Phelps C, Knopman D, Petersen RC, Frank R, Schenk D, Masterman D, Siemers ER, Cedarbaum JM, Gold M, Miller DS, Morimoto BH, Khachaturian AS, Mohs RC (2011) Revision of the criteria for Alzheimer's disease: a symposium. Alzheimers Dement 7:e1–12

Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K (2011) A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. Int J Geriatr Psychiatry 26:937–943

Devanand DP, Mintzer J, Schultz SK, Andrews HF, Sultzer DL, de la Pena D, Gupta S, Colon S, Schimming C, Pelton GH, Levin B (2012) Relapse risk after discontinuation of risperidone in Alzheimer's disease. N Engl J Med 367:1497–1507

Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, Aisen PS, Alzheimer's Disease Cooperative Study Steering C, Siemers E, Sethuraman G, Mohs R, Semagacestat Study G (2013) A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med 369:341–350

Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R, Alzheimer's Disease Cooperative Study Steering C, Solanezumab Study G (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370:311–321

Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA, Breazna A (2010) Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology 74:956–964

Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P (2015) Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open 3:E419–E427

Frakey LL, Salloway S, Buelow M, Malloy P (2012) A randomized, double-blind, placebo-controlled trial of modafinil for the treatment of apathy in individuals with mild-to-moderate Alzheimer's disease. J Clin Psychiatry 73:796–801

Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J (2006) Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol 63:1402–1408

Gallagher D, Herrmann N (2014) Antiepileptic drugs for the treatment of agitation and aggression in dementia: do they have a place in therapy? Drugs 74:1747–1755

Galynker I, Ieronimo C, Miner C, Rosenblum J, Vilkas N, Rosenthan R (1997) Methylphenidate treatment of negative symptoms in patients with dementia. J Neuropsychiatry Clin Neurosci 9:231–239

Garcia-Alberca JM, Pablo Lara J, Gonzalez-Baron S, Barbancho MA, Porta D, Berthier M (2008) Prevalence and comorbidity of neuropsychiatric symptoms in Alzheimer's disease. Actas Esp Psiquiatr 36:265–270

Gareri P, Putignano D, Castagna A, Cotroneo AM, De Palo G, Fabbo A, Forgione L, Giacummo A, Lacava R, Marino S, Simone M, Zurlo A, Putignano S (2014) Retrospective study on the benefits of combined Memantine and cholinEsterase inhibitor treatMent in AGEd patients affected with Alzheimer's disease: the MEMAGE study. J Alzheimers Dis 41:633–640

Gaudig M, Richarz U, Han J, Van Baelen B, Schauble B (2011) Effects of galantamine in Alzheimer's disease: double-blind withdrawal studies evaluating sustained versus interrupted treatment. Curr Alzheimer Res 8:771–780

Gordon SE, Dufour AB, Monti SM, Mattison ML, Catic AG, Thomas CP, Lipsitz LA (2016) Impact of a videoconference educational intervention on physical restraint and antipsychotic use in nursing homes: results from the ECHO-AGE pilot study. J Am Med Dir Assoc 17:553–556

Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH (2009) Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA 302:2557–2564

Hampel H, Ewers M, Burger K, Annas P, Mortberg A, Bogstedt A, Frolich L, Schroder J, Schonknecht P, Riepe MW, Kraft I, Gasser T, Leyhe T, Moller HJ, Kurz A, Basun H (2009) Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study. J Clin Psychiatry 70:922–931

Herrmann N, Gill SS, Bell CM, Anderson GM, Bronskill SE, Shulman KI, Fischer HD, Sykora K, Shi HS, Rochon PA (2007) A population-based study of cholinesterase inhibitor use for dementia. J Am Geriatr Soc 55:1517–1523

Herrmann N, Rothenburg LS, Black SE, Ryan M, Liu BA, Busto UE, Lanctôt KL (2008) Methylphenidate for the treatment of apathy in Alzheimer disease: prediction of response using dextroamphetamine challenge. J Clin Psychopharmacol 28:296–301

Herrmann N, O'Regan J, Ruthirakuhan M, Kiss A, Eryavec G, Williams E, Lanctot KL (2016) A randomized placebo-controlled discontinuation study of cholinesterase inhibitors in institutionalized patients with moderate to severe Alzheimer disease. J Am Med Dir Assoc 17:142–147

Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R (2013) Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther 38:360–372

Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A, Pandita-Gunawardena ND, Hogg F, Clare C, Damms J (2004) The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 63:214–219

Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, Lucas JA, Schneeweiss S (2012) Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ 344:e977

Jansen IH, Olde Rikkert MG, Hulsbos HA, Hoefnagels WH (2001) Toward individualized evidence-based medicine: five "N of 1" trials of methylphenidate in geriatric patients. J Am Geriatr Soc 49:474–476

Janssen IM, Sturtz S, Skipka G, Zentner A, Velasco Garrido M, Busse R (2010) *Ginkgo biloba* in Alzheimer's disease: a systematic review. Wien Med Wochenschr 160:539–546

Johannsen P, Salmon E, Hampel H, Xu Y, Richardson S, Qvitzau S, Schindler R, Group AS (2006) Assessing therapeutic efficacy in a progressive disease: a study of donepezil in Alzheimer's disease. CNS Drugs 20:311–325

Jones R, Sheehan B, Phillips P, Juszczak E, Adams J, Baldwin A, Ballard C, Banerjee S, Barber B, Bentham P, Brown R, Burns A, Dening T, Findlay D, Gray R, Griffin M, Holmes C, Hughes A, Jacoby R, Johnson T, Jones R, Knapp M, Lindesay J, McKeith I, McShane R, Macharouthu A, O'Brien J, Onions C, Passmore P, Raftery J, Ritchie C, Howard R, team D-A (2009) DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease – a multicentre RCT. Trials 10:57

Kaiser T, Florack C, Franz H, Sawicki PT (2005) Donepezil in patients with Alzheimer's disease – a critical appraisal of the AD2000 study. Med Klin (Munich) 100:157–160

Khoo SA, Chen TY, Ang YH, Yap P (2013) The impact of neuropsychiatric symptoms on caregiver distress and quality of life in persons with dementia in an Asian tertiary hospital memory clinic. Int Psychogeriatr 25:1991–1999

Kobayashi H, Ohnishi T, Nakagawa R, Yoshizawa K (2015) The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis. Int J Geriatr Psychiatry 31:892

Leucht S, Helfer B, Dold M, Kissling W, McGrath JJ (2015) Lithium for schizophrenia. Cochrane Database Syst Rev 4:CD003834

Liu CS, Chau SA, Ruthirakuhan M, Lanctot KL, Herrmann N (2015) Cannabinoids for the treatment of agitation and aggression in Alzheimer's disease. CNS Drugs 29:615–623

Livingston G, Katona C (2004) The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis. Int J Geriatr Psychiatry 19:919–925

Lovestone S, Boada M, Dubois B, Hull M, Rinne JO, Huppertz HJ, Calero M, Andres MV, Gomez-Carrillo B, Leon T, del Ser T, investigators A (2015) A phase II trial of tideglusib in Alzheimer's disease. J Alzheimers Dis 45:75–88

Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, Baker AS, Sheppard JM, Frangakis C, Brandt J, Rabins PV (2003) Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. Arch Gen Psychiatry 60:737–746

Lyoo IK, Dager SR, Kim JE, Yoon SJ, Friedman SD, Dunner DL, Renshaw PF (2010) Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: a longitudinal brain imaging study. Neuropsychopharmacology 35:1743–1750

Ma H, Huang Y, Cong Z, Wang Y, Jiang W, Gao S, Zhu G (2014) The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. J Alzheimers Dis 42:915–937

Maletta GJ, Winegarden T (1993) Reversal of anorexia by methylphenidate in apathetic, severely demented nursing home patients. Am J Geriatr Psychiatry 1:234–243

Matsunaga S, Kishi T, Iwata N (2015a) Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: a systematic review and meta-analysis. Int J Neuropsychopharmacol 18(5). doi:10.1093/ijnp/pyu115, Published Mar 5

Matsunaga S, Kishi T, Iwata N (2015b) Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PLoS One 10:e0123289

McCleery J, Cohen DA, Sharpley AL (2014) Pharmacotherapies for sleep disturbances in Alzheimer's disease. Cochrane Database Syst Rev 3:CD009178

McKeith I, Cummings J (2005) Behavioural changes and psychological symptoms in dementia disorders. Lancet Neurol 4:735–742

Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD, Study G (2001) A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 57:481–488

Nelson JC, Devanand DP (2011) A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. J Am Geriatr Soc 59:577–585

Nyth AL, Gottfries CG (1990) The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study. Br J Psychiatry 157:894–901

O'Regan J, Lanctot KL, Mazereeuw G, Herrmann N (2015) Cholinesterase inhibitor discontinuation in patients with Alzheimer's disease: a meta-analysis of randomized controlled trials. J Clin Psychiatry 76:e1424–e1431

Padala PR, Burke WJ, Bhatia SC (2007) Modafinil therapy for apathy in an elderly patient. Ann Pharmacother 41:346–349

Padala PR, Burke WJ, Shostrom VK, Bhatia SC, Wengel SP, Potter JF, Petty F (2010) Methylphenidate for apathy and functional status in dementia of the Alzheimer type. Am J Geriatr Psychiatry 18:371–374

Petracca G, Teson A, Chemerinski E, Leiguarda R, Starkstein SE (1996) A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci 8:270–275

Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Rosenberg PB, Schneider LS, Shade DM, Weintraub D, Yesavage J, Lyketsos CG, Cit ADRG (2014) Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA 311:682–691

Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr, Weiner M, Shinto L, Aisen PS (2010) Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 304:1903–1911

Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, Norman BA, Baranak CC (2004) Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 62:66–71

Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, Lopez OL, Mahoney J, Pasic J, Tan ZS, Wills CD, Rhoads R, Yager J (2016) The American Psychiatric Association Practice Guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry 173:543–546

Robinson RG, Jorge RE, Clarence-Smith K, Starkstein S (2009) Double-blind treatment of apathy in patients with poststroke depression using nefiracetam. J Neuropsychiatry Clin Neurosci 21:144–151

Rosenberg PB, Lanctot KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, Mintzer JE, Investigators A (2013) Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. J Clin Psychiatry 74:810–816

Roth M, Mountjoy CQ, Amrein R (1996) Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. Br J Psychiatry 168:149–157

Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, Reichert M, Ketter N, Nejadnik B, Guenzler V, Miloslavsky M, Wang D, Lu Y, Lull J, Tudor IC, Liu E, Grundman M, Yuen E, Black R, Brashear HR, Bapineuzumab, Clinical Trial I (2014) Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 370:322–333

Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, Aisen PS (2011) A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology 77:556–563

Saumier D, Duong A, Haine D, Garceau D, Sampalis J (2009) Domain-specific cognitive effects of tramiprosate in patients with mild to moderate Alzheimer's disease: ADAS-cog subscale results from the Alphase study. J Nutr Health Aging 13:808–812

Scarpini E, Bruno G, Zappala G, Adami M, Richarz U, Gaudig M, Jacobs A, Schauble B (2011) Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J Alzheimers Dis 26:211–220

Schneider LS, Dagerman K, Insel PS (2006) Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 14:191–210

Schneider LS, Dagerman KS, Higgins JP, McShane R (2011) Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol 68:991–998

Singh RR, Nayak R (2015) Impact of FDA black box warning on psychotropic drug use in noninstitutionalized elderly patients diagnosed with dementia: a retrospective study. J Pharm Pract 29:495

Skene DJ, Vivien-Roels B, Sparks DL, Hunsaker JC, Pevet P, Ravid D, Swaab DF (1990) Daily variation in the concentration of melatonin and 5-methoxytryptophol in the human pineal gland: effect of age and Alzheimer's disease. Brain Res 528:170–174

Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, Herrmann N (2010) A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 68:930–941

Tariot PN, Aisen P, Cummings J, Jakimovich L, Schneider L, Thomas R, Becerra L, Loy R (2009) in Alzheimer's Association International Conference on Alzheimer's Disease Alzheimers Dement, Vienna, pp P84–85

Thompson S, Lanctot KL, Herrmann N (2004) The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease. Expert Opin Drug Saf 3:425–440

Thompson S, Herrmann N, Rapoport MJ, Lanctot KL (2007) Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. Can J Psychiatr 52:248–255

Tjia J, Rothman MR, Kiely DK, Shaffer ML, Holmes HM, Sachs GA, Mitchell SL (2010) Daily medication use in nursing home residents with advanced dementia. J Am Geriatr Soc 58:880–888

Tjia J, Briesacher BA, Peterson D, Liu Q, Andrade SE, Mitchell SL (2014) Use of medications of questionable benefit in advanced dementia. JAMA Intern Med 174:1763–1771

Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, Chen MH, Hemmelgarn B, Straus SE (2013) Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. CMAJ 185:1393–1401

Waldemar G, Gauthier S, Jones R, Wilkinson D, Cummings J, Lopez O, Zhang R, Xu Y, Sun Y, Knox S, Richardson S, Mackell J (2011) Effect of donepezil on emergence of apathy in mild to moderate Alzheimer's disease. Int J Geriatr Psychiatry 26:150–157

Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, Khawaja IS, Diem S, Koffel E, Ouellette J, Butler M, Kane RL (2016) Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. Ann Intern Med 165:1–10

Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P, Donepezil Nordic Study G (2001) A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 57:489–495

World Health Organization (2012) Dementia: a public health priority. World Health Organization, Geneva

Xu J, Wang LL, Dammer EB, Li CB, Xu G, Chen SD, Wang G (2015) Melatonin for sleep disorders and cognition in dementia: a meta-analysis of randomized controlled trials. Am J Alzheimers Dis Other Demen 30:439–447

Psychological Interventions for Older Adults: Evidence-Based Treatments for Depression, Anxiety, and Carer Stress

20

Christina Bryant

Abstract

A wide range of psychological treatments have now been validated for use with older adults. This chapter reviews the evidence for a number of well-established approaches to anxiety and depression and how to implement these therapies with older clients, as well as noting some of their shortcomings. Evidence-based therapies include interpersonal therapy (IPT), cognitive behavioral (CBT) and problem-solving therapy (PST), and, to a lesser extent, reminiscence therapy and short-term psychodynamic therapy. Newer approaches are also emerging, including mindfulness-based approaches, and therapies delivered through the Internet or other electronic means. Evidence for efficacy is most robust for CBT, PST, and IPT for the treatment of depression. Some studies suggest that the treatment of anxiety is less successful, and some researchers have tried to improve the outcomes of anxiety treatment, with mixed results. The chapter also considers issues of particular concern to older adults, such as the stress of caregiving and the implications for therapy of cognitive impairment and comorbid physical illness. Despite the robust support for the efficacy of therapeutic interventions with older adults and the evidence that older adults prefer psychological to pharmacological intervention, older adults are less likely to receive psychological interventions than people of working age. Reasons for this include stigma, the challenges of recognizing and assessing anxiety and depression in older adults, and the lack of suitable services. The chapter concludes with a discussion of how psychological interventions can be made appropriate and available for older adults living in low and middle-income countries.

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_21

Keywords
Psychological intervention • Psychotherapy • Cognitive behavioral therapy • Interpersonal therapy • Caregiver stress • Barriers to treatment

Contents

Introduction

In a much-cited quotation, Freud stated his belief that adults over the age of 50 were no longer suitable for psychoanalytic treatment, as "the elasticity of the mental processes, on which the treatment depends, is as a rule lacking – old people are no longer educable – and, on the other hand, the mass of material to be dealt with would prolong the duration of treatment indefinitely" (Freud 1898). Fortunately, this view has now changed, and we are no longer restricted to only offering clients' long-term psychoanalytically oriented therapies. This chapter will briefly consider issues in relation to assessment for psychological intervention and then examine the wide range of psychological treatments that are now available for older adults. These include well-established approaches to anxiety and depression, such as cognitive behavioral and interpersonal therapy, but also emerging therapies, including mindfulness-based

approaches and therapies delivered through the Internet or other electronic means. The chapter will also consider issues of particular concern to older adults, such as the stress of caregiving and the implications for therapy of cognitive impairment. The chapter then discusses some shortcomings in the current literature, most notably issues relating to the applicability and availability of psychological interventions for older adults living in low- and middle-income countries.

Issues in the Identification and Assessment of the Older Adult in Need of Psychological Intervention

Before psychological interventions are offered to older adults, several prior steps need to have taken place: firstly, the older-adult needs to have presented to a health practitioner with some subjective distress, and secondly, that practitioner needs to have identified that psychological intervention is indicated, and undertaken a psychological assessment, leading to a case formulation. Finally, that psychological intervention also has to be available. Unfortunately, it is well established that these three processes are far from guaranteed.

Stigma remains a major barrier to older adults seeking help for psychological distress. Although the baby boomers are now reaching old age with higher awareness of mental illness and its treatment (Karel et al. 2012), older adults in the 70-plus age group may be less aware of these issues and may see them as a moral failing, rather than treatable conditions (Knight and Pachana 2015). The tendency to stoicism and self-reliance sometimes seen in older people (Bei et al. 2013) may also hold back help-seeking and lead to symptoms not being regarded as worthy of complaint or appropriate targets for treatment (Wetherell et al. 2004). Older adults may also mistrust mental health services (Kessler et al. 2015).

Even if an older person presents to their general practitioner, there is no guarantee that their doctor will enquire about or recognize psychological symptoms. The reasons for this are varied, but include a lower likelihood that GPs will enquire about psychological symptoms (perhaps through having a greater focus on physical health concerns that are likely to be present) and that older people themselves, as already noted, are less likely to volunteer information about psychological symptoms. The older adult may also use language differently to describe psychological symptoms, thus creating further barriers in the communication between patient and health practitioner.

In addition, the presentation of anxiety and depression may be different in older adults, at both a quantitative and qualitative level. With regard to the former, older adults are more likely than younger adults to experience both anxiety and depressive disorders at a sub-threshold level because they do not meet certain diagnostic criteria (Jeste et al. 2005). It has often been stated that the presentation of depression in older adults is qualitatively different from that in younger adults and can be characterized as "depression without sadness," as the older adult may deny subjectively feeling down or sad (Gallo et al. 1997). With respect to anxiety, older adults may more easily

be able to avoid situations that could provoke anxiety (Mohlman et al. 2012a), thus being less aware of the restrictions on their functioning that are the consequences of unrecognized psychological symptoms. For example, an older person may find that impaired hearing leads to anxiety in social situations, which are then avoided; age-related stereotyping may lead to well-meaning friends and relatives to explain this as expected behavior for somebody of their age. In this way a cycle of anxiety avoidance and decline in social participation can quickly set in.

A further challenge to the psychological assessment of older adults is that of comorbidity with physical illness, an important issue given the potential consequences of depression and anxiety on the outcome of medical illnesses and the benefits of addressing both physical and mental health concerns. While it may appear obvious, the presence of a medical illness does not preclude the existence of comorbid depression and anxiety that can exacerbate functional decline and increase the use of health services (Yohannes et al. 2000). Many older adults experience physical health problems and/or take medications that may mimic, mask, or exacerbate anxiety or depression symptoms. The medical and psychological symptoms can be hard to distinguish, however, for example, in the case of diabetes and thyroid disease.

Any consideration of the presentation of psychological distress in older adults needs to recognize the importance of cognitive impairment and dementia, which will have a significant impact on the presentation of symptoms and an individual's ability to identify and describe those. Assessment of anxiety and depression in a person with dementia will require careful questioning of the individual as well as seeking corroboration from somebody who knows the patient well. With respect to anxiety, the individual's own understanding and insight into their cognitive impairment may also be informative, as it is likely that anxious worry decreases as insight declines, when behavioral manifestations of anxiety, such as agitation, become more common (Bierman et al. 2007).

Even assuming the patient and doctor find a common language for speaking about psychological symptoms and the doctor recommends a course of psychological therapy, there is no certainty that such services will be available. Sadly, many psychologists do not regard older adults as a desirable population to work with. For example, in a Portuguese study of 460 undergraduate students, psychology students not only rated lowest in terms of scores on a questionnaire measuring attitude toward older adults compared to the other professional groups interviewed in the study (nursing and social work trainees) but also rated older adults as the lowest in work interest compared to adolescents and younger adults (Gonçalves et al. 2011). Furthermore, the services available may not necessarily match the wishes of the potential clients themselves. Gum and colleagues found that older adults with depression who rated counselling as their preferred treatment were much less likely to receive their desired treatment than those who favored medication (33% compared to 70%) (Gum et al. 2006). Particular groups of clients may face special challenges in receiving appropriate services; the needs of older men may be underrecognized, as community older-adult healthcare may cater more to females (Kaye et al. 2008), as may be those of the LBGTI community (Fredriksen-Goldsen et al. 2013).

Adults from non-Western cultures face even greater obstacles in accessing culturally sensitive services. This is partly because almost all studies of the efficacy of psychological therapy have been carried out in high-income countries from a Western cultural perspective, and there is a dearth of literature on the relevance of psychological therapies to people from diverse cultural backgrounds. Individual psychotherapy is premised on the value of the individual and their right to autonomy and self-determination, yet many Asian cultures prefer harmonious relationships with others above the needs of the individual. CBT emphasizes the collaborative relationship between client and therapist, which may not be compatible with values that emphasize hierarchical and authoritarian social structures, such as those in Chinese cultures (Hodges and Oei 2007). Similarly, clients from an Islamic background may be of the view that the individual is not a free and autonomous being but is, rather, subject to the will of God and may, therefore, struggle with the notion that people can change their thoughts and behavior (Beshai et al. 2013). While a few studies have examined the cultural adaptation of psychological therapies in younger adults, virtually none of this research has involved older adults.

In summary, many factors create barriers to the older person receiving psychological intervention for anxiety, depression, and other disorders in late life. Consequently, it may be, in some cases, that before the question of referral for psychological intervention even arises, older adults have fallen at the first hurdle. Once referred for psychological intervention, the first step is to make a clinically meaningful assessment of the client's presentation.

Assessment for Psychological Intervention

The first task for the clinician is to engage the referred individual and build rapport in an effort to understand the clinical picture. This process is likely to include taking a personal history including important life events that could contribute toward the current symptoms and making enquiries about how they affect the ability to carry out valued activities (Mohlman et al. 2012b). Screening tools may be useful at this point and may help clinicians to gather initial information about the mental state of their patient or client.

A number of screening instruments are widely used with older adults, including the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983a), the Short Anxiety Screening Test (SAST) (Sinoff et al. 1999), the Hamilton Anxiety Scale (HAMA), the Beck Anxiety Inventory (BAI) (Beck et al. 1988), the Beck Depression Inventory (BDI) (Beck et al. 1996), the Geriatric Depression Scale (GDS) (Yesavage et al. 1983), the Rating Scale for Anxiety in Dementia (RAID) (Shankar et al. 1999), and the Geriatric Anxiety Inventory (GAI) (Pachana et al. 2007). Of these, only the GAI, GDS SAST, and RAID were designed specifically for older people. While screening tools may be useful, they will never be sufficient on their own, and there are concerns about their appropriateness in non-English-speaking countries, even though some of the measures described above have been translated into languages other than English. The HADS, for example, has been

translated into to all the major European languages in addition to Arabic, Hebrew, Chinese (both Mandarin and Cantonese), Japanese, Farsi, Malayalam, and Urdu. Further clinical evaluation through structured questioning will be required, and this should lead to a well-developed case formulation. This process is regarded as a fundamental skill of the mental health clinician (Johnstone and Dallos 2013) and is based on integrating information gathered about a client and their symptoms and functioning. Ideally, multiple aspects of the client's background – development, biological, medical, psychiatric, and psychological – are brought together by clinician and client to produce a shared and nuanced understanding of the client's current situation, with a view to generating working hypotheses as to its origins and meaning and developing a treatment plan (Johnstone and Dallos 2013). At this point, the clinician and client are ready to embark on the treatment phase of psychological intervention.

Special Considerations in Relation to Psychological Interventions for Older Adults: Taking into Account Physical Illness and Cognitive Impairment

Before discussing the treatment of specific disorders and therapies, it is important to briefly consider two issues that may affect older adults and their response to psychological intervention, irrespective of the disorder being treated or – perhaps to a lesser extent – the nature of the intervention. These factors are the likelihood that an older person may have comorbid physical health problems and the potential presence of both mild and more severe neurodegenerative disease. Rates of anxiety and depression are very high in the medically unwell (Bryant et al. 2008; Reynolds et al. 2001), and the relationships between physical and mental comorbidity are a complicated one. Essentially, however, chronic medical illnesses can set the stage for demoralization and depression; conversely, depression can amplify the disability of coexisting medical illnesses. These factors may be further complicated by loss, bereavement, insomnia, and depletion of psychosocial resources (Reynolds et al. 2001).

Older depressed adults suffering from a serious physical illness or from cognitive impairments may show lower response to psychological and behavioral treatment for depression as their depressive symptoms may reflect physiological changes (Reynolds et al. 2001) that might not be easily modifiable. Moreover, some treatments may be more difficult to implement when patients are physically ill or cognitively impaired unless they are offered at home, thereby increasing the barriers to accessing services (Pinquart et al. 2007). Even then, the more cognitively impaired client will lack the abstract reasoning capacity required for all but the most behaviorally oriented therapies.

It is, therefore, unfortunate that almost all research on psychological interventions has been conducted with older adults who are relatively young, relatively healthy, and cognitively intact. Participants tend also to self-select into research studies, raising questions about the generalizability of these studies to the frail older person.

Only a few studies have explicitly attempted to address these challenges. For example, Koenig and colleagues compared the effectiveness of standard CBT with CBT that integrated religious elements (RCBT) for clients with serious medical illnesses (Koenig et al. 2015). Both therapies were delivered via the telephone, in order to make it more accessible, and it was thought that a spiritual dimension might be particularly relevant to persons with severe health problems. In fact, depression scores reduced significantly in both conditions, with no superiority of the RCBT.

With respect to clients with cognitive impairment, a body of work by Teri and colleagues has demonstrated the value of a behavioral approach to improving quality of life in older adults with dementia (Logsdon et al. 2007; Teri et al. 1997). Key elements in these programs include the emphasis on increasing patient pleasant events and positive interactions. These programs, however, rely on the caregiver to institute the pleasant events and manage the behavior of the person with dementia, so do not, strictly speaking, constitute a therapy undertaken by the older person themselves. More recently, a meta-analysis by Orgeta et al. (2015) examined data from six randomized controlled trials of psychological treatment for anxiety or depression in people with dementia or mild cognitive impairment. These treatments were diverse in nature and length, but demonstrated clinically significant improvement for depression, but not for self- or caregiver-rated anxiety, quality of life and activities of daily living, or neuropsychiatric symptoms. The authors highlighted the need for well-designed multicenter trials with follow-up periods and the use of standardized treatments (Orgeta et al. 2015).

To our knowledge, only one study to date has attempted to integrate a psychological intervention for anxiety in people with co-occurring cognitive dysfunction (Lenze et al. 2014). Lenze et al. hypothesized that some portion of cognitive dysfunction may be attributable to anxiety and worry and tested whether a mindfulness-based stress reduction (MSBR) intervention delivered over a 12-week period would reduce symptoms of worry in a sample of older adults who had self-reported difficulties with memory or concentration. A total of 34 participants were enrolled in the study, 32 of whom completed the course. There was no control group. At the end of the treatment, there were substantial reductions in worry, and memory and executive function had improved, leading the authors to conclude that the intervention showed promise, but some modifications might be required with respect to the measures of mindfulness that would be used in future studies (Lenze et al. 2014).

Practical Implications of Physical and Cognitive Comorbidity

This raises the question of how to approach treatment of the older adult who does not neatly fit the participants described in research studies. In this case, treatment needs to be individualized and tailored to the presenting problem and history of the patient. One framework that can be helpful for planning treatment is the CALTAP model proposed by Knight (Knight and Poon 2008). CALTAP stands for the **C**ontextual, **A**dult **L**ifespan **T**heory for **A**dapting **P**sychotherapy and is conceived of as a

transdiagnostic, as well as transtheoretical perspective that takes into account important features of late life to assist the clinician in thinking sensitively about their client. Likewise, Laidlaw et al. (2003) emphasize the importance of an accurate case formulation that takes into account the developmental factors that have contributed to the person's beliefs and current difficulties. The clinician also needs an accurate understanding of the extent and nature of cognitive and physical impairments that could make participation in aspects of the therapy more difficult. For example, it would not be useful to set the behavioral goal of taking a long walk with someone who has severe mobility problems. Similarly, some forms of relaxation training may be difficult for a person with persistent pain, while difficulties with abstract reasoning may make behavioral approaches more applicable than cognitive restructuring. A useful guide to adapting therapy to the needs of the older patient is provided by Koder (1998). She suggested a range of very practical tips for adapting CBT for anxiety with patients who have cognitive impairment, but these would be equally applicable to treatment of depression (Koder 1998). These include simplifying the materials used, providing simple written summaries of session material, and using more structured, behavioral techniques, as opposed to abstract cognitive methods. It may be useful to have the caregiver attend sessions, engaging them to assist with the therapy and helping with memory between sessions. Diaries and lists can assist with remembering material and tasks, and any requirements to record activities should be structured and simple. It is important to have explicit, concrete goals, and it is likely that the therapist will be more active and take more initiative in the sessions (Koder 1998). With these general considerations in mind, we turn to a review of treatments for depression in older adults.

The Treatment of Depression in Older Adults

Interpersonal Therapy (IPT) for the Treatment of Depression in Older Adults.

IPT is a well-validated therapy approach for treating depression in older adults and has an intuitive appeal, given its time-limited focus on present concerns and relationships with others, yet remains less widely used than cognitive behavioral therapy (CBT). IPT was developed by Klerman and Weissman in the 1970s in order to provide a manualized treatment for depression (Hinrichsen and Iselin 2014). As the name implies, its premise is that interpersonal events increase the risk of developing depression and that depression can have a significant impact on the ability to carry out interpersonal roles.

Evidence for the Efficacy of IPT for Treatment of Depression

The evidence base for the effectiveness of IPT is impressive: initial studies by Reynolds and colleagues demonstrated the superiority of IPT over placebo, either

with or without antidepressant medication (Reynolds et al. 1999). Reynolds et al. followed a sample of 187 adults with an average age of 67 who were in remission from an episode of unipolar depression and reported that time to relapse was considerably shorter in those who were receiving IPT, and this effect was even greater for those also receiving pharmacological therapy with nortriptyline. These authors also identified that improvements in sleep were a good indicator that remission from depression would be maintained, reporting that 90% of patients reporting good subjective sleep quality by 1 month into continuation treatment remained well for at least 1 year when treated with monthly maintenance interpersonal psychotherapy (Reynolds et al. 1997). Other studies included patients in the acute stage of a depressive episode in a trial of 9 weeks of acute therapy and 16 weeks of maintenance therapy: the authors reported that 78.7% of the participants in the trial achieved full remission (Reynolds et al. 1992).

More stringent methodologies using active control groups, rather than the weaker comparisons with a placebo, have confirmed the efficacy of IPT. A meta-analysis by Ciujpers et al. of 38 randomized control trials (Cuijpers et al. 2011) found a moderate to large effect of IPT in the treatment of acute depression, but did not find that it was superior to other types of psychotherapy, including CBT. This study included adult and older-adult samples, but an earlier meta-analysis by Cuijpers and colleagues had found no evidence that psychotherapy was less efficacious in older adults than in younger age groups (Cuijpers et al. 2009).

Delivery of IPT for Treatment of Depression

IPT treatment is generally carried out through weekly, individual sessions over a 16-week period, and consistent with the evidence base for the therapy sometimes includes further maintenance sessions. The therapy focuses on one to two out of the four key areas of interpersonal functioning that IPT prioritizes, namely, grief and bereavement (especially protracted grief reactions), role transitions (major life changes, such as retirement or move into supported accommodation, or relinquishing of a caring role), role disputes (conflicts with a significant other), and interpersonal deficits, which refers to lack of meaningful relationships, isolation, and loneliness. It is characterized by a number of general features, including a focus on active collaboration between client and therapist, the role of the therapist to provide psychoeducation and convey hope and encouragement to the client. The therapist will provide psychoeducation on the relationship between interpersonal events and depressed mood while also teaching problem-solving skills. Specific techniques include decision and communication analysis, role play, building interpersonal skills, and the use of homework tasks between sessions (Hinrichsen and Iselin 2014).

The course of the therapy has a clear structure of three phases: initial (sessions 1–3), intermediate (sessions 4–13), and termination (sessions 13–16) (Hinrichsen and Iselin 2014). The initial sessions involve assessment of the depressive symptoms and the interpersonal events that may have contributed to the current episode,

psychoeducation about depression, and drawing up an inventory of past and current relationships. The therapist will then provide the client with a case formulation incorporating an understanding of the client's depression and its possible precipitants. The intermediate phase of therapy will then focus on the identified issues. Hinrichsen gives the example of a 75-year-old woman facing the increasing care needs of her husband with Parkinson's disease (Hinrichsen 2008). In this case, the therapist helped her to understand the link between her changing role and her depressive symptoms (psychoeducation and formulation), encouraged the client to obtain more help with caring for her husband (problem solving), and also supported her decision to join an exercise class and make more contact with her sons (to increase her social interactions). In the termination phase, the therapist will encourage discussion of feelings about the ending of therapy, as these may echo previous losses. Progress will be reviewed, emphasizing the active efforts the client has made to bring about change. Therapist and client will also discuss possible future stressors and help available for those. In the example cited above (Hinrichsen 2008), the woman was encouraged to join a support group for carers of relatives with Parkinson's disease, an intervention that integrates a number of key aspects of IPT – problem solving, building interpersonal skills, and making active efforts toward behavioral change.

Strengths and Shortcomings of the IPT Approach

Hinrichsen has been a strong advocate for IPT in older adults and developed a well-regarded training program with a view to making it a more widely available psychological intervention for older adults (Hinrichsen 2008). He cites a number of reasons why it is particularly suitable for older adults: the four core IPT problems are highly relevant to the challenges faced by many in this age group, and the collaborative approach is consistent with general recommendations for working with older adults (Knight and Poon 2008). Moreover, although clinicians should receive formal training and supervision in conducting IPT, the techniques of IPT build on core psychological skills, such as assessment, case formulation, problem solving, and interpersonal skill building. Yet, despite its face value and strong evidence base, IPT is not as widely disseminated as a therapy modality as cognitive behavioral therapy. There are a number of possibly interrelated reasons why this may be the case. Firstly, not many clinical psychology training programs offer substantive training in IPT, rather favoring CBT. Secondly, some authors have suggested that the evidence for IPT is not as strong as for other therapies, thereby questioning its status (Scogin et al. 2005). Finally, it is likely that the use of IPT will remain limited in the UK, since the NICE Guidelines for managing depression in adults endorse CBT and mindfulness, but not IPT (NICE 2013).

In summary, IPT is regarded by its advocates as being highly suitable for older adults, given its short-term, structured approach to interpersonal problems that are highly relevant to this life stage. Despite these advantages, psychologists are far less likely to be trained in its use than in CBT, and it remains less broadly practiced than

the latter. CBT remains the most widely used and extensively researched of the psychological interventions, and we now turn to a consideration of this modality.

Cognitive Behavioral Therapy for the Treatment of Depression

Cognitive behavioral therapy (CBT) has a central focus on how thoughts (cognitions), emotions, and behavior affect one another. Its founding father Aaron Beck stated that the theory was originally developed to understand depressive disorders and is rooted in an information-processing framework (Beck 2005). It follows from this that how we feel and how we behave is shaped by our interpretation of external events. The processing of external events or internal stimuli is biased and therefore systematically distorts the individual's construction of his or her experiences, leading to a variety of cognitive errors or maladaptive ways of thinking. These are often the focus of therapy and include overgeneralization, seeing things in all-or-nothing terms, and personalization. Underlying these distorted interpretations are dysfunctional beliefs incorporated into relatively enduring cognitive structures or schemas. Beck coined the term "the depressive triad" to refer to a cluster of dysfunctional beliefs that encompass negative representations of the self, personal world, and future.

The primary aim of CBT is to uncover and challenge these distortions in order to allow the individual to achieve their goals. Like IPT, the focus is on present problems, rather than uncovering hidden traumas from the past, on a collaborative relationship between client and therapist, and on the therapist taking an active role in the therapy (Beck 2005). The therapeutic strategies and concepts of CBT include exploring the meaning of the individual's thoughts and experiences, identifying consistent themes that may reflect underlying core beliefs, connecting present and past experiences, and setting goals for each session as well as for the long term and using homework to practice between sessions or try new approaches to problems. Sometimes behavioral approaches are used on their own, for example, in the technique of behavioral activation, where clients are encouraged to undertake enjoyable activities in order to improve mood (Scogin and Shah 2012), but it is more usual to use both cognitive and behavioral approaches together, and the next section will focus on evidence for this CBT approach.

Evidence for the Efficacy of CBT for Depression in Older Adults

There appears to be a general consensus that CBT is an efficacious treatment for depression in older adults: a meta-analysis by Pinquart et al. (2007) of 57 studies investigating the efficacy of psychological interventions for depression concluded that effect sizes were large for cognitive and behavioral therapy, but, contrary to their expectations, effect sizes were smaller for major depression than for minor depression. They concluded that major depression may be more difficult to treat with psychotherapy than less severe forms of depression and speculated that this may be

due to the presence of more chronic or severe symptoms and associated cognitive deficits. Pinquart, Duberstein, and Lyness also highlighted significant weaknesses in the literature: the lack of comparison treatment in 38 out of the 57 studies reviewed and the lack of an extended follow-up period to assess the retention – or otherwise – of therapy gains (2007). However, they also demonstrated that increasing age did reduce the effectiveness of CBT, but longer interventions lead to higher dropouts, suggesting that shorter, focused interventions may be more suitable for older adults. A Cochrane review of nine studies of comparing CBT with psychodynamic therapy found both to be more effective than a waiting list control, but neither demonstrated superiority over the other (Wilson et al. 2007). Moreover, CBT's effectiveness disappeared when depression was measured with the Geriatric Depression Scale (Yesavage et al. 1983), rather than the Hamilton Rating Scale for Depression (Hamilton 1960).

A review by Shah et al. (2012) identified eight studies with appropriate control groups that provide support for CBT. In these studies, CBT was either superior to, or not significantly different from, a control condition (brief psychodynamic therapy, bibliotherapy, relaxation training, or behavior therapy). The most recent meta-analysis of this topic (Cuijpers et al. 2014) examined 44 studies comparing psychotherapies to control groups, other therapies, or pharmacotherapy. Again, their unequivocal conclusion was that there was strong evidence for the efficacy of CBT for depression and that in the eight studies directly comparing CBT with another psychotherapy, CBT was somewhat more effective than the other therapies. Moreover, the authors concluded that these gains were maintained even 6 months after intervention. Again, weaknesses in the literature were mentioned: these included the less-than-optimal quality of many included studies; the relatively small number of studies that include effect sizes; the tendency of studies to use a waiting list or a care-as-usual comparison group, rather than active control groups; and the tendency for participants to be in the younger old age bracket, rather than over the age of 75. Similar concerns were raised by Andreescu and Reynolds (2011), who also highlighted issues of high dropout rates from treatment and the effects of using community volunteers, rather than clinical samples (Andreescu and Reynolds 2011).

Delivery of CBT for Treatment of Depression

Like IPT, CBT is also usually delivered as a time-limited and structured therapy with a focus on active collaboration between client and therapist, but with a greater focus on the investigation of the client's thoughts, appraisal, and assumptions (Laidlaw and Thompson 2014). The therapist and client seek to challenge unhelpful thoughts and their underlying assumptions through structured questioning and the development of more adaptive thoughts. Laidlaw and Thompson (2014) suggest that CBT therapy will typically involve 16–20 treatment sessions with early, middle, and late stages in the treatment. In the early phase (approximately the first three sessions), the therapist will help the client to understand the fundamentals of the cognitive

behavioral model, while the therapist must also develop a case conceptualization that enables both to identify maladaptive thoughts and behaviors. In the middle phase of therapy (approximately sessions 4–16), the focus is very much on challenging and restructuring these thoughts by seeking alternative ways of looking at them. Therapists may need to be willing to challenge age-related negative cognitions that may be prominent in older depressed individuals, such as the belief that it is normal to be depressed when you are older or that most older people no longer enjoy seeing friends. These are examples of thoughts that the depressed older person may assume to be correct when they are not factually true. To augment this work, behavioral change should also be encouraged, for example, setting the goal of contacting a friend the client may not have seen for a while. In the final phase of therapy (approximately sessions 17–20), the therapist and client agree on when the therapy will end, review the skills learned and gains made, and make a plan for how these will be maintained. This will typically also include considering potential future challenges and how to cope with them. Readers who wish to learn in greater detail about CBT therapy session skills and plans with older people are referred to the excellent chapters by Shah et al. (2012) and Laidlaw and Thompson (2014).

The question is often raised as to whether CBT needs to be modified for use with older adults. The effectiveness of therapies is often established in samples and settings that are very different from those of the clinician practicing in a public mental health service or even in the private consulting room. Shah et al. (2012) acknowledge the difficulties of following treatment protocols rigidly and suggest that some flexibility will likely be required. For example, some older adults may be reluctant to try out "homework" or writing down records of their thoughts – perhaps these activities bring back memories of school in an era where punishment was not unusual. This needs to be respected and ways found to work differently, for example, by discussing thoughts in session, rather than writing them down. A wide range of age-related factors can also impinge on therapy, from memory and sensory impairment, through comorbidity with physical health problems that may cause pain or disrupt sleep, to internalized stereotypes and misinformation about aging. Laidlaw and colleagues (2003) discuss how these issues might be addressed, for example, by providing a written summary of points covered in a session for client whose memory is impaired. Most importantly, the therapist must draw on a rich conceptualization of the client, their history, context, and presenting problem. One of the best ways to do this is by using Knight's highly recommended CALTAP model that takes into account cultural, cohort, contextual, and maturational aspects of aging (Knight and Poon 2008).

Strengths and Limitations of CBT for the Treatment of Depression

One of the clear strengths of CBT for depression in older adults is that it has its roots in the extensive broader literature for the treatment of depression with CBT. With that approach, it shares a focus on the present, rather than excavating the past, on an active relationship between client and therapist, and on problem solving and setting

goals that can enhance quality of life. As we have seen, there is a solid evidence base for the efficacy of CBT in the treatment of late-life depression (e.g., Cuijpers et al. 2014). Some authors have suggested, however, that the normal declines in fluid intelligence seen in older age may make CBT less suitable and more challenging for this age group because of the demands it places on abstract thinking (Doubleday et al. 2002). In a study examining the relationship between scores on a test of abstract reasoning and benefits from either group CBT or supportive therapy, the authors were surprised to find no significant correlation between level of fluid intelligence and ability to benefit from therapy in the CBT.

In contrast, there was a correlation between abstract reasoning and the ability to benefit from the supportive therapy (2002). The authors concluded that the unstructured nature of the supportive therapy made greater cognitive demands on the participants, whereas the structured nature of CBT provided guidance and direction, making it highly suitable as a therapy for older adults.

On the other hand, it is unlikely that changing cognitions alone will be sufficient to enable financially disadvantaged older people to make changes to their quality of life. Areán and colleagues (2005) compared the efficacy of group CBT alone or in conjunction with case management in a sample of Americans with low incomes and found that CBT alone was insufficient to reduce low-income older adults' feelings of distress in the face of adversity and suggested that older adults may be able to better focus on psychological needs if they are receiving help with basic needs. This highlights the importance of not viewing psychological needs in isolation from other needs – which may be a risk for practitioners using an approach that places considerable emphasis on intellectual processes.

In summary, CBT is probably the most widely available psychological treatment for depression in older adults. Unlike IPT, it is widely taught in clinical psychology training programs and is endorsed as a treatment by bodies such as the UK National Institute for Clinical Excellence (NICE). It also appears to as efficacious a therapy for older adults and those who are younger (Laidlaw and Thompson 2014), though it remains debated whether it is substantially superior to other forms of psychotherapy.

Other Treatment Approaches for Depression

Three other treatment approaches that deserve mention in relation to the treatment of depression are reminiscence therapy, problem-solving therapy (PST), and short-term psychodynamic therapy.

Reminiscence therapy is one of the very few psychological interventions developed specifically for older people and is based on the premise that old age is a time when people naturally recall past events and may gain value from reminiscing about these (Butler 1963). Specifically, reminiscing can provide an opportunity to reflect on the past and integrate it into a meaningful life narrative (Shah et al. 2012). One of its potential strengths is that is draws on past memories, which are often relatively well preserved in older adults, rather than requiring robust working memory capacity. The therapeutic use of reminiscence has given rise to a range of therapies,

including using reminiscence spontaneously and informally, for example, when prompted by photographs, or as a component of another therapy, or as part of a more structured life review (Bahr 2014). All of these can be implemented individually or in a group format. Another strength of this approach is that some studies have demonstrated the efficacy of reminiscence in residential settings (Shah et al. 2012).

Life review therapy has the goal of helping the older person to replace negative beliefs about themselves and their past with more positive recollections, with a view to improving mood and sense of self-efficacy. Typically, it is a short-term structured therapy in which participants are prompted to recall past positive memories and attainments and encouraged to integrate these into a framework that emphasizes agency and identity (Korte et al. 2012). Recent reviews by Bahr (2014) and Cuijpers et al. (2014) both confirmed that life review therapy was efficacious in the treatment of late-life depression.

Problem-solving therapy is another psychological treatment of depression that has been the subject of numerous evaluations (Cuijpers et al. 2007). Based on the premise that depression is often associated with psychosocial stressors to which the individual must find a solution, PST is a practically oriented therapy with a strong focus on present difficulties, rather than understanding the past. Thus, its primary objective is to systematically identify problems, generate alternative solutions for each problem, select the best solution, develop and carry out a plan, and evaluate whether this has solved the problem. Arean et al. (1993) were the first to compare the efficacy of PST with reminiscence therapy in a sample of adults over the age of 55 and reported that 12 sessions of PST and supportive therapy were both superior to wait-list control, but PST had a greater impact on depression status at follow-up (Arean et al. 1993). More recently, a meta-analysis by Cuijpers et al. (2007) demonstrated that PST was equally efficacious in older and younger adults.

PST has been applied in a number of specific contexts, including suicide prevention. A study by Unűtzer and colleagues randomly allocated depressed adults aged 60 and over in primary care settings to usual care or an intervention with a number of components, including either antidepressant medication or PST (Unützer et al. 2002). At the end of the 12-month intervention period, the participants who had received PST reported improvement in quality of life, functioning, and reduced suicidal ideation. The authors noted, however, that 10% of the participants still expressed suicidal ideation, highlighting the difficulties in fully treating depression and suicidality. PST also has the advantage that it can be quite easily combined with other approaches and integrated into a treatment plan for depression or anxiety. This was demonstrated empirically by Wetherell et al. (2011b), who described the use of targeted interventions to address the specific concerns of individuals with generalized anxiety disorder. A helpful clinical description of how to integrate PST into treatment for depression is given by Ghaed et al. (2012). Advocates of short-term or brief psychodynamic therapy propose that its core concepts, such as loss, attachment, and the influence of early relational patterns, provide a powerful way of understanding conscious and unconscious feelings evoked by the aging experience and also in those caring for older adults (Davenhill 2008). The goal of brief

psychodynamic therapy is to develop insight, particularly into conflicts and unresolved issues around dependence and independence, and exploration of unconscious processes, especially as these are enacted in the therapeutic relationship (Scogin et al. 2005). Mourning the losses of old age and effecting a reconciliation between accomplishments and disappointments have also been identified as goals, and it is not hard to see how these can be very relevant to older people (Pinquart et al. 2007).

An early review of psychological treatments for depression (Scogin and McElreath 1994) reported that the effect sizes of three studies of psychodynamic therapy were comparable to those of other therapies. More recently, Scogin et al. (2005) identified two studies of brief psychodynamic therapy, both with small numbers of participants, that met criteria for being evidence-based therapies, with an effect size of $d = 0.57$, but no demonstrable superiority over other therapies, a finding echoed by both Pinquart et al. (2007) and Cuijpers et al. (2014).

Brief psychodynamic therapy has not achieved the wide reach and availability of other psychological interventions. This probably because evidence for its efficacy is sparse compared to other therapies, and relatively few therapists are trained in its provision. Moreover, its emphasis on reflection and insight requires a high level of cognitive functioning and ability to engage in insight-oriented discussion. Nevertheless, its focus on adaptation to loss and resolution of conflicts is highly relevant older adults and may also provide useful insights to help the clinician better understand the psychic processes experienced by their clients.

Psychological Treatments for Anxiety

The Evidence for the Efficacy of CBT for the Treatment of Anxiety

Unlike treatment for depression, there have been suggestions that CBT is less efficacious for the treatment of anxiety in older adults, compared to adults of working age (Gorenstein and Papp 2007). For example, a meta-analysis of CBT interventions for GAD by Nordhus and Pallesen (2003) found a smaller effect size (0.55) than the effect size of 0.71 reported in a meta-analysis of CBT for younger adults by Gould and colleagues (2012). Similar findings have been reported by other authors. A meta-analysis by Hendriks et al. (2008) found moderate effect sizes for CBT over wait-list controls or active treatment, but these were smaller than those commonly reported for interventions in younger adults (Hendriks et al. 2008). Wetherell and colleagues (2013) also addressed the issue of whether older adults benefit as much as younger adults from psychological treatment. They compared the outcomes of therapy for a range of anxiety disorders in younger and older adults aged up 75 years and found that CBT intervention was effective for social anxiety disorder and post-traumatic stress disorder (PTSD), but less so for panic disorder or generalized anxiety disorder (GAD). The effects of the intervention had also declined by the 18-month follow-up, leading the authors to conclude that psychological treatments for anxiety are less effective in older than in younger adults.

Gorenstein and Papp reported that the earliest studies of CBT as treatment for late-life anxiety tended to use nonclinical participants (Gorenstein and Papp 2007). Techniques showing positive effects included relaxation training, visualization-relaxation, and cognitive restructuring, a finding confirmed in a review by Ayers et al. (2007). These authors reported that relaxation training and CBT had demonstrated efficacy for anxiety disorders in older adults, but so too did supportive therapy and interpersonal therapy. Schuurmans et al. (2006) reported the first data to compare the effectiveness of sertraline with individual CBT for older adults with formally diagnosed GAD, panic disorder, social phobia, or agoraphobia (Schuurmans et al. 2006). The CBT treatment consisted of 15 weeks of relaxation, cognitive restructuring, and exposure. The authors reported high attrition in all arms, resulting in quite small numbers for data analysis, but both groups were significantly improved at posttreatment as measured by scores on the Beck Anxiety Inventory (Beck et al. 1988) and Hamilton Anxiety Rating Scale (Hamilton 1960). The effect sizes for CBT were smaller than those for sertraline (0.31–0.58 vs. 0.85–1.08).

The majority of studies have examined treatment for generalized anxiety disorder (GAD) (Andreescu and Varon 2015), which is probably the most prevalent anxiety disorder in late life (Bryant et al. 2008). One of the earliest of these studies was conducted by Stanley and colleagues, who compared a 15-week individually delivered (Stanley et al. 2003) CBT program with a minimal contact control condition (MCC) in which participants received a weekly phone call to monitor symptoms. The intervention had a number of components: education and awareness training, which focused on helping participants to understand the nature of GAD and to identify and monitor associated symptoms; progressive deep muscle relaxation; and cognitive therapy, elements of which included learning to reduce anxiety-producing thoughts through the evaluation of irrational thinking. Participants were taught to identify and monitor anxiety-related thoughts, explore logical errors, and generate alternative explanations. In an effort to make the therapy more acceptable to the participants, the researchers made a number of age and cohort-appropriate changes. For example, material was presented at a slower pace, using more visual and written aids to enhance learning and memory; they also incorporated more patient education and reduced the amount of psychological jargon used. The results showed a significantly greater reduction in anxiety and worry symptoms for CBT (33%) than for MCC (7%), and at posttreatment, only 55% of participants in CBT continued to meet criteria for GAD, relative to 81% in MCC.

Gonçalves and Byrne (2012) performed a meta-analysis of 13 psychotherapy (nearly all CBT) and 14 pharmacotherapy interventions for GAD that included participants over the age of 55, reporting pooled treatment effects that favored active interventions over control, concluding that older adults benefitted from psychotherapy. However, treatment effects were better for psychotherapeutic trials that used a passive control condition (waiting list or minimal contact/care as usual) than when they were compared with pharmacological trials. This echoed the findings of an earlier meta-analysis of behavioral and pharmacological interventions for late-life GAD that pharmacological interventions and their control groups showed stronger improvements in anxiety symptoms than the psychological interventions (Pinquart

and Duberstein 2007). This may be because of the powerful placebo effect that influences the outcome of pharmacological trials, but does not exert an influence in the control conditions of psychological interventions (Gonçalves and Byrne 2012; Pinquart and Duberstein 2007).

Criticisms that have been leveled at the literature on depression treatment have also been applied to the literature on anxiety. Numbers of participants are often small; they tend to be relatively healthy, well-educated younger volunteers, and treatment trials often use group formats that lead to higher dropout rates (Laidlaw and Thompson 2014). Schuurmans et al. commented on the difficulty their therapists encountered in persuading their participants to carry out homework tasks (Schuurmans et al. 2006), which would likely reduce the effectiveness of the intervention. A meta-analysis comparing different treatments for late-life anxiety (Thorp et al. 2009) found that of all the interventions reviewed (relaxation, including progressive muscle relaxation, thought monitoring, cognitive restructuring, exposure methods, response prevention, behavioral activation, and problem solving), relaxation training (RT) may be the most efficacious, and more cognitive approaches did not add additional benefit to those seen with RT. The authors concluded that RT is a brief intervention that brings rapid relief and appears to be acceptable to older adults. Moreover, it is a relatively simple technique that can be more easily taught to a variety of health practitioners than more complex CBT methods.

The literature with respect to the treatment of disorders other than GAD is patchy. For example, Böttche et al. (2012) noted the lack of randomized treatment studies for PTSD (Böttche et al. 2012). Of eight studies they reviewed, six were case series, and only one had a sample size greater than 10, but the authors concluded that cognitive and exposure approaches were promising. This was echoed by Clapp and Beck (2012), who described the course of therapy for three older adults who had experienced motor vehicle accidents, with elements that included graded exposure to avoided situations and cognitive processing of the traumatic incidents; they concluded that the therapy was both acceptable to older clients and effective (Clapp and Beck 2012). Another small study by Thorp et al. (2012) with 11 older veterans with PTSD compared 6 weeks of exposure therapy and found evidence of some superiority to treatment as usual (Thorp et al. 2012).

Similarly, there is a dearth of literature on the treatment of obsessive-compulsive disorder (OCD) in older adults (Carmin and Wiegartz 2000), which also relies heavily on case reports (e.g., Calamari et al. 2012; Price and Salsman 2010). The general consensus seems to be that treatment of OCD in older adults can be effective, but is also challenging, and needs to take into account relevant age-related factors, such as comorbid physical illness and the potential role of carers.

Virtually no studies have specifically targeted panic disorder or social anxiety. Rather, participants with these disorders may be included in a general treatment for anxiety (Schuurmans et al. 2006). One small uncontrolled study reported that ten sessions of CBT delivered over a 12-week period were effective at decreasing panic symptoms (Swales et al. 1996). Another larger study randomly allocated 49 older adults with confirmed diagnoses of panic disorder with agoraphobia to either a waiting list control, paroxetine 40 mg per day or individual CBT delivered in

14 weekly sessions of 50 min (Hendriks et al. 2012). CBT had greater benefit in reducing avoidance symptoms than paroxetine, particularly in those participants who had late onset of the disorder and a shorter duration of illness. The authors concluded that CBT may be preferable to medication for patients whose illness is of shorter duration, but medication may be more effective in those whose condition is long-standing.

Finally, mention should be made of fear of falling, a commonly occurring anxiety almost unique to older adults that does not map well onto existing DSM-5 anxiety categories (Bryant et al. 2013). Said to be the most commonly occurring fear of older adults, with a prevalence of up to 54% in community-dwelling older adults, including among person who have never sustained a fall (Howland et al. 1998), this fear is characterized by typical anxiety symptoms, such as physiological arousal when confronted by the feared situation and marked avoidance of such situations. The activity avoidance can lead to a disabling spiral of declining physical, social, and emotional functioning (Tennstedt et al. 1998). Most treatment programs take a physical rehabilitation approach, with an emphasis on increasing strength and balance (Jung et al. 2009), but attention should also be paid to the psychological aspects of the condition. A randomized control trial by Tennstedt et al. (1998) examined the efficacy of an eight-session group program that included psychoeducation, problem solving, and cognitive therapy with a focus on increasing self-efficacy; the control condition was a social support group. The intervention group reported increased mobility control at posttreatment; 12 months later, gains had declined, but participants still reported improvements in social functioning (Tennstedt et al. 1998). Psychologists can play an important role in the treatment of this condition, especially by working in collaboration with physical therapists in the rehabilitation setting. This is essential in order to provide an integrated approach to the physical and psychological aspects of fear of falling (Freiberger et al. 2012).

Implementing Treatment of Anxiety with CBT

As previously noted, CBT refers to a set of psychological modalities that focus on how unhelpful thinking patterns affect feelings and behavior. Accordingly, the treatment of anxiety with CBT typically uses a number of core elements, including cognitive therapy, which targets unhelpful or maladaptive beliefs, and relaxation training, which can be very beneficial for helping the anxious client to release tension and reduce stress (Ghaed et al. 2012). In addition to these general techniques, the therapist also needs to make an assessment of the nature of the anxiety disorder and target their treatment toward that (Laidlaw et al. 2003). Ghaed, Ayers, and Wetherell also emphasize the importance of taking enough time to explain the rationale for treatment to clients and making sure that they understand the basic elements of CBT.

The anxiety disorders can be broadly grouped into those that are fear-based (panic disorder, specific phobias, social anxiety, and agoraphobia) and GAD, which is characterized by excessive worry. A treatment for a phobia will typically include

elements of learning to reduce the physical symptoms of anxiety through relaxation training and trying to overcome the avoidance of feared situations that often develops as a way of preventing the experience of anxiety from occurring (Laidlaw et al. 2003). This is done through graded exposure; for example, a client who has developed social phobia would be encouraged to start by making a phone call to a friend or relative who is likely to respond positively to the call and slowly work up to more challenging situations, such as going to a coffee morning. It is also important to consider the thoughts that may underlie the avoidant behavior: for example, the older person may feel that they are no longer interesting to others and can then be helped to examine the evidence for whether this is the case or not and to find a more helpful way of thinking. Sometimes, the thoughts have a basis in reality, for example, if an older person with hearing loss fears not being able to keep up with conversations. In this instance, addressing the issue, for example, by encouraging a hearing test, would also be important.

GAD is the most prevalent of the anxiety disorders in older adults and may be precipitated by a wide range of factors, including prior trauma (Laidlaw et al. 2003) and poor coping strategies, feeling isolated, and stressful life events (Vink et al. 2008). Against that background, the older person may find themselves feeling overwhelmed, ruminating, possibly sleeping poorly, and caught in a spiral of negative mood, physical tension, and declining quality of life. Laidlaw et al. (2014) suggest that relaxation may be an effective tool to break this cycle and can be used to help the client to understand and manage the link between worry and physical tension. It is then also important to explore the origin, nature, and consequences of the worrying thoughts and to teach the client strategies for managing worry. These could include thought-stopping, questioning the importance and value of the thoughts, and challenging overestimation of the likelihood that feared scenarios will actually occur. Ghaed et al. further suggest that other techniques, such as addressing sleep hygiene, increasing pleasant events, and improving problem-solving skills, can also be beneficial (Ghaed et al. 2012). For more detailed information, the interested reader is referred to a helpful chapter by Ghaed and colleagues, which describes a potential 20-session treatment plan for an older person with GAD.

Strengths and Limitations of CBT Treatments for Anxiety

As noted, a number of reviews and meta-analyses have confirmed the efficacy of CBT for the treatment of late-life anxiety (e.g., Ayers et al. 2007; Gonçalves and Byrne 2012). For relatively young, healthy, and cognitively able people, it provides a short-term, focused therapy that can enhance skills and empower the older person to learn new ways of coping. Moreover, it may provide a valid alternative to drug treatments, especially benzodiazepines, which have potentially serious side effects for the older person (Glass et al. 2005).

Nevertheless, concerns remain that CBT appears to be less effective for older than younger adults and that the requirement for abstract thought places cognitive

demands that some clients may not be able to meet (Ghaed et al. 2012). Various cognitive skills, especially those related to abstract reasoning, attention, and cognitive flexibility, have emerged as predictors of treatment components and therapeutic outcome (Ayers et al. 2013; Johnco et al. 2014; Mohlman 2013; Mohlman et al. 2003). As a consequence, a number of researchers have attempted to improve the outcomes of CBT treatment by enhancing treatment protocols so that they take into account these potential cognitive challenges. For example, Mohlman and colleagues (2003) compared standard and "enhanced" CBT for GAD. Additional components that enhanced the therapy included the use of memory aids, visual methods of tracking progress, booster phone calls from the therapist, and a perspective-taking exercise to boost understanding of cognitive distortions. Participants in the enhanced condition showed greater reductions in worry and anxiety than the standard CBT group. Mohlman further tested the idea that one way of improving the response to CBT might be to enhance the cognitive capacities needed for engaging in the therapy (Mohlman 2008). Therefore, in a small pilot study, Mohlman tested the value of adding a component designed to strengthen attentional and executive skills in older patients with GAD through attention process training (APT) (Mohlman 2008). Participants were allocated either to eight 90-min weekly sessions of CBT or CBT/APT. The APT components included mental arithmetic exercises, a sustained auditory attention task, and an alternating visual attention task. The CBT/APT group showed a significant improvement in executive skills following the intervention, and worry reduced significantly more in participants in the CBT/ APT condition, compared to those in conventional CBT. Another approach to improving the efficacy of treatment for GAD was reported by Wetherell and colleagues, who developed a "modular" approach to treating GAD (Wetherell et al. 2011b). This small study entailed supplementing pharmacological treatment with a number of CBT components that were tailored to the individual needs of the participants, so that they received supplementary modules depending on their symptom profile. For example, patients who were depressed received a behavioral activation module, whereas patients reporting phobias received an extra module on exposure. The treatment resulted in full remission for most patients. The study adds to a small body of work that is testing more effective ways to treat anxiety in older adults.

In summary, CBT is a widely available psychological treatment for anxiety in older adults. While the literature provides some support for the efficacy of CBT (Andreescu and Varon 2015), the literature has a number of methodological shortcomings, including a preponderance of research conducted without control groups, failure to use demographically representative samples, and a strong focus on GAD (Gould et al. 2012). Some have suggested that it is less efficacious as a therapy for older adults than those who are younger (Nordhus and Pallesen 2003) and that the cognitive elements add little above the contribution of relaxation training (Thorp et al. 2009). Efforts to enhance the ability of older adults to benefit from CBT by teaching cognitive skills show some promise, but are still in their infancy (Mohlman 2013). Another reason for the somewhat disappointing efficacy of CBT may be because researchers have neglected the high comorbidity between anxiety and depression; treatments have targeted either anxiety or depression, but not both

(Gould et al. 2012). We turn, therefore, to a consideration of mixed anxiety and depression.

The Treatment of Mixed Anxiety and Depression

There have been extensive debates about qualitative differences in the presentation of mood disorders in older adults (Jeste et al. 2005; Mohlman et al. 2012a). It has been suggested that a presentation of mixed anxiety and depression is more common than "pure" depression or anxiety in this age group (Blazer et al. 1987) and that nearly one-quarter of depressed older adults have a concurrent anxiety disorder (Lenze et al. 2000). Schoevers et al. reported that the more severe the symptomatology of either, the greater the likelihood of comorbidity (Schoevers et al. 2003). Given the considerable impact of comorbid psychopathology on quality of life (Lenze et al. 2000) and healthcare costs (Vasiliadis et al. 2013), there is a striking lack of attention to the development of treatments that target comorbid anxiety and depression (Wuthrich et al. 2016). To remedy this, Wuthrich et al. conducted a randomized control trial to evaluate the efficacy of group CBT compared to an active control in the form of a nondirective discussion group; the sample comprised 133 older adults diagnosed with both anxiety and depression. Both groups undertook 12 2-h group sessions, from which dropout rates were low. Both conditions resulted in posttreatment reductions in scores on the GDS (Yesavage et al. 1983) and the GAI (Pachana et al. 2007). Those in the CBT condition experienced significantly greater improvements in the severity of their primary disorder, and 54% demonstrated recovery, compared to 24% in the discussion group. Although the gains were maintained at 6-month follow-up, the differences between the CBT and discussion group were no longer significant. Wuthrich et al. (2016) concluded that these results are consistent with other studies reporting benefit for psychological intervention for older adults and suggested that the nonspecific effects of group participation and interaction may be important ingredients in these outcomes.

Emerging Modalities for the Treatment of Anxiety and Depression

The explosion of interest in mindfulness-based therapies is gradually spreading to its application with older adults (Geiger et al. 2016). While these therapies are becoming better-established modalities for the treatment of both depression and anxiety in younger adults (Roemer and Orsillo 2007), their application to late-life anxiety is in its infancy. These approaches differ from CBT in their emphasis on tolerating uncomfortable feelings, seeing these as a normal part of human existence, rather than something to be challenged and replaced with more "adaptive" thought patterns, as they would be in traditional CBT. There is often a focus on developing a practice of mindful meditation and increasing engagement in meaningful life activities. It has been suggested that such an approach may be particularly suited to the

needs of older adults, as many age-related problems, such as declining health, functional impairment, and loss of family or friends, are not amenable to the control-oriented strategies promoted by traditional CBT (Petkus and Wetherell 2013; Wetherell et al. 2011a). Moreover, some of the developmental changes associated with aging, such as reevaluating priorities, reflecting on experience, and willingness to accept and experience the present moment, may provide a good match between the older person and mindfulness approaches (Geiger et al. 2016).

Acceptance and commitment therapy (ACT) is a mindfulness-based therapy that seeks to balance acceptance of thoughts and emotions with commitment to value-directed behavior change. The acceptance component includes mindfulness techniques designed to foster nonjudgmental awareness of experience, such as noticing thoughts without overengagement with or avoidance of thoughts. The goal of the therapy is to increase engagement with meaningful life activities (Hayes et al. 2006). A number of studies of ACT with older adults have now been published. For example, Wetherell and colleagues conducted a small pilot study comparing an ACT intervention to CBT for older adults (mean age 70.8) (Wetherell et al. 2011a). All participants had a primary diagnosis of GAD, and treatment comprised 12 weekly hour-long individual sessions of either ACT or CBT. The ACT protocol focused on values and goals clarification, with an emphasis on willingness to experience emotions, which the authors conceptualized as being primarily acceptance-based strategies, whereas the CBT protocol was focused on psychoeducation and techniques for altering thoughts and behaviors, seen as primarily change-based strategies. While both groups showed reductions in anxiety and depression, there were no dropouts from the ACT group, compared to 2 out 11 participants dropping out of the CBT group, perhaps suggesting that the ACT approach is more acceptable to older adults than CBT.

A much larger study of veterans with depression compared the outcomes of a 12–16-week ACT intervention for younger and older participants (aged >65) (Karlin et al. 2013). Two-thirds of the older participants completed to course, compared to three-quarters of the younger participants, but reductions in depressive symptoms as measured by the BDI (Beck et al. 1988) were substantial and similar to those achieved by the younger participants. A variation of mindfulness-based therapy known as MBCT (mindfulness-based cognitive therapy), which combines mindfulness with cognitive therapy techniques, was investigated as a treatment for depression by Smith et al. (2007) in a sample of 38 participants (mean age 70.5 years), of whom eight dropped out of treatment (Smith et al. 2007). There was no comparison group, but mean depression scores dropped at completion of the intervention and had fallen further at 1-year follow-up. An interesting feature of this study was a qualitative analysis of the participants' views about the intervention. This revealed that they placed high value on having developed greater awareness of themselves and on learning to adopt an attitude of acceptance toward themselves and on gaining greater control over what participants attended to (Smith et al. 2007).

This very preliminary evidence for a range of mindfulness-based approaches, including ACT, is based on a very small number of studies to date. Its proponents suggest that its focus on acceptance of emotions and experiences may make it

particularly suitable for older adults, and the qualitative data from the study by Smith et al. (2007) would appear to support that contention. Taken together with the concerns that CBT may not be as efficacious as we would like with older adults, especially for the treatment of anxiety, it maybe that this group of approaches holds great promise, once further studies have been undertaken (Gillanders and Laidlaw 2014).

Treatments for Carer Stress

It is well documented that caregiving by family members is an indispensible component of care provision for adults with mental and physical impairments (Coon et al. 2012). While some carers are able to find rewards, meaning, and satisfaction in this role (Brand et al. 2016; Quinn et al. 2012), it also an undoubtedly stressful role associated with high levels of physical illness, distress, anxiety, and depression. A systematic review of studies of anxiety prevalence in carers of a family member with dementia found that around one-quarter of all carers met criteria for an anxiety disorder, and this was associated with caregiver burden and coping skills (Cooper et al. 2007). Somewhat lower levels of depression of around 10.5% prevalence in carers have been reported (Mahoney et al. 2005), and these authors noted the particularly high prevalence of psychological symptoms in female carers. Importantly, high levels of distress are associated with moving to residential care facilities (Gaugler et al. 2013).

It is not surprising, then, that there is a substantial literature on interventions to address carer stress (Coon et al. 2012; Elvish et al. 2013). These can be grouped into those that primarily seek to provide psychoeducation and teach carers skills in managing difficult behaviors, those that primarily provide support and counselling, and those that are multicomponent and were systematically reviewed by Coon et al. (2012). A more recent review also identified a fourth category of intervention, namely, those that are technology based (Elvish et al. 2013). One of the earliest examples of a skill-building intervention designed primarily to reduce depression in carers was developed by Mary Mittelman and colleagues (1995). It comprised six individual and family sessions that provided role play and education, if necessary in the carer's home, about how to prevent problem patient behaviors, reduce the frequency and intensity of troublesome behaviors, and react more adaptively to challenging behaviors. Caregivers were encouraged to seek support from members of their social networks, and particularly from their families, and to seek medical attention for themselves when needed. At the end of the study, depression scores were stable in the intervention group, but had increased in the control group. Since then, other studies have suggested that education and skill-building interventions maintain levels of well-being, rather than necessarily being able to improve them (Elvish et al. 2013). In contrast, studies that have a more psychotherapeutic orientation, the majority of which use a CBT approach, may be more effective in reducing anxiety and depression scores (Coon et al. 2012; Elvish et al. 2013). Coon et al. suggest that this may be because these approaches often use highly trained therapists

and there is a direct link between the treatment approach and the aim of reducing symptoms. A recent example of a multicomponent intervention is the START (STrAtegies for RelaTives) program developed by Livingston and colleagues (Livingston et al. 2014). The primary outcome was total score on the HADS (Zigmond and Snaith 1983b), and participants were randomized to either eight individual sessions of a coping intervention delivered by supervised psychology graduates or treatment as usual. The intervention was based on one developed by Gallagher-Thompson and colleagues and included a range of CBT-derived elements, including relaxation, behavioral management, communication strategies, identification and changing of unhelpful thoughts, positive reframing, accessing emotional support, future planning, and increasing occurrence of pleasant events. Every session finished with a relaxation session using an individualized CD, which the participant was encouraged to use in between sessions. At the end of the intervention, and, importantly, up to 24 months later, the intervention group showed clinically significant declines in their total HADS scores and increases in measures of quality of life. Moreover, the authors reported that the intervention could be delivered with high treatment fidelity and was cost-effective (Livingston et al. 2014).

Elvish and colleagues noted the emergence of technology-based interventions to support carers (Elvish et al. 2013). All five studies reviewed used either smart phones or conventional telephones to deliver either counselling-based or psychoeducation-based interventions. The authors concluded that all the interventions demonstrated benefit with respect to depression, carer burden, and social support. The use of technology to deliver healthcare interventions is a rapidly growing field, and we turn now to a consideration of such technologies in the treatment of anxiety and depression in older adults.

Technology-Based Interventions for Anxiety and Depression

Another emerging modality is that of Internet-based interventions. One of the concerns frequently mentioned in relation to older adults is their relatively low uptake of psychological interventions (Gillanders and Laidlaw 2014), and stigma has been proposed as one reason for this. Interventions delivered through the Internet have the potential to overcome stigma and also reach people living in rural and remote areas who do not have easy access to psychological therapies (Titov 2011). There have, however, been only a few studies of Internet-delivered psychotherapy with older adults. Zou and colleagues carried out a pilot investigation ($N = 22$) of the acceptability of Internet-based treatment for GAD that included five lessons, homework tasks, additional resources, a discussion forum, and weekly telephone support from a psychologist (Zou et al. 2012). The lessons introduced basic CBT skills, such as education about the symptoms and treatment of anxiety, graded exposure, challenging unhelpful thoughts, and managing physical symptoms. The final lesson provided information about relapse prevention. Participants reported high levels of satisfaction with the program and reductions in anxiety and stress symptoms. A very recent study conducted by Titov and colleagues also randomly allocated

38 participants with a mean age of 64 to a waiting list or Internet-intervention group, using a five-lesson format, together with homework assignments and regular automated reminder and notification emails (Titov et al. 2015). More than 65% of the treatment group participants reported clinically reliable improvement and recovery in symptoms of depression at posttreatment, and these gains were sustained at 3-month and 12-month follow-up. Moreover, 80% of the participants were satisfied or very satisfied with the course. Titov et al. (2015) concluded that this intervention showed considerable promise and acceptability in this sample of relatively young older adults.

A larger study by Mewton and colleagues investigated the efficacy of a six-session Internet-based intervention designed to reduce stress, anxiety, and disability (Mewton et al. 2013) and targeted toward either depression, GAD, panic disorder, or social anxiety. Again, the components were largely CBT-based and included components such as psychoeducation, behavioral activation, cognitive restructuring, problem solving, graded exposure, relapse prevention, and assertiveness skills. Content was presented in the form of an illustrated story in which the character gains mastery over their symptoms with the help of a clinician. The patient followed the character's journey to recovery across the six lessons. At the end of each lesson, the patient downloaded "homework" tasks which reinforced the content of the lesson (Mewton et al. 2013). Of the 1,340 participants, 225 were aged between 65 and 75; these older participants were more likely to complete all six sessions than the younger age groups and showed an equally good response to the intervention.

There is a popular belief that online treatments may not be appropriate for older adults (Mewton et al. 2013). The current cohort of old-old adults (those over the age of 75) does use the Internet less than younger people, but the baby boomers are active computer users. Age-related issues, such as impairments in vision and cognition, may prevent the uptake of technology-based health interventions by some older adults, but the rapidly growing size of the aging population increases the need to investigate novel ways of delivering psychological interventions to older adults. Notably, the studies reviewed here all referred to their sessions as "lessons," and it may be that this is a more acceptable term for older adults than the term "therapy," which may imply psychological weakness. The majority of studies so far investigating the efficacy of Internet-delivered psychotherapy have not included older adults (Cuijpers et al. 2008). As a result, this field remains very much underresearched. The limited data to date, however, suggest that such interventions may be more acceptable and effective than had previously been thought (Titov et al. 2015).

Issues in the Provision of Psychological Therapies for Older Adults

The foregoing sections have given an overview of the wide variety of evidence-based therapies that are available for use with older adults. In the final section of this chapter, issues in relation to access to psychological services will be considered. There is conflicting evidence regarding the older adults' accessing of psychological

interventions: on the one hand, a body of literature indicates that older adults prefer to use talking therapies than medication (Gum et al. 2006; Mohlman 2012), yet other work attests to the difficulties that they have in accessing such services. For example, Chaplin et al. (2015) presented data from a national audit of the provision of psychological therapies in the UK (Chaplin et al. 2015). They found that older people were significantly underrepresented in the services: on the basis of demographic composition, and taking into account expected rates of psychiatric morbidity, the authors predicted that older adults should account for 13% of the records they audited, but in fact, they represented only 6.4%. In contrast, the older adults were more likely to complete treatment, more satisfied with the service they received, and had better outcomes in terms of symptom reduction, than clients of working age. The authors concluded that work needs to be aimed at increasing access for older adults and ensuring that psychological therapy services are provided on the basis of need rather than age (Chaplin et al. 2015).

If there are barriers to older adults receiving appropriate psychological intervention in high-income countries, these problems are far greater in low- and middle-income countries (LMICs). Patel et al. (2007) reported that only 1% of trials of mental health interventions (pharmacological and psychosocial) were carried out in low-income countries, and the authors made no mention of older adults (Patel et al. 2007). In most LMICs, provision of services is sparse, and staff are trained to a much lower level than expected in high-income countries. For example, 70% of the Chinese mental health workforce is educated to bachelor degree level or lower and receives no ongoing support or supervision (Gao et al. 2010). Some studies have suggested that psychological intervention may be ineffective in situations where poverty is extreme: Patel et al. (2003) found that six sessions of psychological intervention based on CBT did not reduce depression symptoms in a sample of 450 adults in Goa, India (Patel et al. 2003). The authors concluded that the life circumstances and problems faced by participants were often so severe that psychological treatment was unlikely to be of any value unless combined with a community-based social intervention to improve. A more hopeful example of psychological intervention has been developed in Chile, where employing psychologists in primary care and implementing a stepped-care model of depression treatment have been found to be effective in reducing rates of depression, even among women who experienced significant social adversity (Araya et al. 2003). It should be noted, however, that none of these examples focus on older adults, a disturbing observation, giving the rapidly aging population, in LMICs, as well as developed nations.

Conclusion

Older adults in both developed and less developed countries face considerable barriers to receiving appropriate psychological intervention for highly prevalent and disabling conditions, such as anxiety and depression. Such barriers range from stigma experienced by older adults themselves, lack of awareness of psychological

treatments on the part of primary care physicians, and potential difficulties in applying models of intervention that have largely been tested in Western countries. Nevertheless, there is good evidence for the efficacy of interpersonal and cognitive behavioral therapies for the treatment of depression, moderately good evidence for the efficacy of cognitive behavioral therapies for the treatment of anxiety, and good evidence for combined education and skill-building approaches for caregiver stress, and these therapies should be made available to older adults, especially in light of strong evidence that older adults themselves prefer these approaches to pharmacotherapy. Emerging modalities of Internet-based therapies show promise, but much more research needs to address the questions of how to make these therapies more effective, which is likely to involve refining our understanding of the nature of anxiety and depression in older adults. Moreover, psychological disorders do not arise in a vacuum, and psychological intervention cannot undo the effects of poverty and poor physical health. Ideally, psychological therapies should be part of a continuum of care that is embedded in a humane social system in which older people are valued and can receive the services they need.

Cross-References

- ▶ Anxiety in Late Life
- ▶ Dementia and Caregiving
- ▶ Depression in Late Life: Etiology, Presentation, and Management

References

Andreescu C, Reynolds CF (2011) Late-life depression: evidence-based treatment and promising new directions for research and clinical practice. Psychiatr Clin N Am 34(2):335–355

Andreescu C, Varon D (2015) New research on anxiety disorders in the elderly and an update on evidence-based treatments. Curr Psychiat Rep 17(7):1–7. doi:10.1007/s11920-015-0595-8

Araya R, Rojas G, Fritsch R, Gaete J, Rojas M, Simon G, Peters TJ (2003) Treating depression in primary care in low-income women in Santiago, Chile: a randomised controlled trial. Lancet 361(9362):995–1000. doi:10.1016/S0140-6736(03)12825-5

Arean PA, Perri MG, Nezu AM, Schein RL, Christopher F, Joseph TX (1993) Comparative effectiveness of social problem-solving therapy and reminiscence therapy as treatments for depression in older adults. J Consult Clin Psychol 61(6):1003

Areán PA, Gum A, McCulloch CE, Bostrom A, Gallagher-Thompson D, Thompson L (2005) Treatment of depression in low-income older adults. Psychol Aging 20(4):601

Ayers CR, Sorrell JT, Thorp SR, Wetherell JL (2007) Evidence-based psychological treatments for late-life anxiety. Psychol Aging 22(1):8

Ayers CR, Wetherell JL, Schiehser D, Almklov E, Golshan S, Saxena S (2013) Executive functioning in older adults with hoarding disorder. Int J Geriatr Psychiatry 28(11):1175–1181

Bahr S (2014) Reminiscence therapy. In: Pachana NA, Laidlaw K (eds) The Oxford handbook of clinical geropsychology. Oxfoed University Press, Oxford

Beck AT (2005) The current state of cognitive therapy: a 40-year retrospective. Arch Gen Psychiatry 62(9):953–959. doi:10.1001/archpsyc.62.9.953

Beck AT, Epstein N, Brown G, Steer RA (1988) An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 56(6):893
Beck AT, Steer RA, Brown GK (1996) Beck depression inventory-II. Psychological Corporation, San Antonio, pp 78204–72498
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 Ment Health 17(8):992–1002
Beshai S, Clark CM, Dobson KS (2013) Conceptual and pragmatic considerations in the use of cognitive-behavioral therapy with Muslim clients. Cogn Ther Res 37(1):197–206
Bierman E, Comijs H, Jonker C, Beekman A (2007) Symptoms of anxiety and depression in the course of cognitive decline. Dement Geriatr Cogn Disord 24(3):213–219
Blazer D, Hughes DC, George LK (1987) The epidemiology of depression in an elderly community population. The Gerontologist 27(3):281–287. doi:10.1093/geront/27.3.281
Böttche M, Kuwert P, Knaevelsrud C (2012) Posttraumatic stress disorder in older adults: an overview of characteristics and treatment approaches. Int J Geriatr Psychiatry 27(3):230–239. doi:10.1002/gps.2725
Brand C, Barry L, Gallagher S (2016) Social support mediates the association between benefit finding and quality of life in caregivers. J Health Psychol 21(6):1126–1136
Bryant C, Jackson H, Ames D (2008) The prevalence of anxiety in older adults: methodological issues and a review of the literature. J Affect Disord 109(3):233–250
Bryant C, Mohlman J, Gum A, Stanley M, Beekman AT, Wetherell JL, . . ., Lenze EJ (2013) Anxiety disorders in older adults: looking to DSM5 and beyond. . .. Am J Geriatr Psychiatry: Off J Am Assoc Geriatr Psychiatry 21(9):872
Butler RN (1963) The life review: an interpretation of reminiscence in the aged. Psychiatry 26(1):65–76
Calamari JE, Pontarelli NK, Armstrong KM, Salstrom SA (2012) Obsessive-compulsive disorder in late life. Cogn Behav Pract 19(1):136–150
Carmin CN, Wiegartz PS (2000) Successful and unsuccessful treatment of obsessive-compulsive disorder in older adults. J Contemp Psychother 30(2):181–193
Chaplin R, Farquharson L, Clapp M, Crawford M (2015) Comparison of access, outcomes and experiences of older adults and working age adults in psychological therapy. Int J Geriatr Psychiatry 30(2):178–184
Clapp JD, Beck JG (2012) Treatment of PTSD in older adults: do cognitive-behavioral interventions remain viable. Cogn Behav Pract 19(1):126–135. doi:10.1016/j.cbpra.2010.10.002
Coon D, Keaveny M, Valverde I, Dadvar S, Gallagher-Thompson D (2012) Evidence-based psychological treatments for distress in family caregivers of older adults. In: Scogin F, Shah A (eds) Making evidence-based psychological treatments work with older adults. American Psychological Association, Washington
Cooper C, Balamurali T, Livingston G (2007) A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. Int Psychogeriatr 19(02):175–195
Cuijpers P, van Straten A, Warmerdam L (2007) Problem solving therapies for depression: a meta-analysis. Eur Psychiatry 22(1):9–15
Cuijpers P, Van Straten A, Andersson G (2008) Internet-administered cognitive behavior therapy for health problems: a systematic review. J Behav Med 31(2):169–177
Cuijpers P, van Straten A, Smit F, Andersson G (2009) Is psychotherapy for depression equally effective in younger and older adults? A meta-regression analysis. Int Psychogeriatr 21(01):16–24
Cuijpers P, Geraedts AS, van Oppen P, Andersson G, Markowitz JC, van Straten A (2011) Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatr 168(6):581–592. doi:10.1176/appi.ajp.2010.10101411
Cuijpers P, Karyotaki E, Pot AM, Park M, Reynolds CF III (2014) Managing depression in older age: psychological interventions. Maturitas 79(2):160–169. doi:10.1016/j.maturitas.2014.05.027
Davenhill R (2008) Psychoanalysis and old age. In: Woods RT, Clare L (eds) Handbook of the clinical psychology of ageing. Wiley, Chichester

Doubleday EK, King P, Papageorgiou C (2002) Relationship between fluid intelligence and ability to benefit from cognitive-behavioural therapy in older adults: a preliminary investigation. Br J Clin Psychol 41(4):423–428
Elvish R, Lever S-J, Johnstone J, Cawley R, Keady J (2013) Psychological interventions for carers of people with dementia: a systematic review of quantitative and qualitative evidence. Couns Psychother Res 13(2):106–125
Fredriksen-Goldsen KI, Emlet CA, Kim H-J, Muraco A, Erosheva EA, Goldsen J, Hoy-Ellis CP (2013) The physical and mental health of Lesbian, Gay Male, and Bisexual (LGB) older adults: the role of key health indicators and risk and protective factors. The Gerontologist 53(4):664–675. doi:10.1093/geront/gns123
Freiberger E, Häberle L, Spirduso WW, Rixt Zijlstra GA (2012) Long-term effects of three multicomponent exercise interventions on physical performance and fall-related psychological outcomes in community-dwelling older adults: a randomized controlled trial. J Am Geriatr Soc 60(3):437–446. doi:10.1111/j.1532-5415.2011.03859.x
Freud S (1898) Sexuality in the aetiology of the neuroses. White Press, 2014, ISBN 1473319951
Gallo JJ, Rabins PV, Lyketsos CG, Tien AY, Anthony JC (1997) Depression without sadness: functional outcomes of nondysphoric depression in later life. J Am Geriatr Soc 45(5):570–578
Gao X, Jackson T, Chen H, Liu Y, Wang R, Qian M, Huang X (2010) There is a long way to go: a nationwide survey of professional training for mental health practitioners in China. Health Policy 95(1):74–81
Gaugler JE, Reese M, Mittelman MS (2013) Effects of the NYU caregiver intervention-adult child on residential care placement. The Gerontologist 53(6):985–997. doi:10.1093/geront/gns193
Geiger PJ, Boggero IA, Brake CA, Caldera CA, Combs HL, Peters JR, Baer RA (2016) Mindfulness-based interventions for older adults: a review of the effects on physical and emotional well-being. Mindfulness 7(2):296–307
Ghaed S, Ayers CR, Wetherell J (2012) Evidence-based psychological treatments for geriatirc anxiety. In: Scogin F, Shah A (eds) Making evidence-based psychological treatments work with older adults. American Psychological Association, Washington
Gillanders D, Laidlaw K (2014) ACT and CBT in older age. In: Pachana NA, Laidlaw K (eds) The Oxford handbook of clinical geropsychology. Oxford University Press, Oxford
Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE (2005) Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 331(7526):1169
Gonçalves DC, Byrne GJ (2012) Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. J Anxiety Disord 26(1):1–11
Gonçalves DC, Guedes J, Fonseca AM, Pinto FC, Martín I, Byrne GJ, Pachana NA (2011) Attitudes, knowledge, and interest: preparing university students to work in an aging world. Int Psychogeriatr 23(02):315–321
Gorenstein EE, Papp LA (2007) Cognitive-behavioral therapy for anxiety in the elderly. Curr Psychiatry Rep 9(1):20–25
Gould RL, Coulson MC, Howard RJ (2012) Efficacy of cognitive behavioral therapy for anxiety disorders in older people: a meta-analysis and meta-regression of randomized controlled trials. J Am Geriatr Soc 60(2):218–229
Gum AM, Areán PA, Hunkeler E, Tang L, Katon W, Hitchcock P, …, Investigators I (2006) Depression treatment preferences in older primary care patients. Gerontologist 46(1):14–22
Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23(1):56–62
Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J (2006) Acceptance and commitment therapy: model, processes and outcomes. Behav Res Ther 44(1):1–25
Hendriks G, Oude Voshaar R, Keijsers G, Hoogduin C, Van Balkom A (2008) Cognitive-behavioural therapy for late-life anxiety disorders: a systematic review and meta-analysis. Acta Psychiatr Scand 117(6):403–411
Hendriks GJ, Keijsers GP, Kampman M, Hoogduin CA, Oude Voshaar RC (2012) Predictors of outcome of pharmacological and psychological treatment of late-life panic disorder with agoraphobia. Int J Geriatr Psychiatry 27(2):146–150

Hinrichsen GA (2008) Interpersonal psychotherapy as a treatment for depression in later life. Prof Psychol: Res Pract 39(3):306
Hinrichsen G, Iselin M-G (2014) Interpersonal therapy of the treatment of late-life depression. In: Pachana NA, Laidlaw K (eds) The Oxford handbook of clinical greopsychology. Oxford University Press, Oxford
Hodges J, Oei TP (2007) Would Confucius benefit from psychotherapy? The compatibility of cognitive behaviour therapy and Chinese values. Behav Res Ther 45(5):901–914
Howland J, Lachman ME, Peterson EW, Cote J, Kasten L, Jette A (1998) Covariates of fear of falling and associated activity curtailment. The Gerontologist 38(5):549–555
Jeste DV, Blazer DG, First M (2005) Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients. Biol Psychiatry 58(4):265–271
Johnco C, Wuthrich V, Rapee R (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. Behav Res Ther 57:55–64
Johnstone L, Dallos R (2013) Formulation in psychology and psychotherapy: making sense of people's problems. Routledge, New York
Jung D, Lee J, Lee S-M (2009) A meta-analysis of fear of falling treatment programs for the elderly. West J Nurs Res 31(1):6–16
Karel MJ, Gatz M, Smyer MA (2012) Aging and mental health in the decade ahead: what psychologists need to know. Am Psychol 67(3):184
Karlin BE, Walser RD, Yesavage J, Zhang A, Trockel M, Taylor CB (2013) Effectiveness of acceptance and commitment therapy for depression: comparison among older and younger veterans. Aging Ment Health 17(5):555–563
Kaye L, Crittenden J, Charland J (2008) Invisible older men: what we know about older men's use of healthcare and social services. Generations 32(1):9–14
Kessler E-M, Agines S, Bowen CE (2015) Attitudes towards seeking mental health services among older adults: personal and contextual correlates. Aging Ment Health 19(2):182–191
Knight BG, Pachana NA (2015) Psychological assessment and therapy with older people. Oxford University Press, Oxford
Knight BG, Poon CY (2008) Contextual adult life span theory for adapting psychotherapy with older adults. J Ration Emot Cogn Behav Ther 26(4):232–249
Koder D-A (1998) Treatment of anxiety in the cognitively impaired elderly: can cognitive-behavior therapy help? Int Psychogeriatr 10(02):173–182
Koenig HG, Pearce MJ, Nelson B, Shaw SF, Robins CJ, Daher NS, . . ., King MB (2015) Religious vs. conventional cognitive behavioral therapy for major depression in persons with chronic medical illness: a pilot randomized trial. J Nerv Ment Dis 203(4):243–251. doi:10.1097/nmd.0000000000000273
Korte J, Bohlmeijer E, Cappeliez P, Smit F, Westerhof G (2012) Life review therapy for older adults with moderate depressive symptomatology: a pragmatic randomized controlled trial. Psychol Med 42(06):1163–1173
Laidlaw K, Thompson L (2014) Cognitive-behaviour therapy with older people. In: Pachana NA, Laidlaw K (eds) The Oxford handbook of clinical geropsychology. Oxford University Press, Oxford
Laidlaw K, Thompson L, Dick-Siskin L, Gallagher-Thompson D (2003) Cogntive-behaviour therapy with older people. Wiley, Chichester
Lenze EJ, Mulsant BH, Shear MK, Schulberg HC, Dew MA, Begley AE, . . ., Reynolds CF, I (2000) Comorbid anxiety disorders in depressed elderly patients. Am J Psychiatry 157(5):722–728. doi:10.1176/appi.ajp.157.5.722
Lenze EJ, Hickman S, Hershey T, Wendleton L, Ly K, Dixon D, . . ., Wetherell JL (2014) Mindfulness-based stress reduction for older adults with worry symptoms and co-occurring cognitive dysfunction. Int J Geriatr Psychiatry 29(10):991–1000
Livingston G, Barber J, Rapaport P, Knapp M, Griffin M, King D, . . ., Walker Z (2014) Long-term clinical and cost-effectiveness of psychological intervention for family carers of people with dementia: a single-blind, randomised, controlled trial. Lancet Psychiatry 1(7):539–548

Logsdon RG, McCurry SM, Teri L (2007) Evidence-based interventions to improve quality of life for individuals with dementia. Alzheimer's Care Today 8(4):309
Mahoney R, Regan C, Katona C, Livingston G (2005) Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. Am J Geriatr Psychiatry 13(9):795–801
Mewton L, Sachdev PS, Andrews G (2013) A naturalistic study of the acceptability and effectiveness of internet-delivered cognitive behavioural therapy for psychiatric disorders in older Australians. PLoS ONE 8(8):e71825
Mittelman MS, Ferris SH, Shulman E, Steinberg G, Ambinder A, Mackell JA, Cohen J (1995) A comprehensive support program: effect on depression in spouse-caregivers of AD patients. The Gerontologist 35(6):792–802. doi:10.1093/geront/35.6.792
Mohlman J (2008) More power to the executive? A preliminary test of CBT plus executive skills training for treatment of late-life GAD. Cogn Behav Pract 15(3):306–316
Mohlman J (2012) A community based survey of older adults' preferences for treatment of anxiety. Psychol Aging 27(4):1182
Mohlman J (2013) Executive skills in older adults with GAD: relations with clinical variables and CBT outcome. J Anxiety Disord 27(1):131–139
Mohlman J, Gorenstein EE, Kleber M, de Jesus M, Gorman JM, Papp LA (2003) Standard and enhanced cognitive–behavior therapy for late-life generalized anxiety disorder: two pilot investigations. Am J Geriatr Psychiatry 11(1):24–32
Mohlman J, Bryant C, Lenze EJ, Stanley MA, Gum A, Flint A, . . ., Craske MG (2012a) Improving recognition of late life anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders: observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. Int J Geriatr Psychiatry 27(6):549–556
Mohlman J, Sirota KG, Papp LA, Staples AM, King A, Gorenstein EE (2012b) Clinical interviewing with older adults. Cogn Behav Pract 19(1):89–100
NICE. (2013). The NICE guideline on the treatment and management of depression in adults: 1–707. Retrieved from
Nordhus IH, Pallesen S (2003) Psychological treatment of late-life anxiety: an empirical review. J Consult Clin Psychol 71(4):643
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. Br J Psychiatry 207(4):293–298. doi:10.1192/bjp.bp.114.148130
Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E (2007) Development and validation of the geriatric anxiety inventory. Int Psychogeriatr 19(01):103–114
Patel V, Chisholm D, Rabe-Hesketh S, Dias-Saxena F, Andrew G, Mann A (2003) Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: a randomised, controlled trial. Lancet 361(9351):33–39
Patel V, Araya R, Chatterjee S, Chisholm D, Cohen A, De Silva M, . . ., van Ommeren M (2007) Treatment and prevention of mental disorders in low-income and middle-income countries. Lancet 370(9591):991–1005
Petkus AJ, Wetherell JL (2013) Acceptance and commitment therapy with older adults: rationale and considerations. Cogn Behav Pract 20(1):47–56
Pinquart M, Duberstein PR (2007) Treatment of anxiety disorders in older adults: a meta-analytic comparison of behavioral and pharmacological interventions. Am J Geriatr Psychiatry 15(8):639–651
Pinquart M, Duberstein P, Lyness J (2007) Effects of psychotherapy and other behavioral interventions on clinically depressed older adults: a meta-analysis. Aging Ment Health 11(6):645–657
Price MC, Salsman NL (2010) Exposure and response prevention for the treatment of late-onset obsessive-compulsive disorder in an 82-year-old man. Clin Case Stud 9(6):426–441
Quinn C, Clare L, McGuinness T, Woods RT (2012) The impact of relationships, motivations, and meanings on dementia caregiving outcomes. Int Psychogeriatr 24(11):1816–1826

Reynolds RC, Frank E, Perel JM, Imber SD, Cornes C, Morycz RK, . . ., Rifai AH (1992) Combined pharmacotherapy and psychotherapy in the acute and continuation treatment of elderly patients with recurrent major depression: a preliminary report. Am J Psychiatry 149:1687–1687

Reynolds CR, Frank E, Houck PR, Mazumdar S, Dew MA, Cornes C, . . ., Kupfer DJ (1997) Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? Am J Psychiatry 154(7):958–962

Reynolds IC, Frank E, Perel JM 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(1):39–45. doi:10.1001/jama.281.1.39

Reynolds CF III, Alexopoulos GS, Katz IR, Lebowitz BD (2001) Chronic depression in the elderly. Drugs Aging 18(7):507–514

Roemer L, Orsillo SM (2007) An open trial of an acceptance-based behavior therapy for generalized anxiety disorder. Behav Ther 38(1):72–85

Schoevers R, Beekman A, Deeg D, Jonker C, Tilburg W v (2003) Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression in later life: results from the AMSTEL study. Int J Geriatr Psychiatry 18(11):994–1001

Schuurmans J, Comijs H, Emmelkamp PM, Gundy CM, Weijnen I, Van Den Hout M, Van Dyck R (2006) A randomized, controlled trial of the effectiveness of cognitive–behavioral therapy and sertraline versus a waitlist control group for anxiety disorders in older adults. Am J Geriatr Psychiatry 14(3):255–263

Scogin F, McElreath L (1994) Efficacy of psychosocial treatments for geriatric depression: a quantitative review. J Consult Clin Psychol 62(1):69

Scogin F, Shah A (2012) Making evidence-based psychological treatments work with older adults. American Psychological Associaiton, Washington, DC

Scogin F, Welsh D, Hanson A, Stump J, Coates A (2005) Evidence-based psychotherapies for depression in older adults. Clin Psychol Sci Pract 12(3):222–237

Shah A, Scogin F, Floyd M (2012) Evidence-based psychological treatments for geriatric depression. In: Scogin F, Shah A (eds) Making evidence-based psychological treatments work with older adults. American Psychological Association, Washington, DC

Shankar KK, Walker M, Frost D, Orrell MW (1999) The development of a valid and reliable scale for rating anxiety in dementia (RAID). Aging Ment Health 3(1):39–49. doi:10.1080/13607869956424

Sinoff G, Ore L, Zlotogorsky D, Tamir A (1999) Short anxiety screening test – a brief instrument for detecting anxiety in the elderly. Int J Geriatr Psychiatry 14(12):1062–1071

Smith A, Graham L, Senthinathan S (2007) Mindfulness-based cognitive therapy for recurring depression in older people: a qualitative study. Aging Ment Health 11(3):346–357

Stanley MA, Beck JG, Novy DM, Averill PM, Swann AC, Diefenbach GJ, Hopko DR (2003) Cognitive-behavioral treatment of late-life generalized anxiety disorder. J Consult Clin Psychol 71(2):309

Swales PJ, Solfvin JF, Sheikh JI (1996) Cognitive-behavioral therapy in older panic disorder patients. Am J Geriatr Psychiatry 4(1):46–60. doi:10.1097/00019442-199624410-00006

Tennstedt S, Howland J, Lachman M, Peterson E, Kasten L, Jette A (1998) A randomized, controlled trial of a group intervention to reduce fear of falling and associated activity restriction in older adults. J Gerontol Ser B Psychol Sci Soc Sci 53(6):P384–P392

Teri L, Logsdon RG, Uomoto J, McCurry SM (1997) Behavioral treatment of depression in dementia patients: a controlled clinical trial. J Gerontol Ser B Psychol Sci Soc Sci 52B(4): P159–P166. doi:10.1093/geronb/52B.4.P159

Thorp SR, Ayers CR, Nuevo R, Stoddard JA, Sorrell JT, Wetherell JL (2009) Meta-analysis comparing different behavioral treatments for late-life anxiety. Am J Geriatr Psychiatry 17(2):105–115

Thorp SR, Stein MB, Jeste DV, Patterson TL, Wetherell JL (2012) Prolonged exposure therapy for older veterans with posttraumatic stress disorder: a pilot study. Am J Geriatr Psychiatry 20(3):276–280. doi:10.1097/JGP.0b013e3182435ee9

Titov N (2011) Internet-delivered psychotherapy for depression in adults. Curr Opin Psychiatry 24(1):18–23. doi:10.1097/YCO.0b013e32833ed18f

Titov N, Dear BF, Ali S, Zou JB, Lorian CN, Johnston L, . . ., Fogliati VJ (2015) Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. Behav Ther 46(2):193–205. doi:10.1016/j.beth.2014.09.008

Unützer J, Katon W, Callahan CM, Williams JW Jr, Hunkeler E, Harpole L, . . ., Lin EH (2002) Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 288(22):2836–2845

Vasiliadis H-M, Dionne P-A, Préville M, Gentil L, Berbiche D, Latimer E (2013) The excess healthcare costs associated with depression and anxiety in elderly living in the community. Am J Geriatr Psychiatry 21(6):536–548. doi:10.1016/j.jagp.2012.12.016

Vink D, Aartsen MJ, Schoevers RA (2008) Risk factors for anxiety and depression in the elderly: a review. J Affect Disord 106(1):29–44

Wetherell JL, Kaplan RM, Kallenberg G, Dresselhaus TR, Sieber WJ, Lang AJ (2004) Mental health treatment preferences of older and younger primary care patients. Int J Psychiatry Med 34 (3):219–233. doi:10.2190/qa7y-tx1y-wm45-kgv7

Wetherell JL, Liu L, Patterson TL, Afari N, Ayers CR, Thorp SR, . . ., Sorrell JT (2011a) Acceptance and commitment therapy for generalized anxiety disorder in older adults: a preliminary report. Behav Ther 42(1):127–134

Wetherell JL, Stoddard JA, White KS, Kornblith S, Nguyen H, Andreescu C, . . ., Lenze EJ (2011b) Augmenting antidepressant medication with modular CBT for geriatric generalized anxiety disorder: a pilot study. Int J Geriatr Psychiatry 26(8):869–875

Wilson K, Mottram P, Vassilas C (2007) Psychotherapeutic treatments for older depressed people. Cochrane Database Syst Rev 1:CD004853

Wuthrich V, Rapee R, Kangas M, Perini S (2016) Randomized controlled trial of group cognitive behavioral therapy compared to a discussion group for co-morbid anxiety and depression in older adults. Psychol Med 46(04):785–795

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO (1983) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17 (1):37–49

Yohannes AM, Baldwin RC, Connolly MJ (2000) Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. Int J Geriatr Psychiatry 15(12):1090–1096

Zigmond AS, Snaith RP (1983a) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370

Zigmond AS, Snaith RP (1983b) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370

Zou JB, Dear BF, Titov N, Lorian CN, Johnston L, Spence J, . . ., Sachdev P (2012) Brief internet-delivered cognitive behavioral therapy for anxiety in older adults: a feasibility trial. J Anxiety Disord 26(6):650–655

Dementia and Caregiving

21

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Abstract

In the absence of effective options, interpersonal and environmental management provided by carers forms the foundation of dementia care. Much is known about carers, those family members providing care for someone in their family with dementia, but a comprehensive understanding of their assessment, journey through the stages of caregiving, self-perception, and definition of their own needs is lacking. To ensure carers can engage fully in providing dementia care, carers must be supported and sustained. This chapter will describe current evidence for understanding family carers in dementia and highlight key components of a suite of evidence-informed innovative programs and interventions. Carers deserve to be a consistent target of specific systematic assessment and care, and it can be said that the care of carers is a necessary component of the system of care of individuals with dementia. There are proven interventions for carers that address carer needs and can be brought to scale and disseminated. One

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_22

such intervention is the Reitman Centre CARERS Program. Carers are the focus of the program with the goal of equipping them with specific skills and knowledge, including problem solving and communication techniques, to sustain them in their difficult and unfamiliar role. Looking after family carers by maximizing their abilities and minimizing their burden will ensure that they are able to be full partners in the care of patients with dementia.

Keywords

Dementia • Informal carers • Caregiver burden • High-risk carer • Working carer

Contents

Introduction

As the world's population ages, the prevalence of dementia and the demand for dementia care are increasing (Alzheimer's Disease International 2015). The formal health-care system has responded by developing a variety of specialized interventions and services to deliver timely and appropriate dementia care. Unfortunately, current interventions for dementia are only modestly effective. Furthermore, even if a comprehensive dementia care system could be developed, paid care, whether provided by the state or privately purchased, could not meet demand and would be too expensive to be considered as anything other than supplementary (Canadian Home Care Association 2013; Health Council of Canada 2012). In the absence of effective, sustainable options, the interpersonal and environmental management provided by members of the patient's family forms the foundation of dementia care. Much is known about these family carers, who they are, what they do, and

their value and vulnerabilities, but less is known about their assessment, their journey through the stages of caregiving, their self-perception, and definition of their own needs. It is essential that these gaps be closed to ensure that carers are supported and sustained and able to engage fully in the provision of dementia care. Failure to do so will lead to carer burnout, societal and systemic burden, and unmet dementia care needs. Carers have been the focus of a significant body of research as their vulnerability and their central role in dementia management and the health-care system have been increasingly recognized by clinicians and policymakers alike. This chapter will describe the current evidence base for understanding and addressing family carers in dementia and then describe an evidence-informed innovative comprehensive model of carer services developed at the Cyril & Dorothy, Joel & Jill Reitman Centre for Alzheimer's Support and Training ("Reitman Centre"). The creation of the center was made possible through the generosity of the Reitman family who provided a private endowment in 2008. Since then, it has been sustained by competitive federal and provincial government, research, and project grants. Beginning with a focus on innovative, evidence-based clinical interventions for carers, the center went on to establish itself as a leading academic center for comprehensive care of carers comprised of a comprehensive clinical center, a training institute for professionals, an academic research center in caregiving, and a center for policy initiatives and system development.

Carers in Dementia: Definition

No one term has been universally endorsed to identify family members providing care for someone in their family with dementia. Various terms have been suggested such as care partner, caregiver, and carer. In this chapter, family members providing care for someone with dementia will be referred to as "carer." Similarly, the family member with dementia has been variously described, commonly referred to as "loved one." However, as those who work with carers know, the person receiving care is not always loved, given the conflict that is inevitable in some family relationships. Hence, in this chapter we will refer to those being cared for as family members with dementia or care recipients.

The first task in creating a picture of family carers may lie in the label "carer" and its definition. A definition is essential to frame the discussion and delineate the range of carers' needs. Various definitions exist in the literature, but when formulating a definition, it is often wise to consult those concerned for guidance as to how they would define themselves. That approach is challenging since family members do not often identify themselves as "carer" but rather think of themselves as spouse or child. Further, who a carer is and how they see themselves are not fixed but rather evolve as the carer transitions through the stages of caregiving. A simple definition is used for the following discussion and comes from the Health Council of Canada (2012) who defines carers as, "family members, friends, or others who are providing unpaid care."

Carers provide needed support to family members, often for age-related challenges or for specific illnesses like dementia, cardiovascular disease, or cancer

(Sinha 2013; National Alliance for Caregiving 2015). Though men are engaged in caregiving in increasing numbers, women are more intensively involved, making up the majority of carers and devoting more time to caregiving than their male counterparts (Hoff 2015; National Alliance for Caregiving 2015; Sinha 2013). A significant portion of carers fall in the 45–64-year age range with those in this group most often providing care to their aging parents (or parents-in-law) (Carers 2016; National Alliance for Caregiving 2015; Sinha 2013). Carers in this age group are often also engaged in paid employment and may be caring for children (Carers 2016; Sinha 2013). The number of individuals aged 65 years and older providing care is growing as the population ages, and spouses assume care for frail partners (Hoff 2015; Sinha 2013; Turcotte 2013). Older carers often provide more intense live-in caregiving devoting more hours per week for a longer duration than younger or non-spouse carers (Carers 2016; CIHI 2010; Sinha 2013). In addition, older carers are more likely to be the only one supporting the care recipient (National Alliance for Caregiving 2015). This group is particularly vulnerable because they may be experiencing health problems of their own (CIHI 2010; Sinha 2013). Furthermore, being a spouse rather than another relative can make the caregiving more stressful (CIHI 2010; IPA 2002). Carers of all ages often feel they have no choice in whether they take on caregiving responsibilities (National Alliance for Caregiving 2015) and frequently feel unprepared for their new role (National Alliance for Caregiving 2015).

Family carers perform a number of essential tasks (CIHI 2010; Hollander et al. 2009; Lund 2005; National Alliance for Caregiving 2015; Sinha 2013) including helping with basic activities of daily living such as eating, bathing, and dressing and more complex or instrumental activities of daily living such as managing home finances, household repairs, transportation, and maintenance of safety. Beyond these more practical concerns, carers also provide emotional support (Baumgarten et al. 1992) and serve as advocates for care recipients within the health-care system, identifying needed services and recruiting professional and other help as required (Lund 2005; National Alliance for Caregiving 2015).

The practical and emotional support family carers provide has enormous value to their individual family member, helping to preserve function, promote dignity, and ensure safety. In dementia, family involvement is associated with benefits for the care recipient including better psychological and psychosocial well-being (McCallion et al. 1999) and higher patient life satisfaction (Mitchell and Kemp 2000). In addition, the care families provide can allow those with dementia living in the community to age at home rather than rely on institutional care (Cranswick and Dosman 2008; Mittelman et al. 2006; Spurlock 2005). Furthermore, carers themselves, at least initially, often express satisfaction with their work and are generally quite ready to accept their new role (Cohen et al. 2002; Kramer 1997).

Beyond the benefits derived within the individual family, the vital work performed by family carers has enormous economic value, even if it tends to occur invisibly, without recognition of its value to the entire community. The annual replacement or imputed cost of the care provided by family members is estimated to be at least £87 billion in the United Kingdom (Buckner and Yeandle 2015), US$450 billion in the United States (Reinhard et al. 2015), A$60.3 billion in Australia

(Deloitte Access Economics Pty Limited 2005), and Cdn$26 billion in Canada (Hollander et al. 2009). In the United Kingdom, it is estimated that the economic value of care provided by informal carers is approaching the amount spent annually in the formal health-care system (Buckner and Yeandle 2015). Increasingly, family carers provide services that the system could not otherwise afford and does not have the capacity to deliver, not only in terms of practical clinical support but, less tangibly, in terms of the familiarity, love warmth, and sense of safety that predominantly resides in family relationships. Therefore, all of society benefits from their work.

Carer's Role in the System of Dementia Care: The Carer-Care Recipient Dyad

Given the primary role that carers play in the system of dementia care, it can be said that dementia cannot be managed without consideration of the needs of both the individual with the disease and the carer: the carer-care recipient dyad (Sadavoy and Wesson 2012). Adoption of the dyadic model requires a shift in focus to include the carer as a primary target of assessment and interventions whose unique and specific needs must be acknowledged, diagnosed, and addressed. Carers are a heterogeneous population whose needs, roles, and responsibilities vary in substance and complexity. An expanded model of carer assessment that encompasses both the carer and the carer-care recipient dyad is necessary to adequately capture this complexity (Sadavoy and Wesson 2012). The assessment approach described below was developed at the Cyril & Dorothy, Joel & Jill Reitman Centre for Alzheimer's Support and Training in the geriatric psychiatry program of the Sinai Health System, Toronto, a clinical unit that provides evidence-based assessments and interventions for carers looking after someone with dementia.

Systematic Clinical Assessment of Family Carers

The comprehensive clinical assessment of carers must include many of the standard components of a psychiatric assessment including consideration of personal, medical, and psychiatric history and treatments. The carer should be thought of as an individual, not simply a provider of care or source of collateral information about the care recipient. Thus, it is essential to gain an appreciation of them as a person through the taking of a careful personal history. Medical history is important in a thorough assessment, too, as caregiving appears to increase susceptibility to physical disease. Carers are known to have poorer physical health and a higher prevalence of physical symptoms than their peers who are not carers (Baumgarten et al. 1992; Hooker et al. 1992; Pruchno and Resch 1989). They visit their doctors more frequently and have higher rates of prescription drug use (Katon et al. 1982), report poorer subjective ratings of health particularly when providing many hours of care (National Alliance on Caregiving 2015; Schulz et al. 1995; Sinha 2013), can have

compromised immune function (Kiecolt-Glaser et al. 1987), and may experience exacerbation of pre-existing medical conditions such as diabetes, hypertension, and other cardiovascular diseases.

An exploration of the carer's mental health is also important to bring to light areas where the carer may be vulnerable in their new role. Carers frequently feel stressed (National Alliance on Caregiving 2015; Sinha 2013) and suffer higher rates of depression and psychiatric drug use than their peers (Alspaugh et al. 1999; Baumgarten et al. 1992; Schulz et al. 1995). They are more likely to suffer a relapse of pre-existing psychiatric illness (Brown et al. 1990; Burns and Rabins 2000) and to use substances such as alcohol more often than is usual in the general population (Saad et al. 1995). Stress is higher for carers who provide more intense caregiving and who perceive that they had no choice in assuming the role of carer (National Alliance on Caregiving 2015).

The assessment of the carer must go beyond the basic elements of a standard psychiatric assessment to include factors which are known to impact carer well-being and ability to successfully perform the caregiving role. Both the carer and the caregiving experience are influenced by factors such as location, culture, and socio-economic conditions that are external and not unique to the particular carer. More significant are those internal qualities unique to the individual carer such as their resilience, coping style, self-confidence, and knowledge of dementia and emotional factors such as their guilt, shame, and grief. "Immature" coping skills such as emotion based coping and high levels of negative affect such as criticism and hostility diminish the carer's effectiveness and ability to manage caregiving tasks (Brodaty 1996; Donaldson et al. 1998; Dunkin and Anderson-Hanley 1998; IPA 2002; Vitaliano et al. 1993). Consideration of all of these carer qualities plus an understanding of the carer-care recipient relationship must form the basis of the systematic assessment of the carer. Key domains of assessment, as developed for the Reitman Centre assessment protocol, are outlined in Table 1.

Careful carer assessment is critical for reasons beyond understanding the carer and ensuring their needs are known and addressed. The carer of the person with dementia faces challenges distinct from those experienced by carers in other chronic illnesses. The assessment must consider factors that might impair the carer and make it difficult for her to continue to perform her role. Caregiving is a difficult job that requires significant changes and accommodation by carers, including changes in the roles they play in relationships with the person they are caring for and others within and beyond the family (Table 2) (Perel 1998). Further, caregiving is not static and requires that carers be flexible in order to adapt to the progression of the disease. As a result, carers are a vulnerable group at high risk for both psychological and physical problems associated with providing care. The constellation of problems carers encounter has been given the name caregiver burden, that is, the physical, psychological, social, and financial hardships experienced by carers providing care to someone with dementia (George and Gwyther 1986; Spurlock 2005; Zarit et al. 1980). Caregiver burden is not an insignificant problem, and it is very unusual for carers not to report significant and growing feelings of burden as they encounter the evolving and escalating challenges of dealing with dementia over many years.

Table 1 Domains of carer assessment

Domain	Key information to be obtained
Medical	Current physical health
	Illness history
	Medication use
Psychiatric	Current mental health
	Psychiatric history especially depression, anxiety, and trauma
	Psychiatric treatment
Personal history	Developmental history
	Personal goals and expectations
	Interpersonal functioning and relationships
	Management of prior grief and loss
Knowledge and understanding of dementia	Confirmation of dementia diagnosis
	When made
	By whom
	Beliefs about dementia
	Emotional reaction to diagnosis and BPSD
	Culturally determined attitudes to dementia
	Stigma
Carer-care recipient relationship	Spouse versus child
	Current relationship
	Relationship history
	Overt and psychological conflict
	Past and present
	Intensity/proximity
	Live-in or live-out carer
	Time devoted to caregiving
	Motivation
	Love versus duty versus resignation
Carer's coping style	Mature/problem focused
	Immature/emotion focused

BPSD behavioral and psychological symptoms of dementia

An appreciation of caregiver burden provides context and justification for the form and content of the carer assessment as many of the questions are designed to elicit characteristics of the carer that may contribute to or mitigate burden. Attention to caregiver burden is also of practical importance. Carers who are overburdened may be unable to engage fully in the provision of care. Thus, it is essential to proactively assess and address carer needs and modify factors that contribute to burden.

Research and clinical experience both confirm that a variety of interacting factors make some carers more vulnerable to the development of caregiver burden including the nature of the illness, the history of the relationship between carer and care recipient, and the personal characteristics of carers themselves. Among the

Table 2 General considerations in adaptation to the role of carer

General considerations in adaptation to the role of carer	
Adapting to impaired partner "undoing of the prior relationship"	Role reversal
	Solo decisions
	Lost confidant
	Lost companionship
	Constant watching
Isolation	Social
	Family
	Altered and uncertain future
	"Trapped forever"
Intense emotions	Grief
	Guilt
	Anger
	Frustration
	Anxiety
	Depression
	Shame
	Bewilderment

characteristics of dementia, it has been demonstrated that carers are most challenged by the array of behaviors that almost inevitably emerge during the course of the illness (Burns and Rabins 2000; CIHI 2010; Dunkin and Anderson-Hanley 1998). The behavioral and psychological symptoms of dementia (BPSD) are involuntary manifestations of the disease process and may include apathy (the most common BPSD symptom); depression and anxiety; sleep cycle disturbances; "resistance" to care, irritability, agitation, and physical aggression; personality change; suspiciousness, paranoid ideation, delusions, and hallucinations; wandering, pacing, and exit seeking; repetitive activities and perseveration; screaming and inappropriate verbalizations; hoarding; inappropriate voiding, or spitting; and inappropriate sexual behavior (CIHI 2010; Donaldson and Burns 1999; Mega et al. 1996; Schulz et al. 1995). Unpredictable behaviors, such as wandering and aggression, verbal and physical abuse, and sleep disturbances, in particular, often overwhelm carers and can precipitate a move to institutional care (CIHI 2010; Haley 1987; IPA 2002;).

BPSD are very difficult for any carer to cope with, and many carers are perplexed by their cause and management. Carers with less knowledge of dementia and its treatment who may believe that BPSD are volitional and within the care recipient's control rather than being a manifestation of the disease are especially challenged (Donaldson et al. 1998; Dunkin and Anderson-Hanley 1998) as are carers who believe BPSD are deliberate attempts to annoy or that BPSD reflect a failure by the care recipient to appreciate the care being provided (Donaldson and Burns 1999; IPA 2002). Carers may attempt to manage BPSD by making demands that exceed the capacity of the care recipient and then criticizing failure, being excessively rigid, or, conversely, being unpredictable or unreliable in responses or routines, reactions that

may only make the situation worse (IPA 2002). Ordinary means of addressing unusual behaviors in others such as reasoning or asking for clarification may no longer work when dealing with someone who has dementia. Further, the behaviors may seem bizarre and uncharacteristic of the person the carer used to know. It can be difficult for carers to maintain a caring, empathic relationship to the person with dementia when their behaviors are so difficult to understand and manage. Hence, empathy may break down. When this happens, the relationship between carer and care recipient loses its intimacy and can collapse (Reis et al. 1994; Williams et al. 1995). This can have significant consequences as outlined below.

Carer: Care Recipient Relationship and the Stages of Caregiving

The relationship between carer and care recipient, both past and present, appears to affect the caregiving experience for both partners in the dyad. A strained past relationship is associated with greater challenges in caregiving, while the reverse is observed when the past relationship was loving and intimate (Dunkin and Anderson-Hanley 1998; Gilleard et al. 1982). The most profound changes experienced by carers are the changes in the relationship with the care recipient, changes that may be felt most by spouse carers. The carer has to negotiate a series of stages as the longstanding collaborative partnership characteristic of most mature relationships is undone. Sadavoy and the Reitman team have developed and adopted a three-stage approach to classifying carers.

In the first stage of caregiving, as the carer begins to realize that something has changed with their spouse or parent, the carer experiences a sense of foreboding which gradually evolves into a recognition that this is more than just "old age." Early reactions include shock and bewilderment as the carer comes to grips with a diagnosis that they may have heard of but know little about. There is a dawning awareness of being at the start of an uncertain and perhaps endless journey. The balance of the relationship remains intact in this early stage but is shifting as one partner takes on more responsibility and the other becomes more dependent. Mutual decision-making about day-to-day activities, treatment planning, and consideration of future directions may continue, but, gradually, the carer assumes a growing burden for decision-making and managing care. The carer still feels able to live her own independent life and retains her identity as spouse or child. However, the help and supervision provided and the frequency of interventions increase, and the carer becomes increasingly consumed by her role. Having a support network of both professionals and nonprofessionals are helpful for the carer transitioning through this stage although most continue to remain relatively independent and engaged in their life.

In the middle stage of caregiving, the carer becomes increasingly essential to all aspects of the care recipient's life. She assumes responsibility for everything as the care recipient loses insight and the ability to communicate and reason. The carer must assist with basic self-care tasks and unilaterally make more decisions about increasingly simpler issues (Burns and Rabins 2000; Donaldson and Burns 1999).

The carer may be confronted with responsibilities, relatively suddenly and sometimes involuntarily, for which she feels both ill-equipped and on her own. For many spouse carers, particularly women, this may be the first time that they are making decisions independently. There is a growing awareness of being trapped in the carer role with little room to plan anything outside of caregiving. Carers may begin to feel isolated and tied down as caregiving responsibilities place limitations on their freedom (Brodaty and Hadzi-Parlovic 1990; Donaldson and Burns 1999; Lund 2005). Caregiving involves a significant expenditure of time and energy, often for years. Therefore, providing care can disrupt or be in conflict with carers' existing familial and social roles, obligations, and responsibilities. Carers tend to work alone and may not have time to nurture or even maintain other relationships, and so they become increasingly cutoff from prior supports. Often to the surprise and resentment of carers, friends and acquaintances outside the family may withdraw when the personality of the person with dementia changes, adding to carers' isolation (Perel 1998). Carers themselves may experience their own loss of self that parallels the similar loss in the care recipient (Dempsey and Baago 1998; Skaff and Pearlin 1992). The spouse or child comes to retain only a diminishing sense of their old role and their old relationship with the care recipient. When the care recipient can no longer communicate or participate in the relationship, the spouse or child may come to see themselves as a carer only, without any other identity (Dempsey and Baago 1998). As one carer said in describing her husband's inability to join in any decision-making, "*Now* I am a caregiver."

In the late stage of caregiving, the carer experiences increased emotional conflict and guilt as she recognizes that she may not be able to continue to provide care at home and is faced with choices that feel "impossible," including the possibility of institutional care. The task of caregiving can seem overwhelming, and the carer may feel that she cannot carry on. The person she knew is gone. The carer often feels that she has become an attendant and manager of care to someone she no longer recognizes (and who, ironically, no longer recognizes her).

The loss of the care recipient's ability to participate in the life of the relationship is accompanied by a range of emotions for the carer, prominent among them are isolation and abandonment. Carers speak of painful loneliness and grief as their spouse, parent, or friend is lost to the disease (Dempsey and Baago 1998; Perel 1998). There is the loss of the person as he or she was and, in some cases, the loss of the dreams the carer had for a shared future together. This is a loss "not of what was but of what could have been" (Lund 2005). This type of unclear loss without the finality of death or resolution has been termed "ambiguous loss" with the ambiguity lying in the fact that, while the person is lost to the carer in many ways, he or she remains physically alive (Boss 1999). The lack of finality characteristic of ambiguous loss precipitates a kind of grief in carers that is different from other types of grief. The mourning process can be prolonged and agonizing for many carers as they experience loss, and attendant grief, repeatedly while confronting the relentless decline that characterizes dementia. This situation is reinforced by the fact that their loss and grief are unrecognized by others and not socially supported. In this way, their mourning is "disenfranchised" meaning that it is grief experienced when

"a loss is not or cannot be openly acknowledged, publicly mourned or socially supported" (Doka 1989). The fact that the person remains present physically but absent psychologically makes ambiguous loss particularly challenging and puts carers at risk for feelings of uncertainty, depression, and withdrawal.

Carers experience a range of other emotions including anxiety (Dura and Kiecolt-Glaser 1991; Schulz et al. 1995), guilt (Akkerman and Ostwald 2004), and frustration and anger (Coon et al. 2003). Carers may be anxious about their caregiving abilities and, even more practically, may have financial concerns resulting from loss of income, missed vocational advancement, and the direct costs of illness such as prescription medications (Brodaty et al. 2003). The decision to admit the care recipient to an institution is most often accompanied by high anxiety, guilt, and feelings of failure as carers question whether they did all they could to keep their family member at home and wonder whether they will be equally well cared for in a long-term care facility (Bass and Bowman 1990). Carers understandably may resent having to take on the job of caring that they did not anticipate or volunteer for, particularly when the past relationship with the care recipient was poor.

Interventions for Carers: The Reitman Centre Model

Given that carers are central to dementia care, it is necessary and appropriate to actively sustain them in their efforts. Various interventions have been designed for carers, and those built on sound evidence-based principles have been shown to be effective in increasing caregiving capacities, relieving burden, and improving carers' lives and those of care recipients (Brodaty et al. 2003; Huis in het Veld et al. 2015; Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Schultz et al. 2003; Sorensen et al. 2002). Carer interventions, as well as the carers they serve, form a heterogeneous group so comparison is difficult (Brodaty et al. 2003) and no single intervention has been shown to meet all carer needs. Interventions have been developed to relieve depression and burden; improve knowledge, psychological well-being, coping skills, and physical health; reduce service utilization; and delay institutionalization. Overall, interventions have been shown to produce some benefit, although this does not always reach statistical significance, effect sizes are small, and it is not clear whether benefits could be sustained by both carers and care recipients (Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Sorensen et al. 2002). Interventions have been developed that target the care recipient and the carer or are multicomponent in nature (Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Sorensen et al. 2002). Those interventions that targeted the carer are delivered via a variety of modalities including psychoeducation, cognitive behavioral therapy, counseling, case management, telephone or Internet support, physical exercise, communications skills, and general support (Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Sorensen et al. 2002). Among those that targeted the care recipient, many were designed to reduce the amount of care provided by carers. They included respite and day-care programs, training to increase competence of the

care recipient to perform activities of daily living, and efforts to improve their mood (Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Sorensen et al. 2002). The interventions were varied and heterogeneous making comparison difficult and, perhaps, unreliable. The effects of the interventions were often weak, transitory, and contradictory (Bourgeois et al. 2002; Schoenmakers et al. 2010). Methodological issues may account for some of the discrepancies in effectiveness. These include inconsistency in the definition and measurement of burden and change in burden, variation in the characteristics of the carers who participated and recruitment biases, and the fact that different interventions used different approaches to alleviate burden. Other variables that may contribute to differences in outcomes between interventions include whether the intervention was conducted in a group versus individual setting, the "dosage" (length, intensity, and frequency of intervention), the age and gender of the carer, the relationship between the carer and the care recipient, and study quality (Pinquart and Sorenson 2006; Schoenmakers et al. 2010; Sorensen et al. 2002). Modern economic pressures on the health-care system have led to a constant search for quick and efficient intervention methods. However, effectively addressing the needs of carers presents a complex challenge, and successful interventions appear to require sophisticated models and complex, integrated methods. Data suggest that the most effective interventions integrate techniques which:

- Are structured and of adequate duration and intensity
- Require active participation of carers
- Include education
- Address emotional needs
- Offer respite
- Promote knowledge transfer
- Promote skill building and carer competence
- Incorporate principles of cognitive behavioral therapy

Examples of evidence-based interventions which incorporate these techniques include the Reitman Centre CARERS Program (Chiu et al. 2013), NYU Caregiver Counseling and Support Intervention (Mittelman 2002; Mittelman et al. 1995, 1996, 2004, 2006, 2007), and the Resources for Enhancing Alzheimer's Caregiver Health (REACH) II Project (Belle et al. 2006; Gitlin et al. 2003; Schulz et al. 2003).

The NYU Caregiver Counseling and Support Intervention (Mittelman 2002; Mittelman et al. 1995, 1996, 2004, 2006, 2007) includes four elements: (1) two individual counseling sessions tailored to each carer's needs, (2) four family counseling sessions delivered to the primary carer and additional family members of his or her choice, (3) a weekly support group, and (4) continuous access to counselors by phone able to address carers' and families' questions and crises as they arise. A sample of 406 spousal carers attending an outpatient research clinic in New York City took part in the program between 1987 and 2006. Participants completed outcome measures at baseline and at regular intervals after enrollment that demonstrated positive impacts on carer depression, assessment of dementia-

related behaviors, and time to nursing home placement that were significant and sustained.

The REACH II intervention combines psychosocial and behavioral elements with the goal of minimizing carer depression and burden while maximizing carers' capacity to manage challenging behaviors and attend to their own self-care. A variety of approaches, including psychoeducation, problem solving, role-playing, skills training, stress management, and telephone support, are used to provide carers with knowledge of dementia, strategies for managing emotional responses to caregiving challenges and stress, and social support (Belle et al. 2006; Gitlin et al. 2003; Schulz et al. 2003). In the randomized control trial of REACH, carers attended 12 individual sessions (9 in person at home and 3 by telephone) and 5 support group sessions and received educational materials and access to conference calling technology (Schulz et al. 2003). The trial was significant for its multisite design and inclusion of a large sample of carers from a variety of groups including White, Hispanic, and African American carers. A number of outcome measures were completed by participants and demonstrated improvements in carers' quality of life and reduction in depression and burden compared to carers receiving educational materials and telephone check-ins only.

The Reitman Centre was designed to address the needs of carers as a primary focus and to respond comprehensively to their needs with an array of services that include individual counseling, marital and family interventions as necessary, and the flagship CARERS Program. "CARERS" stands for Coaching, Advocacy, Respite, Education, Relationship, and Simulation, an acronym that underscores the fact that this is a comprehensive intervention designed specifically to address the needs of carers providing care to an individual with dementia. The CARERS Program is an evidence-based, 10-week small group therapeutic, skills training intervention which integrates the core principles of individual and group psychotherapies and adult learning (Tables 3 and 4). By design, it incorporates those elements which have been demonstrated empirically to be effective in supporting carers, keeping in mind that any carer intervention must have the flexibility to accommodate the diversity of carers and, in the case of working carers, the corresponding labor markets in which they work. Rather than offer general caregiving guidelines or generic solutions, the program is tailored to meet the needs of the individual carer and the specific challenges he or she faces incorporating psychotherapeutic principles, focused psychoeducation, formal problem solving techniques (PST), and skills training using guided simulation and expert coaching as carers practice new skills and strategies.

The groups are facilitated by two mental health professional group leaders. The caregiving challenges experienced by spouses caring for their partner are different from those facing children looking after a parent. Therefore, groups are made up of either spouse carers or adult child carers, but they are not combined. The CARERS Program is designed to accommodate those care recipients who are able to participate. An evidence-informed, manualized arts-based care recipient group is led by a mental health clinician and runs simultaneously with each CARER group session, providing a stimulating environment for care recipients and respite for carers. After

Table 3 Core features of the Reitman Centre CARERS Program

10-week evidence-informed program delivered in small groups of 4–6 carers
Comprised of either spouses or children of people with dementia
Tailored to the individual carer and the specific challenges each carer faces
Led by trained group leaders who are mental health professionals
Uses problem solving techniques and simulation using standardized patients
Emotions are explored, understood, and processed in group therapy
Program goals grounded in known determinants of caregiver burden:
Enhance knowledge
Improve coping/problem solving
Improve emotional regulation
Reduce depression and anxiety
Enhance sense of mastery and self-efficacy
Improve relationship and social interaction
Reduce sense of isolation
Ensure adequate professional support

Table 4 Reitman Centre CARERS Program outline (Chiu et al. 2013)

Session	Objective	Description
1	Development of group cohesion	Group process is introduced
	Dementia education	Connection between group members and leaders is encouraged
		SP[a] is introduced
		Carers' specific questions regarding dementia are addressed
2–4	Introduction and practice of PST	PST[b] method is taught
		Problem-focused approach is encouraged
		Understanding of emotions is incorporated into PST practice
		Link is made between emotions and caregiving effectiveness
		Carers are encouraged to implement solutions at home and report the outcomes of implementation
5–9	Skills training using simulations	SP actively joins the therapeutic process
		Carers practice approaching caregiving challenges differently via role-playing with SP
		Focus is placed on points of interactional conflict and communication
10	Summing up and termination	Gains made are assessed and acknowledged
		Transition into a new and different phase of supportive care is noted
		First maintenance group is scheduled

[a]*SP* simulated patient
[b]*PST* problem solving therapy

the 10-week program finishes, carers return for a monthly 1 h maintenance group for a year and then are offered the opportunity to attend a monthly 1.5 h drop in group for all graduates of the program.

The first CARERS group session is devoted to development of group cohesion and provision of focused dementia education. The group leaders outline the program structure and ground rules. Group members introduce themselves and begin to establish common ground. The questions they each want answered about dementia are sought and addressed. In sessions 2–4, problem solving technique (PST), adapted for carers, is taught. PST is a stepwise approach to addressing problems derived from cognitive behavioral theory (Mynors-Wallis et al. 1997) and originally used to address depression and anxiety. As adapted for carers, PST organizes carer's thinking so that she can identify, prioritize, explicitly define, and develop solutions for current caregiving challenges. It takes difficulties that can seem very abstract, emotional, and unsolvable and converts them to specific and concrete problems for which solutions can be generated. Even as caregiving is acknowledged to be an inherently emotional endeavor, PST shifts the emphasis to finding solutions that fit the carer and her situation. In doing so, PST helps carers utilize task-oriented rather than emotion-focused coping, thereby improving emotional regulation, mood, and caregiving effectiveness and relieving caregiver burden (Chiu et al. 2013). In defining and addressing each carer's unique challenges, the intention is not only to solve some real, present-day caregiving problems but also to provide the carer with a structured method for problem solving that can be applied to future challenges. Thus, PST can also enhance the carer's sense of mastery and self-efficacy over caregiving tasks.

Sessions 5–9 are devoted to experiential learning using simulation. Simulation is a live face-to-face encounter or enactment of a real-life scenario or interaction for therapeutic or educational purposes. A standardized or simulated patient (SP) is present throughout all ten sessions but only takes an active part in the process in sessions 5–9. In sessions 1–4, the SP is a silent observer, listening to each carer's story in preparation for taking on the role in simulation of the individual with dementia being cared for by each carer. Simulation is a widely validated practice with an extensive literature that recognizes SPs as "valid, accurate, feasible and acceptable educational and assessment tools" (Anderson and Kassebaum 1993). Therapeutic simulation, as used in the CARERS Program, is a unique use of simulation that addresses relational, behavioral, and communication challenges faced by carers to promote and coach changes in behaviors, patterns, and attitudes in order to reduce caregiver burden and improve mastery, coping, and the caregiving relationship. Each member of the group has the opportunity to explore specific, present-day challenges that they are encountering in providing dementia care. Carers enact with SPs challenging situations or difficult conversations that are necessary to effective and satisfying caregiving, problem solving, and well-being. The effectiveness of simulation as a mechanism for adult learning is enhanced by practice, debriefing (the carer's reflection on the practice), and expert feedback (group leaders

provide education for gaps in knowledge as identified through the simulation, coach new responses, and guide the carer in processing emotional responses). Essentially, therapeutic simulation allows carers to reenact difficult scenarios taken directly from current experience and actively practice their way to new behaviors. Reflection and feedback, essential components of effective simulation, are built into the process through the use of time-outs and a therapeutically guided process that ensures carers "bridge [the] natural gap between experiencing an event and making sense of it" (Fanning and Gaba 2007). Therapeutic simulation may also enhance the carers' ability to be more attuned to the people they are caring for. They are taught through reflection and practice to pay attention to both verbal and nonverbal cues and to the emotional affect of the care recipient. At the same time, they learn to recognize their own internal impulses and responses that can lead to reactive and less effective behaviors. This attunement often leads the carer to a greater understanding or acceptance of behaviors, the level and nature of the disease, and the quality of communication and relationship. Therapeutic simulation teaches the carers to listen more effectively for clues to what the care recipient is feeling or experiencing and to thoughtfully respond rather than to impulsively or habitually react and, therefore, to be more fully present to what the moment and the relationship requires.

Process

When it is time for the simulations, two chairs are placed slightly away from the group. This provides a frame that sets the simulation apart from the group, maintains a consistent process, and creates reflective safety. The process begins when the carer describes the scenario to the SP. Common situations reenacted in simulation are listed in Table 5. The SP asks questions in order to make the scenario as accurate as possible. The goal is not to replicate the scenario exactly but to create an environment that is similar enough to what actually happened that it will elicit similar emotions and responses. The reenactments focus on a moment, a small but specific slice of the everyday, and rely on very specific actions, behaviors, and words spoken. Specific questions allow the SP to replicate, as closely as possible, what happened and to make the simulation authentic enough to elicit from the carer responses and reactions similar to what they experienced at home. The group leader verifies that the SP has the necessary information and indicates it is time to begin the interaction.

Table 5 Common interpersonal challenges addressed in simulation

Responding to accusations against the carer
Learning to say no to unreasonable demands
Dealing with confusion, opposition, and resistance
Dealing with repetitiveness, angry outbursts, eating, and feeding
Telling others about the illness of the care recipient
Moderating angry expectations of carer

The Group Leader: Therapeutic Guidance of Simulation

In the CARERS Program, simulation is therapeutically guided by group leaders who ascertain fidelity to the principles of therapeutic simulation (see Table 6 for a guide to the process). They ensure containment of the process and watch the group carefully for any reactions group members may have. During the simulation, the group leaders may offer interpretations of what they observe in the simulation and may have to be directive with the carer in order to illicit changes in behavior. They assist the carer to identify misconceptions or assumptions that they may be making about the care recipient; provide additional education about the disease and how it affects reasoning, logic, and memory; and listen and watch for changes in affect and emotional tone that may be triggered by the simulations. This might include reactions based on the history of the relationship and the impact on the relationship of recent changes and other circumstances and life history which can all lead to feelings of anger, loss, guilt, role expectations, anxiety, and fear. Often the expression of unexpressed grief,

Table 6 The process of therapeutic simulation

The process of therapeutic simulation as used in the CARERS Program
Determine the scenario:
The carer provides the details of the encounter to the simulator. The simulator asks questions that will help them to reenact the scenario in a way that closely approximates what actually happened. Important details include:
Location and pertinent activity (if any)
Words that were spoken
Tone
Behavior or actions
Affect
Initial pass of scenario:
The encounter is reenacted by the simulator and the carer as told by the carer. Time-out can be called at any time by the group leader or the carer
Debrief the initial scenario:
The group leader:
Notes and addresses emotion or affective responses that arise
Discusses the reenactment with the carer, elicits their experience, and determines if the simulation successfully captured the actual event
May ask the simulator for feedback
Guides the carer toward a more effective approach (sometimes with suggestions from the group)
Subsequent passes of scenario:
The group leader uses strategic time-outs in order to:
Discuss challenging moments, relational habits, or patterns
Address gaps in knowledge
Identify and process emotional responses
Determine more effective approaches to communication
Receive feedback from simulated patient and group members

Table 7 Measuring clinical outcomes of the CARERS Program

Seven pre/post measures are used to evaluate the CARERS Program's effect on carers' psychological functioning, caregiving skill sets, and stress coping styles:
1. Geriatric depression scale[a,b]
2. Self-mastery scale[c]
3. Role captivity scale[c]
4. Role overload scale[c]
5. Caregiving competence scale[c]
6. 12-item Zarit burden interview[d]
7. Coping inventory for stressful situations[e]
Pre-intervention versus post-intervention findings t-test analysis
Pre- and post-scores are clinically and statistically significantly improved for four constructs:
Emotion-oriented coping style
Overload
Depression
Caregiving competence

[a]Yesavage et al. (1982–1983)
[b]Greeberg (2007)
[c]Pearlin et al. (1990)
[d]Bedard et al. (2001)
[e]Endler et al. (1993)

loss, and other emotions associated with caring for a family member with dementia arise from the simulation process, all of which is therapeutically supported by the group leader. This integration of experiential learning into the therapeutic process provides carers with a chance to practice, in a supportive environment, new approaches to the situations and behaviors they commonly face. It is a vehicle for change in conflicted interpersonal situations. The focus is on the relationship, often a source of considerable distress for carers.

The active participation of carers in both PST and simulation leads to acquisition of knowledge and caregiving skills and competence. It draws on research outcomes suggesting that the most effective interventions for teaching caregiving skills combine direct observation and coaching of carers as they respond to challenging situations while simultaneously integrating the exploration and understanding of individual participant's emotional reactions with the group process. Pre- and post-satisfaction measures from the CARERS Program indicate that simulation does provide carers with important skills and understanding. They learn to ask fewer questions; to validate the feelings of the care recipient through reflecting, rephrasing, and acknowledging; to use simple statements; and to pay attention to and use nonverbal strategies such as tone, touch, and eye contact.

The effectiveness and acceptability of the CARERS Program has been demonstrated through formal outcome evaluation and feedback from program participants. Participants complete standardized assessment tools for depression, caregiving competence, mastery, role overload, role captivity, caregiver burden, and stress coping style (Bédard et al. 2001; Endler et al. 1993; Greenberg 2007; Pearlin et al. 1990;

Yesavage et al. 1982–1983) (Table 7). A pre/post study was conducted with 73 participants who completed the CARERS Program (Chiu et al. 2013). Findings provide support for the effectiveness of the CARERS Program in improving competence, stress coping ability, and mental well-being in carers taking care of family members with dementia. The intervention was shown to be well received by carers. To refine validity of outcome data, the next phase of program evaluation is underway with the inclusion of a control group and a time point of 3 months post program.

The Reitman Centre High Risk Caregiver Program

This program was created as part of a provincial initiative called Behavioral Support Ontario (BSO) to address the need for managing behavioral disturbances (subsumed under the term behavioral and psychological symptoms of dementia or BPSD) associated with dementia. The rationale for focusing on high-risk carers arose from clinical experience in the Reitman Centre CARERS Program which revealed a subset of carers whose psychological and personality structure, relationship to the person with dementia, social situation, and resource challenges put them at great risk of decompensating in their role as carer. High-risk carers are individuals whose personal well-being and/or their ability to care for the care recipient with dementia are significantly jeopardized as a direct result of providing care. High risk does not necessarily imply or equate with crisis. Rather, certain characteristics of some carers place them at higher risk of falling into crisis. An individual's status as a high-risk carer can change over time as they respond to the evolving demands of caregiving with differing degrees of emotional and instrumental stability.

As reviewed above, there is strong evidence that carers are at increased risk for serious health and psychological illness as a direct consequence of caring for an individual with dementia (Baumgarten et al. 1992; Burns and Rabins 2000; National Alliance for Caregiving 2015; Schulz et al. 1995; Sinha 2013). The possibility of poor outcomes for the carer depends on a complex interplay between factors intrinsic to the care recipient, the carer, and the environment in which they live (Brodaty and Hadzi-Parlovic 1990; Donaldson and Burns 1999; CIHI 2010; IPA 2002; Zarit et al. 1986). If a carer lacks the capacity to respond adaptively to their ever-changing circumstances, they can be at increased risk for a significant decline in their own well-being or their ability to continue to provide care (Guberman et al. 2001).

Personality and Coping Style

Clinical experience at the Reitman Centre suggests that personality factors are a key determinant of carer risk levels. A recent review by Ortega and Leung (2015) outlines the importance of a carer's underlying personality style to their coping capacity, as it influences their vulnerability to negative emotions. The personality trait of neuroticism appears to be related to high burden and depression, while extraversion and agreeableness seem protective (Melo et al. 2011). Self-efficacy,

or the sense of one's ability to succeed at given tasks, has been associated with lower caregiver burden (Pearlin et al. 1990). Other personality factors, such as mastery over caregiving tasks, optimism, locus of control, and general self-esteem, all influence carer coping and success (Ortega and Leung 2015).

Coping strategies can similarly positively or negatively affect outcomes for carers. Folkman (1997) explored how carers cope with stress in their environment. She found that carers who are able to apply meaning to stressors tended to experience more positive emotional responses, even when they are simultaneously experiencing negative emotional states. Similarly, Cohen et al. (2002) found that carers who are able to identify positive aspects of caregiving experience less depression and lower burden.

Lazarus and Folkman (1984) posited that different types of coping are valuable in different circumstances. Specifically, positive emotion-focused coping (e.g., getting emotional support from others, positive reframing, acceptance, humor, or religion) can be most helpful when a situation cannot be changed. In contrast, problem-focused coping strategies (e.g., initiating action, planning, and seeking instrumental support) are most useful when situations can be changed (Cooper et al. 2008). Arguably, carers who use dysfunctional coping strategies feel so emotionally overwhelmed by their circumstances that they are unable to see positive aspects of caregiving or feel that all elements of providing care are unchangeable. As such, carers with these characteristics are at the highest risk for negative outcomes for themselves and the care recipient.

State vs. Trait

Clearly, becoming a carer is associated with increased risk for the decline in well-being for some individuals, and certain elements increase that risk. However, it is important to consider how well an individual functioned and coped with stress prior to taking on the role as carer to fully understand their capacity to cope once in the role. Pepin et al. (2013) conceptualized carers' pre-existing internal resources along two dimensions. First, they looked at how well carers were able to respond to the offer of external assistance and whether they were organized in using services. Second, they considered how complex carers' lives had always been, due to such factors as familial abuse, substance use, or impaired health and cognition. They found carers fell on a continuum for both of these dimensions, resulting in some carers starting their carer careers at a disadvantage due to lifelong complexity and their current ability to make use of assistance and, thus, being at the greatest risk for decompensation.

By thinking about carers' intrapsychic attributes overlaid on the specifics of dementia caregiving, high risk for decompensation can be conceptualized as due to a *state* of high risk or a *trait* of high risk. That is, an individual might have been high functioning and coped adaptively throughout their lives, but in a state of high risk for decompensation because of a lack of skills, strategies, or resources to cope with the specific stressors of care for a person with dementia.

Equally, an individual might have had a lifetime of dysfunctional coping because of mental health, personality, or environmental limitations with the addition of caregiving added to this complexity. As such, a carer's situational functioning (*state*) can be distinguished from their underlying constitutional factors (*trait*). Some carers will find themselves overburdened because care demands have exceeded their capacity, but once that situational stress has been relieved (by skills training, therapeutic counseling, or respite), they return to a state of equilibrium. These carers have the constitutional traits they need to cope with the challenges of care, even though they experience stress (Chappell 2011). On the other hand, some carers are overburdened because they lack the constitutional traits to withstand stress in a general sense. State and trait are not independent, of course. An individual's underlying constitutional traits will have affected their mental health history, the history of their relationship with the person with dementia throughout their lives, other relationships that might also have provided support in times of stress, and potentially even affected employment. The concept of risk being influenced by carer state and trait has implications for assessment and interventions. Coping strategies, education, and sensitivity to emotional states may help compensate for unchanging underlying traits that put a carer at a disadvantage.

Elder Abuse

Although often thought of as a separate issue, the factors associated with high risk for a carer's decline are also largely those that predict elder abuse (Beach et al. 2005; Johannesen and LoGiudice 2013). To be clear, not all high-risk carers engage in abusive behavior, but there is a subset of individuals who are struggling with the role of carer who might also be most likely to use dysfunctional and potentially harmful coping strategies and engage in abusive behaviors (e.g., Cooper et al. 2010). Carer behaviors with the potential to harm the care recipient include physical abuse, psychological or emotional abuse, sexual abuse, neglect, and financial abuse (Kohn and Verhoek-Oftedahl 2011).

Harmful carer behaviors could represent a lifelong pattern of abuse in relationships or could be a direct result of the stress of caring for an individual with challenging behaviors (Cooper et al. 2008). In dementia, both carers and care recipients can be at risk for abuse, as aggressive behaviors are common in dementia even without prior abuse in the relationship (Johannesen and LoGiudice 2013). Caring for someone exhibiting abusive behaviors is the strongest predictor of abuse by the carer (Cooper et al. 2010). However, a history of abuse, either by the care recipient toward the carer (e.g., a history of parental abuse toward the carer as a child) or by the carer toward the care recipient (e.g., a history of spousal abuse) is a predictor of abusive behavior occurring after the onset of dementia (American Psychological Association 2012). There is evidence that carers who are more anxious and depressed are more likely to report acting abusively, which can be explained by their reliance on dysfunctional coping

strategies (Cooper et al. 2010). The facts reinforce the importance of identifying carers at increased risk for decline and, for what reason, in order to be able to recognize the red flags that could result in potentially harmful behavior as a coping strategy (Beach et al. 2005).

Assessment of the High-Risk Carer

There is an extensive array of carer assessment measures for both positive and negative effects of caregiving (e.g., Family Caregiver Alliance 2012), but there are few measures of carer risk (e.g., American Medical Association 2002; Czaja et al. 2009; Guberman et al. 2001; Hopkins and Kilik 2015). Measuring risk is challenging because all carers experience stress related to the onset of the care recipient's dementia, but it can be difficult to pinpoint the time when the carer becomes at high risk for their own decline or inability to continue to provide care. Assessing the carer's burden, depression, or anxiety is insufficient because these alone do not capture the complexity of their circumstances or the necessity of adaptation by the carer over time. Asking only about known risk factors such as the severity of BPSD does not capture the emotional response of the carer to the changes in the relationship brought on by these behaviors.

Existing measures of carer risk are structured self-report questionnaires that may not include professional clinical interpretation. As part of the High Risk Caregiver Program at the Reitman Centre, a new one-page guided interview tool has been developed to document and assess risk in a naturalistic fashion. The Dementia Caregiver Interview Guide (DCIG) was designed to (1) guide clinicians in their assessment with carers using a summary of factors associated in the literature with carer risk and (2) provide an easy way for clinicians to document degree of impact of factors and concern about the carer's risk of decompensation.

The DCIG has a checklist format and is organized into five categories identified as relevant to risk in the literature: (1) time spent or intensity in care, (2) care recipient characteristics, (3) carer characteristics, (4) environment, and (5) barriers to accessing resources. These categories are then divided into subcategories with finer gradations of focus. Each subcategory has checkboxes with items recognized as contributing to caregiver burden and risk of decline. Items are checked off as they are revealed spontaneously by the carer or endorsed on further questioning. For each subcategory, the assessor rates the degree of impact that area of concern is having on the carer's experience (i.e., low, medium, or high). The impact ratings provide descriptive information about areas of greatest difficulty for the carer and inform the assessor's overall clinical impression.

The DCIG has two additional elements. The first of these is in the category of Caregiver Self-Identified Overload: in the only preset question on the DCIG, the assessor asks the carer how many days in the last week they felt they had more to do than they could handle or felt "stretched to the limit." In the final element of the DCIG, the assessor uses a seven-point descriptive scale to rate their overall impression of the carer's risk of significant decline in their well-being or the care they can

provide. The assessor uses the following descriptive terms to rate their degree of concern: none, minimal, mild, moderate, marked, severe, and extreme. The overall impression of risk rating in the DCIG is not a quantitatively derived score. The impact ratings on each category inform the final impression of risk, but not in a formulaic way. A carer's responses may generate an overall impression of high risk whether there are many sources of concern rated at a medium level of intensity or one item of high concern.

The DCIG provides a qualitative description of the carer's concerns and a categorization of the degree of risk based on the clinical judgment of the assessor. In contrast to a questionnaire format, the assessor's clinical impression drives the designation of risk on the DCIG rather than a quantitatively derived score. In a recent proof of concept study (Feldman et al. 2017, in preparation), 50 carers were recruited in a convenience sample during their intake assessment for services at the Reitman Centre. Their DCIG overall clinical impression ratings were compared to an existing questionnaire measuring carer risk (Caregiver Risk Screen (CRS); Guberman et al. 2001). The DCIG correlated positively with the CRS (Spearman's rho $= 0.737$; $p < 0.001$) and successfully identified carers at risk, as identified by the CRS (Cohen's kappa $= 0.559$). As such, the DCIG successfully identifies carers at risk for decline in a client-centered, naturalistic manner without sacrificing positive clinical rapport.

Dissemination of the Reitman Centre CARERS Program

An effective intervention must be scalable for dissemination to diverse communities (e.g., geographic, cultural, and linguistic) to ensure access to those in need. The CARERS Program described above was delivered originally in a single location by professionals who were also integral to the program's conceptualization and development. The next phase, therefore, concerned the dissemination of the program in various other settings in a scaling-up process wherein a proven intervention is introduced into a new setting with the goal of producing similarly positive effects in a larger population (McDonald et al. 2006). Broader dissemination of the CARERS Program is underway in other populations of carers at risk including working and rural carers.

The Working Carer

Working carers are those juggling paid employment and caring for someone with dementia at home. The rapid increase in the number of working carers is an emerging trend that has serious social and economic consequences for the world's economies, significantly affecting everything from the stability and functioning of the family unit to the productivity of the labor market. The complex array of stressors and pressures related to being an employee, a carer, a mother or father, and partner has only relatively recently been named and acknowledged in the literature (CIHI 2010;

Cranswick and Dosman 2008; Turcotte 2013). Evidence from the United States, Europe, and Canada has suggested that industry outcomes related to caregiving include lost productivity and high employee turnover, in addition to the immeasurable human and social costs that result from the creation of a conflict between work life and family life(Cynkar and Mendes 2011; Duxbury and Higgins 2012; Feinberg et al. 2011; Sinha 2013; Witters 2011). In 2011 in the United States, carers in the workforce reported missing an average of 6.6 work days per year, the equivalent of $25.6 billion in lost productivity annually (Witters 2011). Furthermore, 54% of working carers reported that caregiving responsibilities negatively affected their job performance to some degree, with 10% describing the impact as "great" and 24% saying that providing care prevented them from devoting more hours to their paid employment (Witters 2011).The need to juggle caregiving and work also impacts the personal lives and well-being of the individual carer (Witters 2011). Carers are less likely to take a promotion because they simply can't afford the time and effort in building their career, may adopt a part-time work schedule, or take early retirement (Cynkar and Mendes 2011; Duxbury and Higgins 2012; Feinberg et al. 2011; Sinha 2013; Witters 2011). According to Alzheimer Society of Canada (2011), Canadians spent over 444 million hours on caring for a relative with dementia in 2011. This represents $11 billion in lost income annually. Looked at from the individual perspective, a family carer in the United States is estimated to forgo $566,443 in wages, $67,202 in pension benefits, and $25,494 in social security benefits for a lifetime total loss of $659,139 (Family Caregiver Alliance 2009). Further, working carers, like all carers, are at disproportionate risk of emotional and physical disorders, higher rates of health-care utilization, and vulnerability to relapse of pre-existing physical illnesses (Alspaugh et al. 1999; Baumgarten et al. 1992; Brodaty and Hadzi-Parlovic 1990; Brodaty et al. 2003; Burns and Rabins 2000; Kiecolt-Glaser et al. 1987; Zarit et al. 1986; Mittelman et al. 2006), any one of which might render them unable to fulfill their diverse and crucial roles at home and at work. Since a productive and viable workforce is essential for economic prosperity of any nation and the care provided to seniors at home by working carers is increasingly important in sustaining the financial viability of health-care systems (Pinquart and Sorensen 2006), it is essential to take steps to ensure the continued retention and productivity of carers in the workplace and at home (Duxbury and Higgins 2012).

While the profile of employees who are challenged by providing care at home is gradually being defined, there are very few if any intervention programs to directly address carer needs as both employees and carers. An effective intervention must be accessible to those who require it. To create a program accessible to working carers, a unique partnership was created between government, employers, and an employee assistance provider to implement an innovative model: the Reitman Centre Working CARERS Program (RCWCP). The principles that form the core of the CARERS Program are preserved in the Working CARERS Program but provided in a format that better suits the needs and schedules of full-time employees and their employers with fewer, shorter sessions provided in the evening. The RCWCP includes dementia psychoeducation, problem solving techniques (PST), simulation, and expert

coaching with attention to emotional issues as they arise. Interestingly, as the program evolved, it became evident that recruitment of employees into the face-to-face group format being offered was a major obstacle. To meet this challenge, all elements of the RCWCP were reframed and adapted for delivery in a small group live, online format. While still in its early phase of development, this methodological change has improved recruitment and access. The online method has also simplified the goal of scaling this program nationally allowing trained expert group leaders to provide services from a central location without regard to geography.

Interventions to support working carers in the performance of their multiple roles benefit all sectors. Working carers are able to continue as productive employees, maintain their income and opportunities for career advancement, contribute to private- and public-sector pension plans, and remain physically and psychologically healthy. Their family members with dementia receive better care and may avoid premature admission to acute or long-term care settings. Employers gain through increased productivity and reduced absenteeism, reduced costs of recruitment and training of new workers, and reduced costs incurred through extended health claims by ill workers. Governments at all levels enjoy direct benefits of well-supported working carers through increased tax revenues from employed workers and decreased costs of Employment Insurance and tax credit programs for carers and indirectly through minimization of health-care costs. Longer-term effects may accrue through stabilization of labor market forces and retention of high-performance staff which, in turn, enhances the overall social and economic infrastructure. A national study of the RCWCP is currently underway to measure its effectiveness in improving working carers' performance, productivity, and well-being.

The Rural Carer

The term "rural" may be defined by population size, access to services, or catchment areas (Goins et al. 2009; O'Connell et al. 2012). For example, Statistics Canada uses the following criteria to define "rural" (Joseph et al. 2007):

- The countryside outside of larger centers
- Towns where individuals live outside of urban commuting zones
- Small populated communities in close proximity where individuals live in an organized economic and social unit
- Predominantly rural regions where individuals live in census divisions with more than 50% of the people non-metropolitan regions where people live outside of large metropolitan regions and locations where individuals have rural postal codes

For those who live there, and for those who have left these communities, the term "rural" has meaning that goes beyond the objective numbers and statistics. To them, "rural" is defined by their collective lived experience as "rural-dwellers" that may be characterized by a lifestyle supportive of well-being and a value system of enhanced

mutual aid, proximity, conviviality, and cooperation (Bollman and Clemenson 2008).

While the physical and mental health needs of rural and urban family carers may be similar, it has been found that both groups access support and services in different manners. The provision of dementia care and support to carers in rural communities presents a unique set of challenges and opportunities. While isolation and burden of care is high, it has been reported that carers caring for persons with dementia may not access formal supports in rural settings (Morgan et al. 2002) due to the stigma of having or having a family member with dementia. Carers' reluctance to acknowledge the family member's dementia diagnosis or to admit that they are unable to manage the situation may militate against service utilization. Systemic issues such as distance and costs may also present as obstacles for carers to access services (Morgan et al. 2002; Smale and Dupuis 2002; Forbes et al. 2006). Alternatively, individuals turn to their own community for support (Andrews et al. 2010), as community cohesion and responsibility in care are highly valued (Morgan et al. 2002).

Adaptability and Feasibility of the Working CARERS Program in Rural Communities

An evidence-based intervention for carers successfully implemented in an urban center may not be well-suited to serve the needs of rural carers. Carefully crafted research with the objectives of understanding the rural communities' needs and subsequently the applicability of the intervention is required. The direct benefits of involving community partners within the entire research project improves the quality and addresses the needs of the community through putting the results into action that benefits the community (Morgan et al. 2002).

The adaptability and feasibility of the Reitman Centre Working CARERS Program has been tested in two Canadian provinces: Manitoba and Nova Scotia. Using principles of Appreciative Inquiry and Participatory Action Research, community stakeholders and working carers were consulted throughout different stages of the study. Phase I of the study involved focus group discussions where community stakeholders including representatives from relevant community agencies (e.g., local chapters of Alzheimer Society) discussed community preparedness, barriers and facilitators of implementation, and the potential impact evidence-based programs such as the Working CARERS Program may have in rural communities. Conducting stakeholder focus groups with community stakeholders and staff for the RCWCP and individual qualitative interviews with prospective working carers is aligned with the principles of community-based participatory research methods. The individuals and communities directly affected by working and caregiving in a rural setting guided and informed the development process.

During phase II of the study, in-depth interviews were conducted with working carers in rural communities to understand their caregiving needs and expectations. The clinical content and mode of delivery of the Working CARERS Program were

iteratively adapted based on qualitative data gathered, and the Working CARERS Program was successfully and securely delivered through a live, web-based video-conferencing tool. Post-group focus groups with participants demonstrated the acceptability and practicality of the intervention and provided insight into the benefits and utility of this delivery format: the live, web-based format allowed for carers from different time zones to attend the program at the same time, in the comfort of their homes, improving accessibility of the program.

Community Adaptation of the CARERS PST Intervention

Health professionals working at the front line in the community serving patients and families dealing with dementia in their homes are routinely confronted with highly complex situations which overwhelm both the practitioner and the families. PST principles of intervention when added to the tool kit of approaches used by professionals in homecare interventions are well suited to reduce the chaos of complex situations and help both professionals and carers sort through problems and come to solutions. In Toronto, Canada, the Reitman Centre entered into a partnership with the Toronto Central Community Care Access Centres (TC-CCAC), a government-funded provider of a range of professional health-care services and resources to individuals in their homes. Care coordinators employed by the TC-CCAC, usually social workers, occupational therapists, or nurses, are the first to connect with patients and families in the community to determine their needs and initiate services. While in-home care is usually instrumentally focused on essential task-oriented support such as ensuring individual patients are bathed, toileted, and fed, the TC-CCAC and Reitman Centre recognized that these professionals have a unique opportunity to leverage their visits to enhance family carers' capacities to manage care at home as well as hone their own skills in managing complex situations. A training program was established at the Reitman Centre to systematically train all TC-CCAC care coordinators to use PST in their work to foster self-care and problem solving skills among carers in their home environment.

To evaluate the intervention, 56 family carers were equally allocated to either the PST intervention or a control group. Those in the control group received usual home visits. Those in the PST group received three 1.5 h visits by a TC-CCAC care coordinator trained to deliver the PST intervention as part of their regular home visits. Coping, mastery, competence, burden, and perceived stress were evaluated in both groups at baseline and post-intervention using standardized assessment tools. The PST-grounded visits demonstrated that problem solving techniques can be learned and delivered in the home by care coordinators and that these visits are more effective than treatment as usual in improving carers' task-oriented coping, mastery, and competence and reducing emotion-oriented coping, burden, and stress (Chiu et al. 2015). Ultimately, this in-home coaching may reduce dependence on other types of primary, community, or institutional care. Beyond the success of implementing the PST model in the community, the project also demonstrated that

effective partnerships can be established between interprofessional groups and community agencies to extend the reach of specialized interventions such as the CARERS Program, producing effective and significant expansion of community services and system capacity (Chiu et al. 2015).

Summary

Carers are integral to the dementia care system. In order to ensure that carers can engage fully in the provision of care, help and support addressing each carer's unique and specific needs must be extended proactively to them. While carers have not previously been considered to be a group with legitimate health-care needs, it is clear that they deserve to be the target of specific care and that the care of carers is a necessary component of the system of care of individuals with dementia. Sustaining carers in their role is a complex challenge given their susceptibility to the development of adverse effects of taking on their role making systematic evaluation of the carer necessary in each case of dementia. Fortunately, there are proven interventions for carers that address carer need and can be brought to scale and disseminated. One such intervention is the Reitman Centre CARERS Program. Carers are the focus of the program with the goal of equipping and sustaining them in this new, difficult, and unfamiliar role. Carers are provided with specific skills and knowledge, including enhanced problem solving and communication and relational techniques, in an effort to increase caregiving capacities and resilience and relieve caregiver burden. Looking after family carers by maximizing their abilities and minimizing their burden will ensure that they can be and feel that they are valid and necessary partners in the care of patients with dementia.

Cross-References

- ▶ Elderly Services, Community Care, and Health Economics of Service
- ▶ Psychological Interventions for Older Adults: Evidence-Based Treatments for Depression, Anxiety, and Carer Stress
- ▶ Successful Aging

References

Akkerman R, Ostwald S (2004) Reducing anxiety in Alzheimer's disease family caregivers: the effectiveness of a nine-week cognitive-behavioral intervention. Am J Alzheimer's Dis Other Dementias 19:117–123

Alspaugh M, Stephen M, Townsend A, Zari S, Greene R (1999) Longitudinal patterns of risk for depression in dementia caregivers: objective and subjective primary stress as predictors. Psychol Aging 14:34–43

Alzheimer Society of Canada (2011) The rising tide: the impact of dementia on Canadian Society. Alzheimer Society of Canada. Available via http://www.alzheimer.ca/~/media/Files/national/Advocacy/ASC_Rising%20Tide_Full%20Report_Eng.ashx. Accessed 1 June 2016

Alzheimer's Disease International (2015) World Alzheimer report 2015. The Global Impact of Dementia. Available via http://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. Accessed 15 Jun 2016

American Medical Association (2002) Caregiver self-assessment tool. Available via http://www.healthinaging.org/files/documents/caregiver.self_assessment.pdf. Accessed 4 Feb 2016

American Psychological Association (2012) Elder abuse and neglect: in search of solutions. Available viahttp://www.apa.org/pi/aging/resources/guides/elder-abuse.aspx. Accessed 4 Jul 2016

Anderson M, Kassebaum D (1993) Proceedings of the AAMC's consensus conference on the use of standardized patients in the teaching and evaluation of clinical skills. Acad Med 68:437–483

Andrews M, Stewart N, Morgan D (2010) Dementia awareness in norther nursing practice. Canadian J of Nursing Research 42:56–73

Bass D, Bowman K (1990) The transition from caregiving to bereavement. Gerontologist 30:35–42

Baumgarten M, Battista R, Infante-Rivard C, Itanely J, Becker R, Gautier S (1992) The psychological and physical health of family members caring for an elderly person with dementia. J Clin Epidemiol 45:61–70

Beach S, Schulz R, Williamson G, Miller L, Weiner M, Lance C (2005) Risk factors for potentially harmful informal caregiver behavior. J Am Geriatr Soc 53:255–261

Bédard M, Molloy D, Squire L, Dubois S, Lever J, O'Donnell M (2001) The Zarit burden interview: a new short version and screening version. The Gerontologist 41:652–657

Belle S, Burgio, Burns R, Coon D, Czaja S, Gallagher-Thompson et al (2006) Enhancing the quality of life of dementia caregivers from different ethnic or racial groups: a randomized, controlled trial. Ann Intern Med 145:727–738

Bollman R, Clemenson H (2008) Structure and change in Canada's rural demography: an update to 2006, Statistics Canada Rural and Small Town Canada Analysis Bulletin Catalogue no. 21-006-X, vol 7, No. 7 via http://www.statcan.gc.ca/pub/21-006-x/21-006-x2007007-eng.pdf. Accessed 6 Jul 2016

Boss P (1999) Ambiguous loss: learning to live with unresolved grief. Cambridge University Press

Bourgeois M, Schulz R, Burgio L, Beach S (2002) Skills training for spouses of patients with Alzheimer's disease: outcomes of an intervention. Study J Clin Geropsychol 8:53–73. doi:10.1023/A:1013098124765

Brodaty H (1996) Caregivers and behavioral disturbances: effects and interventions. Int Psychogeriatr 8(Suppl 3):455–458

Brodaty H, Hadzi-Parlovic D (1990) Psychosocial effects on carers of living with persons with dementia. Aust N Z J Psychiatry 24:351–361

Brodaty H, Green A, Koschera A (2003) Meta-analysis of psychosocial interventions for carers of people with dementia. J Am Geriatr Soc 51:657–664

Brown P, Potter J, Foster B (1990) Caregiver burden should be evaluated during geriatric assessment. J Am Geriatr Soc 38:455–460

Buckner L, Yeandle S (2015) Valuing carers 2015. The rising value of carers' support. Carers UK. Available via http://www.carersuk.org/for-professionals/policy/policy-library/valuing-carers-2015. Accessed 15 Jun 2016

Burns A, Rabins P (2000) Carer burden and dementia. Int J Geriatr Psychopharmacol 15:S9–S13

Canadian Home Care Association (2013) Portraits of home care in Canada. Available via http://www.cdnhomecare.ca/media.php?mid=3394. Accessed 27 Jun 2016

Canadian Institute for Health Information (CIHI) (2010) Caring for seniors with Alzheimer's disease and other forms of Dementia. Available via https://secure.cihi.ca/free_products/Dementia_AIB_2010_EN.pdf. Accessed 2 Jul 2016

Carers UK (2016) State of caring 2016. Available via http://www.carersuk.org/for-professionals/policy/policy-library/state-of-caring-2016. Accessed 20 Jun 2016

Chappell N (2011) Population aging and the evolving care needs of older Canadians: an overview of the policy challenges, IRPP study 21. Institute for Research on Public Policy, Montreal
Chiu M, Pauley T, Wesson V, Pushpakumar D, Sadavoy J (2015) Evaluation of a problem solving techniques intervention for informal carers of patients with dementia receiving in-home care. Int Psychogeriatr 27:937–948
Chiu M, Wesson V, Sadavoy J (2013) Improving caregiving competence, stress coping, and mental well-being in informal dementia carers. World J Psychiatr 3:65–73. Available via http://www.wjgnet.com/2220-3206/full/v3/i3/65.htm. Accessed 2 Jul 2016
Cohen C, Colantonio A, Vernich L (2002) Positive aspects of caregiving: rounding out the caregiver experience. Int J Geriatr Psychopharmacol 17:184–188
Coon D, Thompson L, Steffen A, Sorocco K, Gallagher-Thompson D (2003) Anger and depression management: psychoeducational skill training interventions for women caregivers of a relative with dementia. The Gerontologist 43:678–689
Cooper C et al (2008) Coping strategies, anxiety and depression in caregivers of people with Alzheimer's disease. Int J Geriatr Psychiatry 23:929–936
Cooper C et al (2010) The determinants of family carers' abusive behaviour to people with dementia: results of the CARD study. J Affect Disord 121:136–142
Cranswick K, Dosman D (2008) Elder care: what we know today. Statistics Canada, Ottawa
Cynkar P, Mendes E (2011) More than one in six American workers also act as caregivers. Available via http://www.gallup.com/poll/148640/one-six-american-workers-act-caregivers.aspx. Accessed 5 Jul 2016
Czaja S et al (2009) Development of the risk appraisal measure: a brief screen to identify risk areas and guide interventions for dementia caregivers. J Am Geriatr Soc 57:1064–1072
Deloitte Access Economics Pty Limited (2005) The economic value of informal care. Access Economics, Kingston
Dempsey M, Baago S (1998) Latent grief: the unique and hidden grief of carers of loved ones with dementia. Am J Alzheimer's Dis 13:84–91
Doka K (ed) (1989) Disenfranchised grief: recognizing hidden sorrow. Lexington Books, Lexington
Donaldson C, Burns A (1999) Burden of Alzheimer's disease: helping the patient and the carer. J Geriatr Psychiatry Neurol 12:21–28. doi:10.1177/089198879901200106
Donaldson C, Tarrier N, Burns A (1998) Determinants of carer stress in Alzheimer's disease. Int J Geriatr Psychopharmacol 13:248–256
Dunkin J, Anderson-Hanley C (1998) Dementia caregiver burden. A review of the literature and guidelines for assessment and intervention. Neurology 51(Suppl 1):S53–S60
Dura J, Kiecolt-Glaser J (1991) Sample bias in caregiving research. J Gerontol 45:P200–P204
Duxbury L, Higgins C (2012) Revisiting work-life issues in Canada: the 2012 National Study on Balancing work and caregiving in Canada. School of Business, Carleton University, Canada. Available via http://newsroom.carleton.ca/wp-content/files/2012-National-Work-Long-Summary.pdf. Accessed 5 Jul 2016
Endler N, Parker J, Butcher J (1993) A factor analytic study of coping styles and the MMPI-2 content scales. J Clin Psychol 49:523–527
Family Caregiver Alliance (2009) Caregiving. Available via https://www.caregiver.org/caregiving. Accessed 27 Sept 2016
Family Caregiver Alliance (2012) Selected caregiver assessment measures: a resource inventory for practitioners. 2nd edn. Available via https://www.caregiver.org/selected-caregiver-assessment-measures-resource-inventory-practitioners-2012. Accessed 11 May 2016
Fanning R, Gaba D (2007) The role of debriefing in simulation-based learning. Simul Healthc 2:115–125. doi:10.1097/SIH.0b013e3180315539
Feinberg L, Reinhard S, Houser A, and Choula R (2011) Valuing the invaluable: 2011 update. The growing contributions and costs of family caregiving. AARP Public Policy Institute. Available via http://assets.aarp.org/rgcenter/ppi/ltc/i51-caregiving.pdf. Accessed 5 Jul 2016
Feldman R, Chiu M, Lawson A, Sadavoy J (2017) A novel assessment of caregiver risk: the Dementia Caregiver Interview Guide (DCIG). International Psychogeriatrics (in preparation)

Folkman S (1997) Positive psychological states and coping with severe stress. Soc Sci Med 45:1207–1221
Forbes D, Morgan D, Janzen B (2006) Rural and urban Canadians with dementia: use of health care services. Can J Aging 25:321–330
George L, Gwyther I (1986) Caregiver wellbeing: a multidimensional examination of family caregivers of demented adults. Gerontologist 26:253–259
Gilleard C, Boyd W, Watt G (1982) Problems in caring for the elderly mentally infirm at home. Arch Gerontol Geriatr 1:151–158
Gitlin L, Belle S, Burgio L, Czaja S, Mahoney D, Gallagher-Thompson D, Burns R, Hauck W, Zhang S, Schulz R, Ory M (2003) Effect of multicomponent interventions on Caregiver Burden and depression: the REACH multisite initiative at 6-month follow-up. Psychol Aging 18:361–374
Goins R, Spencer S, Byrd J (2009) Research on rural caregiving: a literature review. J Appl Gerontol 28:139–170
Greenberg S (2007) How to try this: the geriatric depression scale: short form. Am J Nurs 107:60–69
Guberman, N, Keefe, J, Fancey, P, Nahmiash, D, Barylak, L (2001) The caregiver risk screen. Developed as part of a project: development of screening and assessment tools for family caregivers funded by the Health Transition Fund. Available at http://www.msvu.ca/site/media/msvu/CRS%20%20English%20WATERMARK.pdf. Accessed 11 Apr 2016
Haley W (1987) The family caregiver's role in Alzheimer's disease. Neurology 48(Suppl 6): S25–S29
Health Council of Canada (2012) Seniors in need, caregivers in distress: what are the homecare priorities for seniors in Canada? Available via http://www.healthcouncilcanada.ca/rpt_det_gen.php?id=348. Accessed 2 Jul 2016
Hoff A (2015) Current and future challenges of family care in the UK. Future of an aging population: evidence review. UK Government, Foresight Future of an Aging Population Project. Available via https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/454514/gs-15-18-future-ageing-family-care-er09.pdf. Accessed 2 Jul 2016
Hollander M, Liu G, Chappell N (2009) Who cares and how much? The imputed economic contribution to the Canadian healthcare system of middle-aged and older unpaid caregivers providing care to the elderly. Health Q 12:38–47
Hooker K, Monahan D, Shifre K, Hutchinson C (1992) Mental and physical health of spouse caregivers: the role of personality. Psychol Ageing 7:367–375
Hopkins R, Kilik, L (2015) Providence Care Kingston Caregiver Stress Scale administration and interpretation manual. Available via http://www.providencecare.ca/clinical-tools/Kingston-Scales/Pages/Caregiver-Stress-Scale.aspx. Accessed 4 Feb 2016
Huis in het Veld J, Verkaik R, Mistiaen P, van Meijel B, Francke (2015) The effectiveness of interventions in supporting self-management of informal caregivers of people with dementia; a systematic meta review. Geriatrics 15:147. doi:10.1186/s12877-015-0145-6
International Psychogeriatric Association (IPA) (2002) Module 4: role of caregivers. In International Psychogeriatric Association, Behavioural and Psychological Symptoms of Dementia (BPSD) Educational Pack
Johannesen M, LoGiudice D (2013) Elder abuse: a systematic review of risk factors in community-dwelling elders. Age Ageing 42:292–298
Joseph G, Leach B, Turner S (2007) Caring at a distance: working women, rural to urban migration and the compassionate care challenge. Status of Women Canada Available via http://www.worklifecanada.ca/cms/resources/files/261/CADfinalreporttoSWCcomplete.pdf. Accessed 6 Jul 2016
Katon W, Kleinman A, Rosen G (1982) Depression and somatization: a review. Am J Med 72:241–247
Kiecolt-Glaser J, Glaser R, Shuttleworth E, Dyer C, Ogrocki P, Speicher C (1987) Chronic stress and immunity in family caregivers of Alzheimer's disease victims. Psychosom Med 48:181–189

Kohn R, Verhoek-Oftedahl W (2011) Caregiving and elder abuse. Med Health/Rhode Island 94:47–49
Kramer B (1997) Gain in the caregiving experience: where are we? What next? The Gerontologist 37:218–232
Lazarus R, Folkman S (1984) Stress, appraisal, and coping. Springer Publishing Company, New York
Lund M (2005) Caregiver, take care. Geriatr Nurs 26:152–153
McCallion P, Toseland R, Lacey D, Banks S (1999) Educating nursing assistants to communicate more effectively with nursing home residents with dementia. The Gerontologist 39:456–458
McDonald S, Keesler V, Kauffman N, Schneider B (2006) Scaling-up exemplary interventions. Educ Res 35:15–24. doi:10.3102/0013189X035003015
Mega M, Cummings J, Fiorello T, Gornbein J (1996) The spectrum of behavioral changes in Alzheimer's disease. Neurology 46:130–135
Melo G, Maroco J, de Mendonca A (2011) Influence of personality on caregivers's burden, depression and distress related to BPSD. Int J of Geratric Psychiatry 26:1275–1282
Mitchell J, Kemp B (2000) Quality of life in assisted living homes: a multidimensional analysis. J Gerontol B Psychol Sci Soc Sci 55:P117–P127
Mittelman M (2002) Family caregiving for people with Alzheimer's disease: results of the NYU spouse caregiver intervention study. Generations 26:1
Mittelman M, Haley W, Clay O, Roth D (2006) Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. Neurology 67:1592–1599
Mittelman M, Roth D, Clay O, Haley W (2007) Preserving health of Alzheimer caregivers: impact of a spouse caregiver intervention. Am J Geriatr Psychiatry 15:780–789
Mittelman M, Ferris S, Shulman E, Steinberg G, Ambinder A, Mackell J, Cohen J (1995) A comprehensive support program: effect on depression in spouse-caregivers of AD patients. Gerontologist 35:792–802
Mittelman M, Ferris S, Shulman E, Steinberg G, Lein B (1996) A family intervention to delay nursing home placement of patients with Alzheimer disease. J Am Med Assoc 276:1725–1731
Mittelman M, Roth D, Coon D, Haley W (2004) Sustained benefit of supportive intervention for depressive symptoms in Alzheimer's caregivers. Am J Psychiatry 161:850–856
Morgan D, Semchuk K, Stewart N, D'Arcy C (2002) Rural families caring for a relative with dementia: barriers to use of formal services. Soc Sci Med 55:1129–1142
Mynors-Wallis L, Davies I, Gray A, Barbour F, Gath D (1997) A randomized controlled trial and cost analysis of problem-solving treatment for emotional disorders given by community nurses in primary care. Br J Psychiatry 170:113–119. doi:10.1192/bjp.170.2.113
National Alliance for Caregiving and AARP (2015) Caregiving in the US 2015. Available via http://www.caregiving.org/wp-content/uploads/2015/05/2015_CaregivingintheUS_Final-Report-June-4_WEB.pdf
O'Connell M, Germaine N, Burton R, Stewart N, Morgan D (2012) Degree of rurality is not related to dementia caregiver distress, burden, and coping in a predominantly rural sample. J Appl Gerontol 32:1015–1029
Ortega V, Leung P (2015) Personality and dementia caring: a review and commentary. Curr Opin Psychiatry 28:57–65
Pearlin L, Mullan J, Semple S, Skaff M (1990) Caregiving and the stress process: an overview of concepts and their measures. The Gerontologist 30:583–594
Pepin R, Williams A, Anderson L, Qualls S (2013) A preliminary typology of caregivers and effects on service utilization of caregiver counseling. Aging Ment Health 17:495–507
Perel V (1998) Psychosocial impact of Alzheimer disease. J Am Med Assoc 279:1038–1039
Pinquart M, Sorensen S (2006) Helping caregivers of persons with dementia: which interventions work and how large are their effects? Int Psychogeriatr 18:577–595
Pruchno R, Resch N (1989) Aberrant behaviours in Alzheimer's disease: mental health effects on spouse carers. J Gerontol 44:S177–S182

Reinhard S, Feinberg L, Choula R, House A (2015) Valuing the invaluable: 2015 update. Undeniable progress, but big gaps remain. Available via http://www.aarp.org/content/dam/aarp/ppi/2015/valuing-the-invaluable-2015-update-new.pdf. Accessed 19 May 2016

Reis M, Gold D, Gauthier S (1994) Personality traits as determinations of burden and health complaints in caregiving. Int J Aging Hum Dev 39:257–271

Saad K, Hartman J, Ballared C, Kurina M, Graham C, Wilcock G (1995) Coping by the carers of dementia suffers. Age Aging 24:495–498

Sadavoy J, Wesson V (2012) Refining dementia intervention: the caregiver-patient Dyad as the unit of care. Can Geriatr Soc J Can Med Educ 2:5–10

Schoenmakers B, Buntinx F, Delepereire J (2010) Factors determining impact of care-giving on caregivers of elderly patients with dementia. A systematic literature review. Maturitas 66:191–200

Schulz R, Belle S, Czaja S, Gitlin L, Wisniewski S, Ory M (2003) Introduction to the special section on resources for enhancing Alzheimer's caregiver health (REACH). Psychol Aging 18:357–360

Schulz R, O'Brien A, Bookwala J, Fleissner K (1995) Psychiatric and physical morbidity effects of dementia caregiving: prevalence correlates and cause. Gerontologist 35:771–791

Sinha M (2013) Portrait of Canadian caregivers. Statistics Canada. http://www.statcan.gc.ca/pub/89-652-x/89-652-x2013001-eng.pdf. Accessed 14 Jun 2016

Skaff M, Pearlin L (1992) Caregiving: role engulfment and the loss of self. The Gerontologist 32:656–664. doi: http://dx.doi.org/10.1093/geront/32.5

Smale B, Dupuis S (2002) Highlights: preliminary results from the study on needs of caregivers of persons with Alzheimer disease or a related dementia and community support services in Ontario. Murray Alzheimer Research and Education Program/Alzheimer Society of Ontario/Caregivers' Association of Ontario, Waterloo

Sorensen S, Pinquart M, Duberstein P (2002) How effective are interventions with caregivers? An updated meta-analysis. The Gerontologist 42:356–372

Spurlock W (2005) Spiritual well-being and caregiver burden in Alzheimer's caregivers. Geriatr Nurs 26:154–161

Turcotte M (2013) Family caregiving: what are the consequences? Statistics Canada. Available via http://www.statcan.gc.ca/pub/75-006-x/2013001/article/11858-eng.pdf

Vitaliano P, Young H, Russo J, Romano J, Magana-Amato A (1993) Does expressed emotion in spouses predict subsequent problems among care recipients with Alzheimer's disease? J Gerontol 48:202–209

Williams R, Briggs R, Coleman P (1995) Carer rated personality changes associated with senile dementia. Int J Geriatr Psychopharmacol 10:231–236

Witters D (2011) Caregiving costs US economy nearly $25.2 billion in lost productivity. Available via http://www.gallup.com/poll/148670/caregiving-costs-economy-billion-lost-productivity.aspx. Accessed 5 Jul 2016

Yesavage J, Brink T, Rose T, Lum O, Huang V, Adey M, Leirer V (1982-1983) Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17:37–49

Zarit S, Reever K, Bach-Peterson J (1980) Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 20:1980

Zarit S, Todd P, Zarit J (1986) Subjective burden of husbands and wives as caregivers: a longitudinal study. The Gerontologist 26:260–266

Prevention of Alzheimer's Disease and Alzheimer's Dementia

22

Tom C. Russ, Craig W. Ritchie, and Karen Ritchie

Abstract

This chapter will consider the prevention of dementia. The often neglected distinction between Alzheimer's disease and Alzheimer's dementia (and the formal inclusion of this distinction in the 2011 diagnostic criteria) will form our main focus, and, in particular, the consequent relevance of the life course paradigm in epidemiology that influences from any stage of life could potentially increase or decrease one's risk of dementia. We will consider a number of risk factors for Alzheimer's disease (i.e., primary prevention) including early life factors, intelligence and education, proxies for early life factors, midlife risk factors, multiple risk factors, and environmental factors. In considering prevention of Alzheimer's dementia (i.e., secondary prevention), we will consider the relevance of the theory of cognitive or brain reserve. We will briefly consider attempts at disease modification in dementia (i.e., tertiary prevention) and the

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_23

multiple trial failures seen in recent decades. After outlining the policy context, we will consider two important prevention initiatives: the PREVENT program and the European Prevention of Alzheimer's Dementia (EPAD) project.

Keywords
Prevention • Alzheimer's disease • Alzheimer's dementia • Delirium • Depression

Contents

Introduction - Alzheimer's Disease and Alzheimer's Dementia

Prevention is traditionally divided into primary, secondary, and tertiary prevention. Primary prevention refers to preventing a condition developing in the first place in healthy people which, as will be seen below, is more complicated than it might first appear in dementia. Secondary prevention either prevents the disease recurring or becoming clinically manifest. In the context of dementia, the aim of secondary prevention is to prevent or delay the clinical onset of Alzheimer's dementia in individuals who already have the pathological changes of Alzheimer's disease in their brain. Tertiary prevention refers to attempts to modify the disease and its symptomatic course once it has become symptomatically apparent (e.g., as prodromal Alzheimer's dementia where change is detected on cognitive tests designed to detect dementia but there is no impairment in everyday living) so that patients do not progress to later, higher morbidity stages of the condition. Figure 1 outlines how these distinctions apply to Alzheimer's disease and dementia. It is clear that defining these categories relies on a comprehensive understanding of the natural history of the condition in question. However, in the case of Alzheimer's

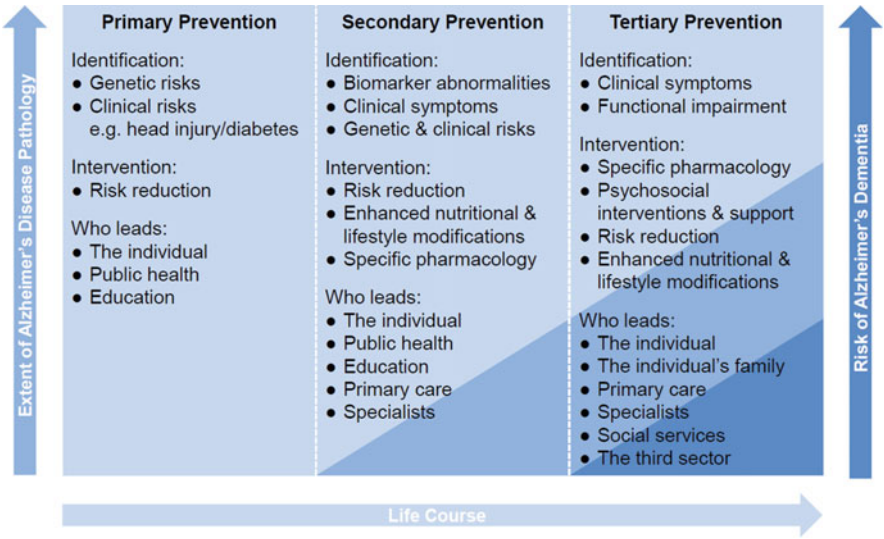

Fig. 1 Primary, secondary, and tertiary prevention of Alzheimer's disease and dementia

disease, there remain a great number of unanswered questions about its etiology and subsequent development. Nevertheless, we will attempt to summarize our current understanding of the pertinent aspects of this increasingly common condition.

The Origins of Alzheimer-Type Neuropathology

Alzheimer's disease is widely considered a condition of later life. However, it is increasingly clear that Alzheimer's *disease* begins decades earlier as covert brain changes, with Alzheimer's *dementia*, in contrast, being a late manifestation of this disease which is clinically overt (Ritchie et al. 2015). Unselected autopsy studies of brains from individuals of all ages demonstrate that the neuropathological changes characteristic of Alzheimer's disease (both amyloid and tau pathology, but particularly the former) begin to develop years – or even decades – before the clinical onset of symptoms (Braak and Braak 1991, 1997; Braak and Del Tredici 2010; Braak et al. 2011).Despite substantial evidence for this important distinction, many authors are often guilty of imprecise language, most often by using the ambiguous abbreviation "AD."

Indeed, many people without dementia have substantial Alzheimer-type pathology. This has been seen in autopsy studies, in vivo imaging studies, and evidence from CSF biomarkers. The Religious Orders Study and the Memory and Aging Project in the USA (Bennett et al. 2006) as well as the UK MRC Cognitive Function and Ageing Study (Wharton et al. 2011) all found that approximately a third of people who died without dementia had substantial Alzheimer-type

pathology in their brains at autopsy. This evidence is corroborated in living people with normal cognition, of whom rates of amyloid positivity on PET scanning range from 10% in 50-year-olds to 44% in 90-year-olds, with higher rates in people who carry the ε4 allele of *APOE* or who have some cognitive impairment (Jansen et al. 2015). Findings from studies of CSF biomarkers ($A\beta_{42}$, total tau, and phosphorylated tau) give broadly similar results suggesting that a large minority of cognitively intact older adults have Alzheimer's disease (Randall et al. 2013). However, this may at least in part be due to the fact that the cognitive tests used in designating individuals as "cognitively intact" have been relatively crude measures of higher level functions and have been unable to capture decline in specific brain structures.

Data supporting the use of biomarkers for the diagnosis of dementia in general are currently limited and variable in quality (Noel-Storr et al. 2013), though they seem be able to differentiate people with dementia successfully from controls (Olsson et al. 2016). Three recent Cochrane Diagnostic Test Accuracy Reviews highlighted this as they demonstrated that amyloid-β levels (a core pathological lesion in Alzheimer's disease) whether measured in CSF (Ritchie et al. 2014) or using PET imaging (Vacante et al. 2015; Zhang et al. 2014) had very low specificity but better sensitivity for people with mild cognitive impairment subsequently developing Alzheimer's dementia.

Taken together, all this evidence leads to the conclusion that Alzheimer's *disease* (neuropathological changes in the brain) and Alzheimer's *dementia* (cognitive decline and behavioral functional decline) are not identical but, rather, two related, parallel phenomena.

The New Diagnostic Criteria

In 2011, the Alzheimer's Association updated the 1984 McKhann criteria for Alzheimer's disease (also known as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association or NINCDS-ADRDA criteria; McKhann et al. 1984). These updated criteria marked such a substantial modification of the concept of Alzheimer's disease that they constituted a suite of papers almost 50 pages long (Albert et al. 2011; Gauthier et al. 2011; Herrup 2011; Jack et al. 2011; Khachaturian 2011; Korczyn 2011; Lyketsos 2011; McKhann et al. 2011; Sperling et al. 2011).

The change with arguably the biggest impact was the introduction of an explicit period of "preclinical" Alzheimer's disease, when Alzheimer's disease was present in the brain (and could theoretically be identified using biomarkers) but without clinical symptoms (Sperling et al. 2011). Thus, the distinction made above between Alzheimer's *disease* and Alzheimer's *dementia* has been made explicit in the most widely used criteria, albeit using slightly different language. The title of the article introducing the preclinical Alzheimer's disease concept begins "Towards defining the preclinical stages of Alzheimer's disease,"

highlighting the fact that there is still much to learn about this important period, not least because this may well be a window of opportunity to intervene and delay or prevent the onset of clinical dementia. However, it is now accepted that the whole life course is relevant to dementia risk, an approach which will be developed in the next section.

Life Course Epidemiology

We have already seen that Alzheimer's disease begins decades before Alzheimer's dementia. Clearly, the triggers for these early brain changes must also lie earlier in life than previously thought. Many chronic conditions are now thought to relate to influences at all stages of the life course, and this has led to the development of a new paradigm in epidemiology, that of *life course epidemiology* (Ben-Shlomo and Kuh 2002; Kuh and Ben-Shlomo 2004). This model simply suggests that factors from all stages of development – i.e., at any point in the life course – may influence (either increase or decrease) an individual's probability of developing the condition in question. Risk may be accumulated over time or a particular factor may influence risk only at a particular point in time (a critical period) or more at one point in time than at other times (a sensitive period). This ties in with the observation that the most significant risk factor for dementia – by far – is chronological age (at least until about 90 years old), and, thus, improving risk modeling for dementia (and any hope of preventing it) will necessarily involve better understanding of the process of brain aging itself (Brayne 2007).

The growing consensus that a longer period of an individual's life may be relevant to their dementia risk has led to the widespread application of this paradigm to Alzheimer's disease (Whalley 2015; Whalley et al. 2006). An advantage of this life course approach is that it provides a framework to help disentangle the genetic and epigenetic factors as well as complex gene-environment interactions which most probably work together to determine dementia risk. It also lays the foundation for interventions – principally at a public health level – targeting groups and focusing resources with modification of risks during critical or sensitive periods based on the evidence, though individual, tailored risk factor modification is also feasible if accurate probability models are developed which highlight the factors relevant to any given individual. In the next section, we will consider putative modifiable risk factors for preventing Alzheimer's disease and Alzheimer's dementia.

Prevention of Alzheimer's Disease

The long list of failures of interventions tried in people with established dementia adds weight to the idea that Alzheimer's dementia might represent the later stages of a long process and that secondary prevention may be more successful with intervention at an earlier stage and/or younger age when the brain is better preserved. If the neuropathological changes of Alzheimer's disease begin in midlife, this means

that interventions which are truly primary prevention would need to begin earlier than that. Therefore, it would be helpful from a methodological point of view to have a reliable method to identify early brain changes of Alzheimer's disease in vivo, in order to identify people in whose brains not even the very early stages of Alzheimer's disease are detectable. Many middle-aged people with no symptoms of dementia are in fact likely to have early Alzheimer's disease and considered therefore at high probability of developing Alzheimer's dementia. Thus, true primary prevention initiatives would have to go "upstream" and begin in early adulthood, if not even earlier in life.

We defined primary prevention above as attempting to prevent Alzheimer's disease developing in the first place and have just suggested that many midlife prevention studies were, in fact, secondary prevention – the prevention of Alzheimer's dementia in people who already had some Alzheimer's disease in their brains. Nevertheless, in the sections which follow, we will consider primary prevention at two levels: the individual and the population. Individual-level risk factors could potentially be targeted at any stage of the life course and, indeed, could be the focus of population-wide public health interventions or, in the case of rare but highly potent risk factors (e.g., severe head injury), targeted interventions in selected populations. Population-level risk factors, on the other hand, have been relatively understudied, and in this chapter, we will focus on environmental risk factors and a geographical approach through disease mapping.

Early Life Events

We have seen that the life course paradigm suggests that risk and protective factors from all periods of life are potentially relevant. Until recently, there has been no evidence directly linking birth parameters with brain aging. An indirect link can be inferred from the influence of birth weight (and parental social class) on cognitive function at age of 11 years (Shenkin et al. 2001) which, in turn, is a risk factor for dementia, possibly more so for vascular dementia than Alzheimer's dementia (Whalley et al. 2000; McGurn et al. 2008). However, a recent retrospective cohort study as part of the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study in Iceland demonstrated that lower birth weight was associated with slower processing speed and poorer executive function at aged 75 years, but only in those with lower educational attainment (Muller et al. 2014). It can be seen that there are complex interplays between cognition, education, and socioeconomic status which need to be further clarified, but this finding that birth weight – hypothesized to be a measure of the intrauterine environment – is related to cognitive function in later life is an exciting one which echoes other such findings in the area of "fetal origins of adult diseases" (Barker 1990; Calkins and Devaskar 2011).

Another early life risk factor for dementia which has been identified is early parental death which has been linked with later Alzheimer's dementia in a study in Gothenburg, Sweden (Persson and Skoog 1996), the Cache County Study (Norton et al. 2009, 2011) and the Aberdeen Birth Cohort Study (Whalley et al. 2013). One

explanation for this association could be a detrimental effect on socioeconomic position through loss of earning potential, particularly since there is some attenuation with remarriage of the bereaved parent (Norton et al. 2011). However, there is also a suggestion of critical periods – loss of father before the age of 5 years and loss of mother in adolescence – which could be consistent with a response to traumatic loss at crucial developmental periods (Norton et al. 2011). It has been further suggested that the relationship may be modulated by *APOE* genotype (Ritchie et al. 2011).

Intelligence and Education

We alluded above to the association between lower early life intelligence and an increased risk of dementia in later life, possibly more so for vascular dementia than Alzheimer's dementia (Whalley et al. 2000; McGurn et al. 2008; Russ et al. In Press). These findings come from the Aberdeen and Lothian Birth Cohort and Scottish Mental Survey Cohort studies which were made possible by the discovery in the 1990s of the results of intelligence tests sat by all 11-year-olds in Scotland in the summers of 1932 and 1947 which allowed these individuals to be followed up in later life (Scottish Council for Research in Education 1933, 1949; Deary et al. 2009, 2012; Whalley et al. 2011).

A similarly serendipitous discovery has come from the Nun Study which examined early life linguistic ability inferred from autobiographical essays written by the nuns shortly before taking their religious vows (Snowdon 2011). The measures of linguistic ability derived from these documents were "idea density" and "grammatical complexity." Lower levels of both measures – particularly the former – were associated with poorer cognition in later life and an increased risk of pathologically confirmed Alzheimer's dementia (Riley et al. 2005; Snowdon et al. 1996).

Over and above individual intelligence, shorter duration of education has also been linked with dementia risk. A recent meta-analysis of all available published studies found a pooled effect size of 83% increase in dementia incidence (95% confidence interval 63–105%) in studies without adjustment for other variables and a 72% (52–96%) increase in studies which did adjust for relevant confounders (Prince et al. 2014). The same report found that education seemed to explain some reported associations between occupation and dementia risk.

Proxies for Early Life Factors

Measurement of early life factors in the context of dementia research is challenging. Recall later in life is prone to reporting bias (Batty et al. 2005). On the other hand, few studies have contemporary measures of early life factors associated with sufficiently long follow-up for dementia to have developed. Therefore, some researchers have begun to look instead for proxies for early life experience. One example is the association between physical stature and dementia. Maximal height is attained in the

first two decades of life and, in addition to being influenced by genes, is regarded as a marker of early life experience, including illness, adversity, nutrition, and psychosocial stress (Batty et al. 2006). Thus, height could be considered a proxy for these factors. The fact that shorter height is associated with an increased risk of dementia leads one to conclude that such early life adversity may influence the individual's subsequent risk of developing dementia (Rosness et al. 2015; Russ et al. 2014). However, this association is seen more strongly (or solely) in men which may relate to male children being more sensitive to their early environments (Russ et al. 2014).

Another measure which captures relevant exposures throughout the life course is pulmonary function (estimated by a variety of spirometric measures, including forced expiratory volume, forced vital capacity, and peak expiratory flow) which is influenced by smoking, illness, and socioeconomic deprivation at various stages of life. The association between poorer lung function and increased dementia risk further supports the life course perspective in dementia and points to the possible importance of these factors in the development of the disease (Russ et al. 2015b; Yoon et al. 2015). However, the picture is more complicated here. While it is difficult to imagine how shorter height might, in itself, affect dementia risk, poorer lung function could plausibly be a risk factor in its own right, affecting the brain through hypoxia, reduced oxygenation of brain tissues with the associated hypercapnic state leading to a lower brain pH which is known to drive amyloid-β aggregation (Atwood et al. 1998), as well as being a risk marker because of the factors mentioned above which influence it.

Midlife Risk Factors

A number of risk factors – many also being risk factors for cardiovascular disease – measured in midlife have been linked with subsequent dementia risk, notably hypertension and obesity (Prince et al. 2014). However, both of these physical parameters change over the life course which can complicate the interpretation of their association with dementia risk. Blood pressure, for example, decreases in the years preceding a diagnosis of dementia (Skoog et al. 1996). This could lead one to the erroneous conclusion that lower blood pressure in later life was a risk factor for dementia when this relationship is, in fact, an example of reverse causality. The relationship observed between trajectories of blood pressure and later dementia risk is even more complex and affected by treatment with antihypertensive drugs (Joas et al. 2012).

The association between body mass index (BMI) and dementia may be even more complex still. An association between being underweight and an increased risk of dementia was recently reported from a large study of two million patients in primary care (Qizilbash et al. 2015), and this seems to have been replicated in the Whitehall I Study (Kivimaki et al. 2015). Since this contradicts the received opinion that raised BMI is associated with dementia risk (Daviglus et al. 2010a, b; Prince et al. 2014), there has been a great deal of speculation regarding this finding. Suggested explanations have included the possibility that investigators conflated midlife and late-life

BMI measurement by including individuals aged 40–80 years at baseline in the study (Strand et al. 2015) and the hypothesis that the focus should be on weight loss rather than absolute BMI in relation to dementia (van der Burg et al. 2015). The latter point seems to be supported by the finding that different trajectories in BMI can be seen in those who go on to develop dementia compared to those who do not (Gustafson et al. 2012).

Multiple Risk Factors

Seven potentially modifiable individual-level risk factors for Alzheimer's disease have been highlighted as particularly important: in early life, educational attainment; in midlife, hypertension and obesity; and throughout the life course, diabetes, smoking, depression, and physical inactivity (Barnes and Yaffe 2011). Approximately half of Alzheimer's dementia cases worldwide were estimated to be attributable to these risk factors, and a 10% reduction in each could theoretically prevent a million cases worldwide; a 25% reduction would prevent three million cases. However, these risk factors are not independent – many people who are obese in midlife will also have diabetes, for example. Therefore, a further analysis taking this into account estimated that eliminating all the risk factors would prevent 28% cases of Alzheimer's dementia worldwide (Norton et al. 2014). Smaller, more feasible reductions of 10% (or 20%) in each of these risk factors were estimated to prevent 8% (or 15%) cases worldwide by 2050. However, factors such as confounding, bias, and reverse causality are likely to complicate the association between risk factor and dementia in the real world and reduce the true effects of such projected estimated impacts of risk factor reduction. Unmeasured confounders, especially those appearing at earlier ages, could have easily been overlooked leading to erroneous propositions for effective intervention. Bias – the consequence of selective mortality or incomplete follow-up – could also mean that these findings might not translate completely into the real world. Finally – and probably most relevant to dementia given what we know of its natural history – reverse causality must always be very carefully considered, i.e., the possibility that the early stages of the condition (i.e., preclinical or prodromal Alzheimer's disease) might influence the risk factors themselves.

Thus, the best evidence regarding risk factors on late-life dementia incidence points to a small number of educational, cardiovascular, and metabolic risks (Ritchie et al. 2010). However, much of the epidemiological work in this area relies on older cohorts and therefore ignores exposures and subclinical comorbidities earlier in life which may have delayed impact.

Environmental Risk Factors

Investigating geographical variation in disease has proved a fruitful approach in other areas of medicine and is now being studied in dementia. The geographical

distribution of dementia risk is not random and varies from location to location (Whalley 2012), and a systematic review summarizing studies which compared two sites using identical methodologies at each (thus removing the possibility that any differences might result from methodological differences between studies) concluded that there was evidence at all geographical scales for geographical variation in dementia prevalence and incidence (Russ et al. 2012). However, there were very few large-scale (i.e., small area) studies which would be the only ones showing this variation in sufficient detail to shed light on possible risk factors which may be behind this geographical variation. More recently, a small-area Bayesian disease-mapping study of the HARMONY (Dementia in Swedish Twins) and related cohorts found two- to threefold higher odds of dementia in the north of Sweden compared to the south after the removal of genetic and shared environmental variance, suggesting that this variation is the result of environmental risk factor(s) (Fig. 2; Russ et al. 2015a). Indeed, the importance of the influence of environmental differences between children from the same family has been described as "[o]ne of the most importance findings that has emerged from human behavioral genetics" (Plomin and Daniels 2011). A complementary study using a narrow age cohort of people born in

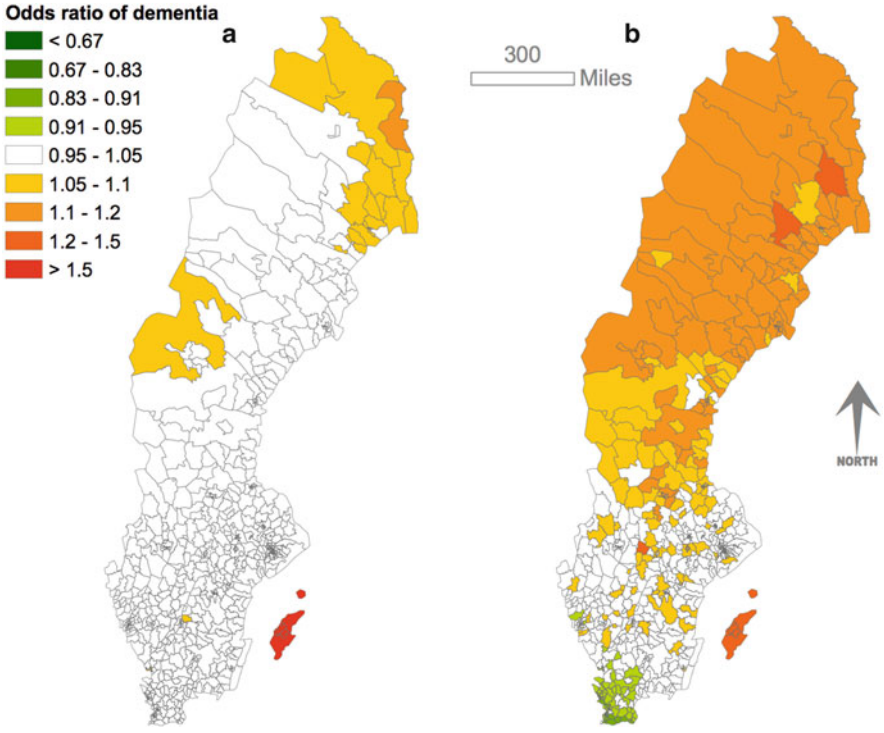

Fig. 2 Age-adjusted odds ratio of dementia in male (**a**) and female (**b**) Swedish twins with twin-level random effects (likely to capture genetic and shared environmental variance) removed (Russ et al. 2015a) (Reproduced with permission from the publisher, Wolters Kluwer Health, Inc.)

the UK in 1921 followed up into their ninth decade showed no variation in dementia odds based on the county of school attended aged 11 years but with substantial variation, broadly similar to Sweden, based on residential location after the age of 60 years (Fig. 3; Russ et al. 2015a).

These findings have now been corroborated in Italy (Fig. 4) and, furthermore, in the southern hemisphere (Russ et al. 2016). In New Zealand, dementia mortality, in women, at least is higher in South Island compared to North Island (Fig. 5) – this inverse pattern to the northern hemisphere could suggest a relationship with latitude. In Chile, however, a more complex pattern of geographical spread of dementia risk was seen (Fig. 6).

Geographical variation in dementia risk has thus been consistently observed in several countries. The factors responsible are being actively investigated, but there are several possible environmental factors which may be related (Killin et al. 2016): vitamin D deficiency and air pollution, in particular. Vitamin D has been linked to brain health through a variety of mechanisms including amyloid clearance and cerebrovascular function (Annweiler et al. 2013, 2015; Balion et al. 2012; Littlejohns et al. 2014). Individuals living at higher latitudes have lower serum vitamin D levels (Brouwer-Brolsma et al. 2013). Thus, vitamin D deficiency could be a plausible explanation for the geographical variation in dementia described above. Another possibility is selenium which has been linked to brain health (Berr et al. 2012; Loef et al. 2011) and which is present in the soil at lower levels in the north of Sweden compared to the south (Parkman and Hultberg 2002). Ambient air pollution – particularly particulate matter with aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) – has also been consistently linked with brain health (Clifford et al. 2016). Indeed, there is evidence that it is associated with loss of white matter which might represent accelerated brain aging (Chen et al. 2015). This might explain the particularly high dementia mortality observed in the Santiago Metropolitan Region, an area with high levels of air pollution (Fig. 6; Russ et al. 2016).

Clearly much more detailed research is required to clarify the mechanisms behind the observed geographical variation in dementia risk, but it seems to be a fruitful avenue to pursue alongside more well-established efforts such as cardiovascular disease risk. However, it is also important to remember that this approach has led to the identification of potential risk factors, for example, aluminum in drinking water, whose status remains highly controversial (Flaten 2001; Killin et al. 2016; Martyn et al. 1989; Yegambaram et al. 2015).

Prevention of Alzheimer's Dementia

We saw above that it appears that you may need Alzheimer's pathology to develop Alzheimer's dementia, but you can have Alzheimer's pathology and still enjoy normal cognitive health well into later life. There is evidence that delaying the clinical onset of symptoms would have substantial effects on the number of people

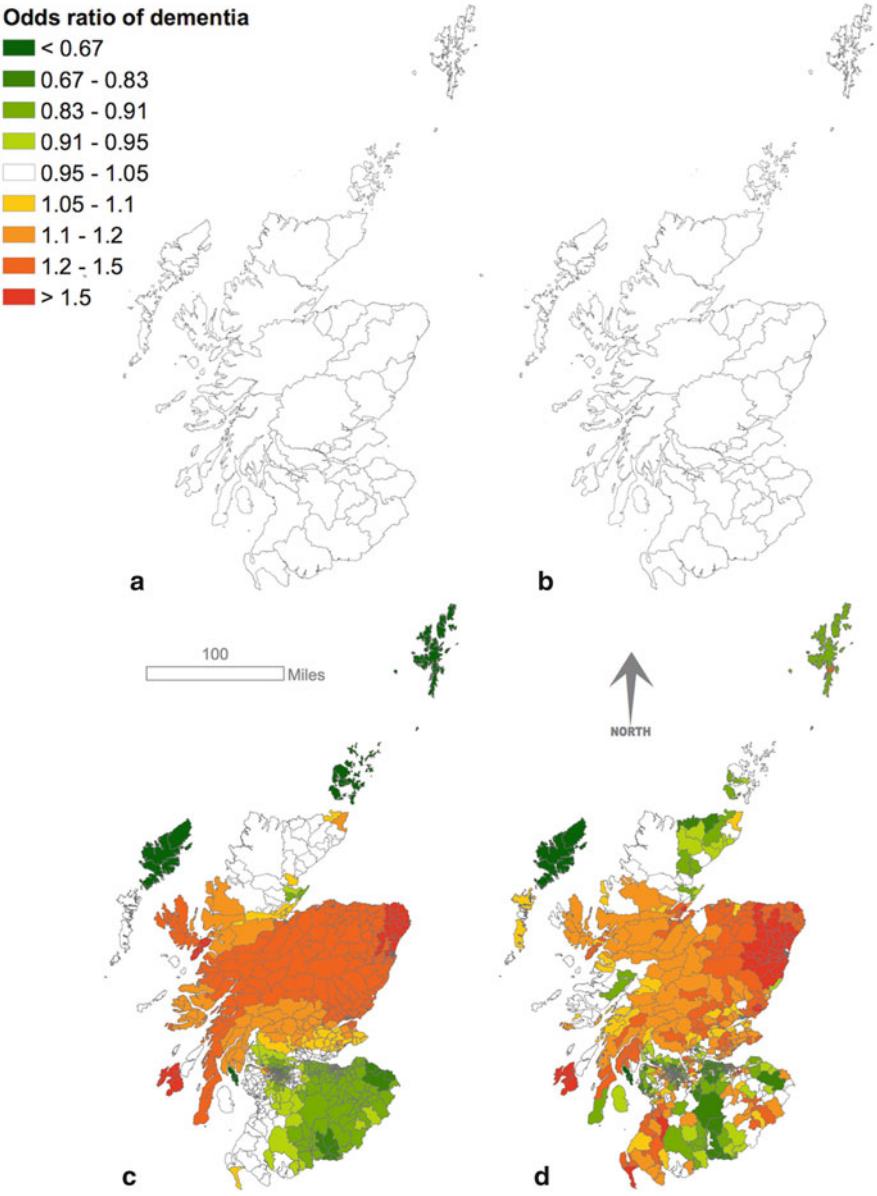

Fig. 3 Age-adjusted odds ratio of dementia in the Scottish Mental Survey 1932 cohort – childhood: males (**a**), females (**b**); adulthood: males (**c**), females (**d**) (Russ et al. 2015a) (Reproduced with permission from the publisher, Wolters Kluwer Health, Inc.)

with dementia by compressing morbidity, therefore increasing the number of years spent disease-free (Brookmeyer et al. 1998, 2007; Ritchie et al. 2016). Indeed, because of the long, clinically silent latent period of Alzheimer's disease, rather

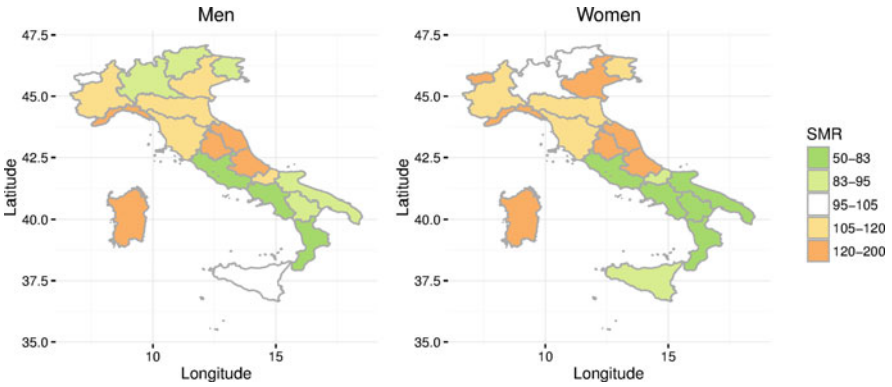

Fig. 4 Dementia Standardised Mortality Ratios by region of Italy for men and women (Russ et al. 2016). This figure is reproduced under a Creative Commons License (CC BY-NC-ND) (The final, published version of this article is available at http://www.karger.com/?doi=10.1159/000447449)

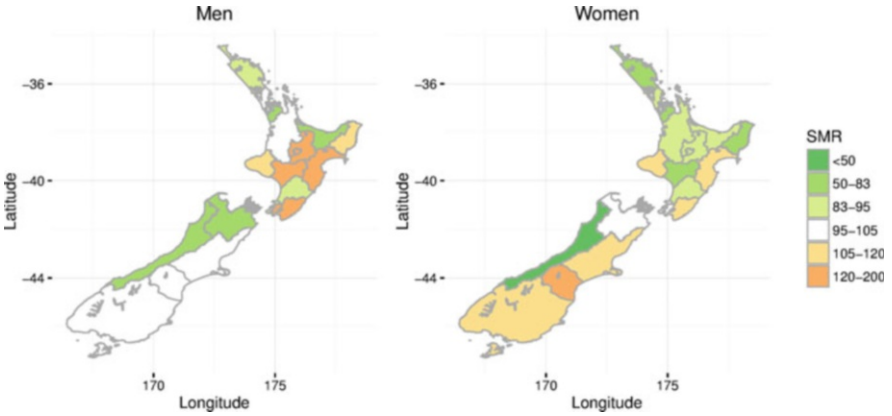

Fig. 5 Dementia Standardised Mortality Ratios by District Health Board of New Zealand for men and women (population aged 50 years and older) (Russ et al. 2016). This figure is reproduced under a Creative Commons License (CC BY-NC-ND) (The final, published version of this article is available at http://www.karger.com/?doi=10.1159/000447449)

than representing primary prevention, many midlife intervention studies would probably fall under our definition of secondary prevention.

Cognitive/Brain Reserve

We have already seen that the "preclinical" period of Alzheimer's disease – i.e., before someone develops the clinical symptoms of Alzheimer's dementia, commonly cognitive changes, predominantly memory, and functional decline – is likely to be a good point to intervene in order to delay or prevent the clinical onset of dementia. However, one question we have not yet addressed is what influences the timing of the clinical

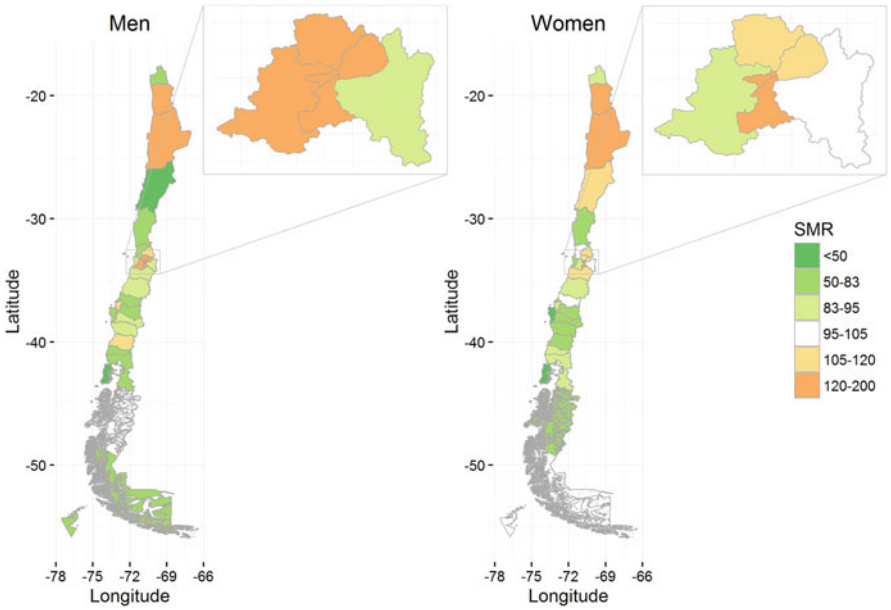

Fig. 6 Dementia Standardised Mortality Ratios by Health Service area of Chile for men and women *Inset*. Santiago Metropolitan Region (magnified) (Russ et al. 2016). This figure is reproduced under a Creative Commons License (CC BY-NC-ND) (The final, published version of this article is available at http://www.karger.com/?doi=10.1159/000447449)

onset of these symptoms? Many people without dementia have Alzheimer's disease in their brains – why is it that they do not have any symptoms of dementia?

A relevant theory to consider when seeking an answer to this question is that of cognitive reserve – that certain people's brains are more resilient to the pathological changes of aging and Alzheimer's disease (Stern 2012). This concept includes the overlapping ideas of brain reserve and cognitive reserve. The former primarily reflects structural differences, for example, numbers of neurons, whereas the latter refers to a more active process in which the brain adapts to compensate for age- or disease-related changes by altering or optimizing its function. Support for the idea of cognitive reserve comes from the association between lower educational and occupational attainment and increased dementia risk, suggesting that brain changes resulting from positive learning and occupational experiences could render the brain less susceptible to insult (Valenzuela and Sachdev 2006). A corollary of the ability of being able to tolerate more pathology before the clinical onset of dementia (i.e., people with greater cognitive reserve) is that such people decline more rapidly after diagnosis, analogous to a dam being broken – the dam in question being built through the person's life through education (Stern et al. 1995, 1999). Further biological support for the concept of cognitive reserve can be found in the observation that people with dementia with greater educational attainment show decreased

parietotemporal blood flow on PET scans compared to people with dementia with the same levels of clinical symptoms but who left school at a younger age (Stern et al. 1992). A linked finding is that levels of neuropathology do not seem to relate well to levels of clinical symptoms. This is particularly the case for amyloid though tau levels in the brain may relate better to symptoms (Arriagada et al. 1992).

Disease Modification of Dementia

Findings from intervention studies in late life in people with dementia – including those looking at medication (Mangialasche et al. 2010) or risk factor modification (McGuinness et al. 2009, 2014) – have been uniformly disappointing. Indeed, the only pharmacological treatments currently available are symptomatic in their effect and do not modify the course of the disease, though there was much excitement surrounding the results of a trial of the antibody Aducanumab in a mouse model of amyloid deposition (Sevigny et al. 2016).

In the context of dementia, tertiary prevention would encompass both disease-modifying treatments targeting individuals who have already shown cognitive and/or functional decline (i.e., prodromal Alzheimer's dementia) as well as pharmacological treatments targeting symptom profiles and psychosocial interventions. Disappointingly, though there have been a large number of studies targeting disease modification over the last two decades in this population, they have been predominantly negative (Mangialasche et al. 2010; Schneider et al. 2014). Perhaps this stands to reason when we consider the patho-clinical course being proposed for Alzheimer's disease, whereby people with even mild Alzheimer's dementia may in fact have very severe Alzheimer's disease which has been occult (using current technologies) for decades. In effect, people with Alzheimer's dementia already have end-stage brain failure with multiple concurrent pathological processes being relevant. Therefore, a single targeted approach to one pathology is highly unlikely to produce substantial clinical benefit. There was much interest in findings presented at the 2015 Alzheimer's Association International Conference that a sample of participants in the negative phase 3 trials of solanezumab (Doody et al. 2014; Siemers et al. 2016) with mild Alzheimer's dementia who were allocated during the double-blind phase to the treatment group have subsequently declined more slowly than participants who were in the control group, despite both groups receiving the treatment after the end of the trials (Liu-Seifert et al. 2015). However, while this single positive finding is encouraging, the effect remains small and merely maintained people in a state of dementia without recovery to an earlier phase of the clinical syndrome. Moreover, these findings will require corroboration in further ongoing trials, and, practically speaking, it is unlikely that an expensive treatment administered as an infusion would become widely used in clinical practice, particularly given the small effect size. However, if asymptomatic people showing evidence of Alzheimer's disease could be identified using what will come to be known as

"partner diagnostics," the impact of disease modification for secondary prevention is likely to be much more meaningful and therefore cost-effective.

Policy Context

The conclusions of the US National Institutes of Health State-of-the-Science Conference on "Preventing Alzheimer's Disease and Cognitive Decline" (Daviglus et al. 2010a, b) were not optimistic: "Currently, no evidence of even moderate scientific quality exists to support the association of any modifiable factor . . . with reduced risk for Alzheimer disease" (Daviglus et al. 2010b). They made several recommendations for future research, including robust definitions of the outcome used in dementia studies, involving caregivers in estimating daily function and instituting robust new population-based cohort studies as well as using existing cohort studies, for example, of cardiovascular disease risk factors, participants in which are aging. A more optimistic statement entitled simply "Dementia (Including Alzheimer's Disease) can be Prevented" appeared following the G8 Dementia Summit in London. They concluded that more work was required to discover further modifiable risk factors for dementia but, importantly, that "[t]here is already sufficient evidence to justify immediate action . . . [i.e.] tell people that adopting a healthy lifestyle may help to ward off dementia as it does for other diseases"(Smith and Yaffe 2014). The authors estimated that public health measures such as smoking cessation, adopting the Mediterranean diet, preventing obesity and diabetes, avoiding excessive alcohol consumption, and treating hypertension could prevent 20% of new cases of dementia over the next 10 years. The Blackfriars Consensus on brain health and dementia (Lincoln et al. 2014; Public Health England and UK Health Forum 2014), which came out around the same time, was fuelled in its optimism by reports of decreasing dementia prevalence. Its focus was the etiological overlap between vascular risk and dementia and concluded that "[t]he scientific evidence is evolving rapidly and sufficient to justify considered action and further research on dementia risk reduction, both by reducing the modifiable risk factors and improving the recognised protective factors" (Public Health England and UK Health Forum 2014). They too called for more population-based cohort studies (both new and existing cohorts) and highlighted the MRC-funded Dementias Platform UK and the EU Joint Programme on Neurodegenerative Disorders.

Alzheimer's Disease International's (ADI) 2014 World Alzheimer Report focused entirely on risk reduction (Prince et al. 2014). It reviewed the evidence for various risk factors for dementia: developmental and early life factors, psychological factors, lifestyle-related factors, and cardiovascular disease risk factors. There was strong evidence for potentially causal associations between low educational attainment, midlife hypertension, and smoking and diabetes (both at any stage of life) with dementia. There was also evidence supporting physical and cognitive activity, but the possibility of reverse causality still remained. They highlighted the importance of cognitive/brain reserve and vascular pathology.

Prevention Initiatives

In Fig. 1, we outlined the concept of secondary prevention as it applies to Alzheimer's disease and Alzheimer's dementia. That is, that, in contrast to people with advanced, symptomatic disease, people with evidence of disease but no (or minimal) symptoms may derive maximal benefit from disease-modifying interventions or combinations of interventions. The benefit is likely to be maximal because of two facts: first, the disease processes will be at an earlier phase and therefore more likely to be susceptible to intervention; second, since dementia is recognized as being the end point of brain failure with multiple pathological processes contributing to the clinical phenotype, specific interventions lead to little, if any, net clinical benefit. It is highly unlikely that all neurodegenerative disease pathologies emerge simultaneously – it is much more likely that this is a sequential process. If this sequence could be defined empirically, it would be possible to target the most upstream, potentially triggering process which could fundamentally affect the disease course and therefore lead to maximal (clinical) benefit.

The search for Alzheimer's disease decades before dementia is expected to develop and is the specific focus of programs like PREVENT (Ritchie and Ritchie 2012, 2013). PREVENT comprises six research domains: (1) identifying risk factors, (2) characterizing risk in midlife, (3) biological and cognitive expression of neurodegenerative disease, (4) developing surrogate markers for a reduction in dementia incidence, (5) secondary prevention intervention studies, and (6) formulating the social, political, and ethical framework for applying risk screening and intervention programs (Ritchie et al. 2013). Such projects hypothesize that earlier life disease will be a more specific indicator of later dementia than it has been shown to be – in multiple projects – in later life.

There are three major challenges when testing novel interventions for the secondary prevention of Alzheimer's dementia:

(1) We need empirically derived disease models for secondary prevention, but how can we assess research participants from a biological and clinical perspective to derive data which can be used to improve these models – for example, which biomarkers should we be investigating? How does one measure cognition in preclinical (i.e., unimpaired) populations which capture underlying brain impairment? What other features – possibly not currently studied – might be relevant to these models?
(2) How do we take these probability models and apply them to real people in order to stratify them by their probability of decline – which is necessary in the placebo group to drive effect in the proof-of-concept clinical trial?
(3) How, in the absence of either of these, can you create the simulations necessary for adaptive trial designs to test novel interventions?

These three challenges are precisely why the European Prevention of Alzheimer's Dementia EPAD) project was started (Ritchie et al. 2016; Vaudano et al. 2015). This

Innovative Medicines Initiative-funded public-private partnership will develop a rolling longitudinal cohort study of 6,000 people without dementia drawn from pre-existing cohort studies. Every participant will undergo detailed biological and clinical testing (including PET amyloid imaging, CSF- and blood-based biomarkers in addition to a bespoke cognitive outcome measure, EPAD clinical evaluation). Thus, participants in the EPAD longitudinal cohort study will act as a "readiness cohort" for the trial (described below).

The cohort will also generate a vast amount of data for improved disease modeling in the context of secondary prevention. For example, it will be possible to create individualized three-dimensional probability scores based on risk factors, biomarkers, and clinical measures. Using these probability scores, subpopulations with evidence of amyloid pathology (or whatever the target pathology relevant to the proposed therapy is) and who are likely to decline during the proposed duration of the trial will be able to be identified. The trial will be perpetual with new (combinations of) drugs being introduced regularly and others being withdrawn as they show futility or success, the latter graduating to phase 3 confirmatory studies.

The trial itself will use adaptive methodologies to optimize selection of subjects as well as attempting to control multiple factors which could be responsible for the recurrent failures of trials in the recent past. These include reducing screen failures to a minimum through knowledge of every subject's disease status pre-baseline, measuring the post-randomization effect of drugs by using run-in data from the longitudinal cohort study, continuous updating of disease models using all available data from the trial and cohort study, and finally minimizing measurement bias through a dedicated network of EPAD Trial Delivery Centres to ensure the highest standards of data quality.

While the main focus of EPAD is pharmacological approaches, other (non-pharmacological) multimodal approaches are showing promising results. Preliminary results from the first 2 years of follow-up of the FINGER study (Kivipelto et al. 2013; Ngandu et al. 2014) indicated that the multi-domain intervention (diet, exercise, cognitive training, and vascular risk monitoring) resulted in slower decline in the intervention group than in the group receiving general health advice (Ngandu et al. 2015). This finding that a simple, noninvasive intervention could have an effect on the rate of cognitive decline in individuals at risk of developing dementia is very encouraging, though any effects on dementia incidence are still awaited. Another trial investigating the "Mediterranean-Dietary Approach to Systolic Hypertension diet intervention for neurodegenerative delay" (MIND) also gave encouraging results suggesting that adhering to this diet could slow cognitive decline (Morris et al. 2015). However, the PreDIVA trial did not find that their multi-domain intervention reduced the incidence of dementia (Richard et al. 2009; van Charante et al. 2016). Nevertheless, even if lifestyle interventions do not impact on incidence of dementia, they may still have an effect on prevalence by delaying disease onset.

Table 1 Trends in dementia prevalence and incidence

Country	Year	Trend
UK (Matthews et al. 2016)	2016	Decreasing incidence
Sweden (Qiu et al. 2013)	2013	Decreasing incidence
UK (Matthews et al. 2013)	2013	Decreasing prevalence
Netherlands (Schrijvers et al. 2012)	2012	Decreasing incidence
USA (Rocca et al. 2011)	2011	Decreasing prevalence and incidence
USA (Langa et al. 2008)	2008	Decreasing prevalence
Spain (Lobo et al. 2007)	2007	Decreasing prevalence (men)
USA (Manton et al. 2005)	2005	Decreasing prevalence

Decreasing Rates of Dementia

There is growing evidence that the prevalence and incidence of dementia are reducing over time (Langa 2015; Wu et al. 2014). Table 1 summarizes the published evidence pointing to these encouraging trends in high-income countries. On the other hand, there is some evidence that dementia rates in Japan may be increasing, rather than the reverse (Dodge et al. 2012).This seems plausible considering Japan's demographic structure, but there are a number of methodological complications in interpreting these findings. There seems to be a paucity of adequate data to examine trends in low- to middle-income countries (Wu et al. 2014).

Hypothesized mechanisms include decreased rates of cardiovascular disease (a public health success story) and increased levels of educational attainment in more recent generations – paralleling the mechanisms of vascular risk and cognitive reserve highlighted in the ADI report above (Prince et al. 2014). However, even with reductions in dementia prevalence of approximately 20%, the projected demographic trends of an aging population worldwide will dwarf these reductions and result in substantial increases in the absolute number of people with dementia, particularly in low- to middle-income countries (Prince et al. 2013). Furthermore, changing risk factor profiles in recent generations – such as inactivity, obesity, etc. – may also work to reduce these modest reductions observed in current dementia rates in the future.

Conclusions

In conclusion, we have seen that appreciating the complex natural history of Alzheimer's disease and dementia is core to any attempt to prevent this important condition, and using the abbreviation "AD" can lead to a great deal of unhelpful ambiguity. We have considered a broad selection of risk factors relating to primary, secondary, and tertiary prevention as well as considering two major prevention programs (PREVENT and EPAD) which will hopefully both further elucidate the

disease processes culminating in dementia and lead to prevention or delay of the clinical onset of this debilitating condition. The fact that a number of studies – in high-income countries, at least – report decreasing rates of dementia should be taken as encouraging and that this seemingly overwhelming condition is amenable to prevention initiatives, but the job is far from over!

References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:270–279

Annweiler C, Llewellyn DJ, Beauchet O (2013) Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 33:659–674

Annweiler C, Dursun E, Feron F, Gezen-Ak D, Kalueff AV, Littlejohns T, Llewellyn DJ, Millet P, Scott T, Tucker KL, Yilmazer S, Beauchet O (2015) 'Vitamin D and cognition in older adults': updated international recommendations. J Intern Med 277:45–57

Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42:631

Atwood CS, Moir RD, Huang X, Scarpa RC, Bacarra NME, Romano DM, Hartshorn MA, Tanzi RE, Bush AI (1998) Dramatic aggregation of Alzheimer Aβ by Cu(II) is induced by conditions representing physiological acidosis. J Biol Chem 273:12817–12826

Balion C, Griffith LE, Strifler L, Henderson M, Patterson C, Heckman G, Llewellyn DJ, Raina P (2012) Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology 79:1397–1405

Barker DJ (1990) The fetal and infant origins of adult disease. BMJ 301:1111–1111

Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 10:819–828

Batty GD, Lawlor DA, Macintyre S, Clark H, Leon DA (2005) Accuracy of adults' recall of childhood social class: findings from the Aberdeen children of the 1950s study. J Epidemiol Community Health 59:898–903

Batty GD, Shipley MJ, Langenberg C, Marmot MG, Davey Smith G (2006) Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study. Ann Oncol 17:157–166

Bennett D, Schneider J, Arvanitakis Z, Kelly J, Aggarwal N, Shah R, Wilson R (2006) Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66:1837–1844

Ben-Shlomo Y, Kuh D (2002) A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 31:285–293

Berr C, Arnaud J, Akbaraly TN (2012) Selenium and cognitive impairment: a brief-review based on results from the EVA study. Biofactors 38:139–144

Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259

Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18:351–357

Braak H, Del Tredici K (2010) The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol 121:171–181

Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 70:960–969

Brayne C (2007) The elephant in the room – healthy brains in later life, epidemiology and public health. Nat Rev Neurosci 8:233–239

Brookmeyer R, Gray S, Kawas C (1998) Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 88:1337–1342

Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007) Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 3:186–191

Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R, Feskens EJ, Gallagher CJ, Hypponen E, Llewellyn DJ, Stoecklin E, Dierkes J, Kies AK, Kok FJ, Lamberg-Allardt C, Moser U, Pilz S, Saris WH, van Schoor NM, Weber P, Witkamp R, Zittermann A, de Groot LC (2013) Vitamin D: do we get enough? A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. Osteoporos Int 24:1567–1577

Calkins K, Devaskar SU (2011) Fetal origins of adult disease. Curr Probl Pediatr Adolesc Health Care 41:158–176

Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, McArdle JJ, Manson JE, Chui HC, Espeland MA (2015) Ambient air pollution and neurotoxicity on brain structure: evidence from women's health initiative memory study. Ann Neurol 78:466–476

Clifford A, Lang L, Chen R, Anstey KJ, Seaton A (2016) Exposure to air pollution and cognitive functioning across the life course–a systematic literature review. Environ Res 147:383–398

Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M (2010b) NIH state-of-the-science conference statement: preventing Alzheimer's disease and cognitive decline. NIH Consens State Sci Statements 27:1–30

Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly JES, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M (2010a) National Institutes of Health State-of-the-Science Conference Statement: preventing Alzheimer disease* and cognitive decline. Ann Intern Med 153:176–181

Deary IJ, Whalley LJ, Starr JM (2009) A lifetime of intelligence: the Scottish Mental Surveys of 1932 and 1947. American Psychological Association, Washington, DC

Deary IJ, Gow AJ, Pattie A, Starr JM (2012) Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. Int J Epidemiol 41:1576–1584

Dodge HH, Buracchio TJ, Fisher GG, Kiyohara Y, Meguro K, Tanizaki Y, Kaye JA (2012) Trends in the prevalence of dementia in Japan. Int J Alzheimer's Dis 2012:956354

Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E, Liu-Seifert H, Mohs R (2014) Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 370:311–321

Flaten TP (2001) Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. Brain Res Bull 55:187–196

Gauthier S, Patterson C, Gordon M, Soucy J-P, Schubert F, Leuzy A (2011) Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." A Canadian perspective. Alzheimers Dement 7:330–332

Gustafson DR, Backman K, Joas E, Waern M, Ostling S, Guo X, Skoog I (2012) 37 years of body mass index and dementia: observations from the prospective population study of women in Gothenburg, Sweden. J Alzheimers Dis 28:163–171

Herrup K (2011) Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Addressing the challenge of Alzheimer's disease in the 21st century. Alzheimers Dement 7:335–337

Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:257–262

Jansen WJ, Ossenkoppele R, Knol DL et al (2015) Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 313:1924–1938

Joas E, Backman K, Gustafson D, Ostling S, Waern M, Guo X, Skoog I (2012) Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. Hypertension 59:796–801

Khachaturian ZS (2011) Revised criteria for diagnosis of Alzheimer's disease: National Institute on Aging-Alzheimer's Association diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:253–256

Killin LOJ, Starr JM, Shiue IJ, Russ TC (2016) Environmental risk factors for dementia: a systematic review. BMC Geriatr 16:175

Kivimaki M, Singh-Manoux A, Shipley MJ, Elbaz A (2015) Does midlife obesity really lower dementia risk? Lancet Diabetes Endocrinol 3:498

Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, Antikainen R, Backman L, Hanninen T, Jula A, Laatikainen T, Lindstrom J, Mangialasche F, Nissinen A, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H (2013) The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. Alzheimers Dement 9:657–665

Korczyn AD (2011) Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". Alzheimers Dement 7:333–334

Kuh D, Ben-Shlomo Y (2004) A life course approach to chronic disease epidemiology. Oxford University Press, Oxford

Langa KM (2015) Is the risk of Alzheimer's disease and dementia declining? Alzheimers Res Ther 7:1

Langa KM, Larson EB, Karlawish JH, Cutler DM, Kabeto MU, Kim SY, Rosen AB (2008) Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? Alzheimers Dement 4:134–144

Lincoln P, Fenton K, Alessi C, Prince M, Brayne C, Wortmann M, Patel K, Deanfield J, Mwatsama M (2014) The Blackfriars Consensus on brain health and dementia. Lancet 383:1805–1806

Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PH, Fried L, Kestenbaum BR, Kuller LH, Langa KM, Lopez OL, Kos K, Soni M, Llewellyn DJ (2014) Vitamin D and the risk of dementia and Alzheimer disease. Neurology 83:920–928

Liu-Seifert H, Siemers E, Holdridge KC, Andersen SW, Lipkovich I, Carlson C, Sethuraman G, Hoog S, Hayduk R, Doody R, Aisen P (2015) Delayed-start analysis: Mild Alzheimer's disease patients in solanezumab trials, 3.5 years. Alzheimer's Dement: Transl Res Clin Interv 1:111–121

Lobo A, Saz P, Marcos G, Dia J, De-la-Camara C, Ventura T, Montañes J, Lobo-Escolar A, Aznar S (2007) Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta Psychiatr Scand 116:299–307

Loef M, Schrauzer GN, Walach H (2011) Selenium and Alzheimer's disease: a systematic review. J Alzheimers Dis 26:81–104

Lyketsos CG (2011) Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". New Criteria New Era Alzheimer's Dement 7:328–329

Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M (2010) Alzheimer's disease: clinical trials and drug development. Lancet Neurol 9:702–716

Manton K, Gu X, Ukraintseva S (2005) Declining prevalence of dementia in the US elderly population. Adv Gerontol 16

Martyn C, Osmond C, Edwardson J, Barker D, Harris E, Lacey R (1989) Geographical relation between Alzheimer's disease and aluminium in drinking water. Lancet 333:61–62

Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, Brayne C, M. R. C. C. Function and A. Collaboration (2013) A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 382:1405–1412

Matthews F, Stephan B, Robinson L, Jagger C, Barnes L, Arthur A, Brayne C, A. S. C. Collaboration (2016) A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nat Commun 7:11398

McGuinness B, Todd S, Passmore P, Bullock R (2009) Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. Cochrane Database Syst Rev 4:CD004034

McGuinness B, Craig D, Bullock R, Malouf R, Passmore P (2014) Statins for the treatment of dementia. Cochrane Database Syst Rev 7:CD007514

McGurn B, Deary IJ, Starr JM (2008) Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. Neurology 71:1051–1056

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–939

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (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. Alzheimers Dement 7:263–269

Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, Aggarwal NT (2015) MIND diet slows cognitive decline with aging. Alzheimers Dement 11:1015

Muller M, Sigurdsson S, Kjartansson O, Jonsson PV, Garcia M, von Bonsdorff MB, Gunnarsdottir I, Thorsdottir I, Harris TB, van Buchem M, Gudnason V, Launer LJ (2014) Birth size and brain function 75 years later. Pediatrics 134:761–770

Ngandu T, Lehtisalo J, Levalahti E, Laatikainen T, Lindstrom J, Peltonen M, Solomon A, Ahtiluoto S, Antikainen R, Hanninen T, Jula A, Mangialasche F, Paajanen T, Pajala S, Rauramaa R, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2014) Recruitment and baseline characteristics of participants in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)-a randomized controlled lifestyle trial. Int J Environ Res Public Health 11:9345–9360

Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, Mangialasche F, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, Kivipelto M (2015) A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385:2255–2263

Noel-Storr AH, Flicker L, Ritchie CW, Nguyen GH, Gupta T, Wood P, Walton J, Desai M, Solomon DF, Molena E, Worrall R, Hayen A, Choudhary P, Ladds E, Lanctot KL, Verhey FR, McCleery JM, Mead GE, Clare L, Fioravanti M, Hyde C, Marcus S, McShane R (2013) Systematic review of the body of evidence for the use of biomarkers in the diagnosis of dementia. Alzheimers Dement 9:e96–e105

Norton MC, Østbye T, Smith KR, Munger RG, Tschanz JT (2009) Early parental death and late-life dementia risk: findings from the Cache County Study. Age Ageing 38:340. afp023

Norton MC, Smith KR, Østbye T, Tschanz JAT, Schwartz S, Corcoran C, Breitner JC, Steffens DC, Skoog I, Rabins PV (2011) Early parental death and remarriage of widowed parents as risk factors for Alzheimer disease: the Cache County study. Am J Geriatr Psychiatry 19:814–824

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 13:788–794

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 15:673–684

Parkman H, Hultberg H (2002) Occurrence and effects of selenium in the environment – a literature review. IVL Swedish Environmental Research Institute, Göteborg
Persson G, Skoog I (1996) A prospective population study of psychosocial risk factors for late onset dementia. Int J Geriatr Psychiatry 11:15–22
Plomin R, Daniels D (2011) Why are children in the same family so different from one another? Int J Epidemiol 40:563–582
Prince M, Guerchet M, Prina M (2013) The global impact of dementia 2013–2050. Alzheimer's Disease International, London
Prince M, Albanese E, Guerchet M, Prina M (2014) World Alzheimer report 2014. Dementia and risk reduction: an analysis of protective and modifiable factors. Alzheimer Disease International, London
Public Health England and UK Health Forum (2014) Blackfriars Consensus on promoting brain health: reducing risks for dementia in the population. UK Health Forum, London
Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L (2013) Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 80:1888–1894
Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, Evans SJ, Pocock SJ (2015) BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol 3:431–436
Randall C, Mosconi L, de Leon M, Glodzik L (2013) Cerebrospinal fluid biomarkers of Alzheimer's disease in healthy elderly. Front Biosci (Landmark Ed) 18:1150–1173
Richard E, Van den Heuvel E, Moll van Charante EP, Achthoven L, Vermeulen M, Bindels PJ, Van Gool WA (2009) Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. Alzheimer Dis Assoc Disord 23:198–204
Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR (2005) Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging 26:341–347
Ritchie CW, Ritchie K (2012) The PREVENT study: a prospective cohort study to identify mid-life biomarkers of late-onset Alzheimer's disease. BMJ Open 2
Ritchie K, Carriere I, Ritchie C, Berr C, Artero S, Ancelin M-L (2010) Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ 341:c3885
Ritchie K, Jaussent I, Stewart R, Dupuy AM, Courtet P, Malafosse A, Ancelin ML (2011) Adverse childhood environment and late-life cognitive functioning. Int J Geriatr Psychiatry 26:503–510
Ritchie CW, Wells K, Ritchie K (2013) The PREVENT research programme – a novel research programme to identify and manage midlife risk for dementia: the conceptual framework. Int Rev Psychiatry 25:748–754
Ritchie C, Smailagic N, Noel-Storr AH, Takwoingi Y, Flicker L, Mason SE, McShane R (2014) Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 6:Cd008782
Ritchie K, Ritchie CW, Jaffe K, Skoog I, Scarmeas N (2015) Is late-onset Alzheimer's disease really a disease of midlife? Alzheimers Dement (NY) 1:122–130
Ritchie CW, Molinuevo JL, Satlin A, Truyen L, van der Geyten S, Lovestone S (2016) Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. Lancet Psychiatry 3:179–186
Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, Gao S, Unverzagt FW, Langa KM, Larson EB (2011) Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement 7:80–93
Rosness TA, Strand BH, Engedal K, Chemali Z, Bjertness E (2015) What does height tell us about the risk of dementia? Int J Geriatr Psychiatry 30:776–777
Russ TC, Batty GD, Hearnshaw GF, Fenton C, Starr JM (2012) Geographical variation in dementia: systematic review with meta-analysis. Int J Epidemiol 41:1012–1032

Russ TC, Kivimaki M, Starr JM, Stamatakis E, Batty GD (2014) Height in relation to dementia death: individual participant meta-analysis of 18 UK prospective cohort studies. Br J Psychiatry 205:348–354

Russ TC, Gatz M, Pedersen NL, Hannah J, Wyper G, Batty GD, Deary IJ, Starr JM (2015a) Geographical variation in dementia: examining the role of environmental factors in Sweden and Scotland. Epidemiology 26:263–270

Russ TC, Starr JM, Stamatakis E, Kivimaki M, Batty GD (2015b) Pulmonary function as a risk factor for dementia death: an individual participant meta-analysis of six UK general population cohort studies. J Epidemiol Community Health 69:550–556

Russ TC, Murianni L, Icaza G, Slachevsky A, Starr JM (2016) Geographical variation in dementia mortality in Italy, New Zealand, and Chile: the impact of latitude, vitamin D, and air pollution. Dement Geriatr Cogn Disord 42:31–41

Russ TC, Hannah J, Batty GD., Booth CC, Deary IJ, Starr JM (In Press) Childhood cognitive ability and incident dementia: the 1932 Scottish Mental Survey into their tenth decade. Epidemiology.

Schneider LS, Mangialasche F, Andreasen N, Feldman H, Giacobini E, Jones R, Mantua V, Mecocci P, Pani L, Winblad B, Kivipelto M (2014) Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. J Intern Med 275:251–283

Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM (2012) Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology 78:1456–1463

Scottish Council for Research in Education (1933) The intelligence of Scottish children: a national survey of an age-group. University of London Press, London

Scottish Council for Research in Education (1949) The trend of Scottish intelligence: a comparison of the 1947 and 1932 surveys of the intelligence of eleven-year-old pupils. University of London Press, London

Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A (2016) The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537:50–56

Shenkin SD, Starr JM, Pattie A, Rush MA, Whalley LJ, Deary IJ (2001) Birth weight and cognitive function at age 11 years: the Scottish Mental Survey 1932. Arch Dis Child 85:189–196

Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pontecorvo MJ, Dean RA, Demattos R (2016) Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer's disease patients. Alzheimer's Dement: J Alzheimer's Assoc 12:110–120

Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Oden A, Svanborg A (1996) 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141–1145

Smailagic N, Vacante M, Hyde C, Martin S, Ukoumunne O, Sachpekidis C (2015) (18)F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 1:Cd010632

Smith AD, Yaffe K (2014) Dementia (including Alzheimer's disease) can be prevented: statement supported by international experts. J Alzheimers Dis 38:699–703

Snowdon DA (2011) Aging with grace: the Nun Study and the science of old age. How we can all live longer, healthier and more vital lives. Fourth Estate, London

Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR (1996) Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun study. JAMA 275:528–532

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (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. Alzheimers Dement 7:280–292
Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 11:1006–1012
Stern Y, Alexander GE, Prohovnik I, Mayeux R (1992) Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol 32:371–375
Stern Y, Tang MX, Denaro J, Mayeux R (1995) Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. Ann Neurol 37:590–595
Stern Y, Albert S, Tang MX, Tsai WY (1999) Rate of memory decline in AD is related to education and occupation: cognitive reserve? Neurology 53:1942–1947
Strand BH, Langballe EM, Rosness TA, Engedal K, Bjertness E (2015) Does midlife obesity really lower dementia risk? Lancet Diabetes Endocrinol 3:498–499
Valenzuela MJ, Sachdev P (2006) Brain reserve and dementia: a systematic review. Psychol Med 36:441–454
van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, Hoevenaar-Blom MP, Vermeulen M, van Gool WA (2016) Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet 388:797–805
van der Burg JM, Pijl H, Campman YJ, Roos RA, Aziz NA (2015) Does midlife obesity really lower dementia risk? Lancet Diabetes Endocrinol 3:499–500
Vaudano E, Vannieuwenhuyse B, Van Der Geyten S, van der Lei J, Visser PJ, Streffer J, Ritchie C, McHale D, Lovestone S, Hofmann-Apitius M, Truyen L, Goldman M (2015) Boosting translational research on Alzheimer's disease in Europe: the innovative medicine initiative AD research platform. Alzheimers Dement 11:1121
Whalley LJ (2012) Spatial distribution and secular trends in the epidemiology of Alzheimer's disease. Neuroimaging Clin N Am 22(1–10):vii
Whalley LJ (2015) Understanding brain aging and dementia: a life course spproach. Columbia University Press, New York
Whalley LJ, Starr JM, Athawes R, Hunter D, Pattie A, Deary IJ (2000) Childhood mental ability and dementia. Neurology 55:1455–1459
Whalley LJ, Dick FD, McNeill G (2006) A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 5:87–96
Whalley LJ, Murray AD, Staff RT, Starr JM, Deary IJ, Fox HC, Lemmon H, Duthie SJ, Collins AR, Crawford JR (2011) How the 1932 and 1947 mental surveys of Aberdeen schoolchildren provide a framework to explore the childhood origins of late onset disease and disability. Maturitas 69:365–372
Whalley LJ, Staff RT, Murray AD, Deary IJ, Starr JM (2013) Genetic and environmental factors in late onset dementia: possible role for early parental death. Int J Geriatr Psychiatry 28:75–81
Wharton SB, Brayne C, Savva GM, Matthews FE, Forster G, Simpson J, Lace G, Ince PG (2011) Epidemiological neuropathology: the MRC Cognitive Function and Aging Study experience. J Alzheimers Dis 25:359–372
Wu Y-T, Matthews FE, Brayne C (2014) Dementia: time trends and policy responses. Maturitas 79:191–195
Yegambaram M, Manivannan B, Beach TG, Halden RU (2015) Role of environmental contaminants in the etiology of Alzheimer's disease: a review. Curr Alzheimer Res 12:116–146
Yoon S, Kim J-M, Kang H-J, Bae K-Y, Kim S-W, Shin I-S, Yoon J-S (2015) Associations of pulmonary function with dementia and depression in an older Korean population. Psychiatry Invest 12:443–450
Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, Feng J (2014) (11)C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 7:Cd010386

Elderly Suicide and Suicide Prevention

23

Ajit Shah and Sofia Zarate-Escudero

Abstract

With the elderly population rising and suicide rates increasing with age the total number of eldrly suicides will increase. This chapter reviews the literature on the epidemiology and risk factors for elderly suicides and attempted suicides at an individual and population level. Additionally, it also developes theories on pathways to suicide, including the epidemiological transition hypothesis. Finally, the extant literature on prevention of suicide is also reviewed.

Keywords

Elderly suicide • Attempted suicide • Suicide prevention

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6_24

Introduction

The proportion of older people in the general population is increasing worldwide due to increased life expectancy and reduced mortality (Oeppen and Vaupel 2002). In developed countries this has particularly increased the size of the oldest-old group (80+ years) (Jeune and Skytthe 2001; Shah 2007a; Christensen et al. 2009). Suicide rates, in many countries, generally increase with aging (Shah 2007b; Bertolote and De Leo 2012). However, despite reductions in old-age mortality, including that due to suicides (Bertolote and De Leo 2012), suicide remains a major cause of death in older adults worldwide (Shah et al. 2015a, b). The existing literature on suicides and attempted suicides and the prevention of suicides in old age is examined.

Definition

The World Health Organization (WHO) defines suicide as an act of deliberately killing oneself. However, most studies and official statistics use the legal definition of suicide. Whether a death is recorded as suicide will depend upon the country's legal criteria for the proof of suicide (Shah and Ganesvaran 1994; Dennis et al. 2001; Wasserman et al. 2005; Kapusta et al. 2011), adequacy of death registration facilities

(Shah and Ganesvaran 1994; Shah and De 1998), cultural and religious factors, and the stigma attached to suicide (Wasserman et al. 2005; Abrahams et al. 2005).

In Austria, the threshold for classifying a death as suicide is low, whereby officers of the Federal Statistics Division may count the death as suicide if there is suspicion, even without legal evidence (Etzersdorfer and Fischer 1993). In Australia, New Zealand, and the United Kingdom (UK), only the coroner can record a death as being due to suicide, and the suicide must be proved beyond reasonable doubt, and if there is reasonable doubt, then an open or an accidental verdict for the cause of death is returned (Shah and De 1998; Dennis et al. 2001). Thus, the legal definition may depend upon the intention to kill oneself. However, suicidal intention is not a static phenomenon and fluctuates (Ganesvaran and Rajarajeshwaran 1988). This was illustrated in a Sri Lankan study, where an overdose of an agricultural organophosphate is usually fatal a few days later because there is no antidote, but a significant number of individuals changed their suicidal intent after taking the overdose, but still died; this was labeled "fatal deliberate self-harm" (Ganesvaran and Rajarajeshwaran 1988). Moreover, clear differences have been observed in the reporting of suicidal intention by the patients themselves, by the nursing staff, and by the junior doctors in an old-age psychiatry unit (Bell and Shah 1999); the same study also demonstrated wide daily variations in suicidal intent reported by the patients over a period of a week. Stengel (1977) stated that victims do not want either to live or to die but want both at the same time, usually one more than the other. Furthermore, suicidal behaviors including refusal to eat and noncompliance with treatment are not uncommon in older people and are often unrecognized; these have been variously referred to as "sub-intentional suicide," "hidden suicide," and "indirect self-destructive behavior" (Nelson and Farberow 1980; Conwell et al. 1986; McIntosh and Hubbard 1988; Hasegawa et al. 1992; De Leo 2015; Shah and Erlangsen 2015). Thus, it is likely that official statistics may underestimate the true rate of suicide. Therefore, it has been suggested that accidental deaths and those due to undetermined causes should also be included in suicide studies (O'Donnell and Farmer 1995; Dennis et al. 2001; Linsley et al. 2001; Chang et al. 2010; Kapusta et al. 2011; De Leo 2015; Shah and Erlangsen 2015), but they have not always been utilized. However, this may be less important within individual countries when trends in suicide rates over time are examined (Pritchard 1992).

Research Methodology

Epidemiological studies have examined national or regional suicide rates and methods of suicide and associated factors. In-depth studies of individual suicides have been utilized to understand the characteristics of individuals contributing to suicides and the method of suicides. Novel approaches with the use of qualitative methods in psychological autopsy studies (Kjolseth et al. 2009) and in studies of those who had suicide attempts (Bonnewyn et al. 2014a, b, 2015) are emerging to complement the more traditional studies. Different age cutoffs

including 50 years, 60 years, 65 years, and 80+ years have been used in different studies.

Epidemiological Studies

Epidemiological studies have examined gender-specific suicide rates in older people, age-associated trends, and trends in suicide rate over time in individual regions and countries and in comparative cross-national studies across different countries. Data from such studies has been used to examine societal-level risk and protective factors and to demonstrate the independent effects of age, cohort, and period on suicide rates.

Study Designs: Individual-Level Risk and Protective Factors

Individual-level risk and protective factors have been examined in in-depth studies of individual suicides. Such studies are generally retrospective, and the most important witness is absent (Shah and Ganesvaran 1994; Shah and De 1998); as suicide is a comparatively rare event, prospective studies examining individual suicides are difficult to conduct. Older studies were largely descriptive and included in-depth studies of single cases (Alexopoulos 1991; Rosowsky 1993), a small (N<50) (Barraclough 1971; Finkel and Rosman 1995; Horton-Deuth et al. 1992) or large (N>50) (Conwell et al. 1991; Cattell and Jolley 1995; Heikkinen and Lonnqvist 1995; Watanabe et al. 1995; Waern et al. 1996) case series. Recent studies have included comparison groups of younger suicide victims (Modestin 1989; Shah and Ganesvaran 1997a, b; Heikkinen and Lonnqvist 1995; Burvill 1995), demographic data from the general population (Barraclough 1971; Watanabe et al. 1995), accidental deaths (Cattell 1988), sudden deaths (Draper et al. 2014), deaths due to natural causes (Harwood et al. 2001, 2006), deaths matched from the death register (Preville et al. 2005), and alive participants from primary care, health insurance registry, or the community (Conwell et al. 2000; Waern et al. 2002a, b; Chiu et al. 2004; Duberstein et al. 2004; Juurlink et al. 2004; Voaklander et al. 2008). Comparison groups using younger suicide victims and general population demographic data do not allow for the effects of age, period, and cohort on suicides (Shah and Ganesvaran 1994; Shah and De 1998). The use of accidental deaths in the comparison group may also be problematic because they may contain concealed suicides (Holding and Barraclough 1975; O'Donnell and Farmer 1995; Dennis et al. 2001; Linsley et al. 2001; Chang et al. 2010; Kapusta et al. 2011; De Leo 2015; Shah and Erlangsen 2015); hence, a large Canadian study of Coroner's records used a live comparison group (Juurlink et al. 2004). The comparison group participants in remaining studies were matched to the suicide group for differing combinations of age, gender, race and time of death, and geographical area, and this would, in part, negate the effect of age, period, and cohort on the suicide. One study (Draper et al. 2014) used sudden deaths as a comparison group because they attempted to identify differences between the two groups of unpredictable deaths and possible prevention opportunities during the last contact.

Data Collection: Individual-Level Risk and Protective Factors

Methods of data collection in studies of individual suicides include psychological postmortem, coroner's inquest data, case notes, and case registers. Psychological postmortem, also referred to as psychological autopsy, involves collection of standardized data by interviewing informants familiar with the suicide victim's psychological, social, and medical characteristics (Ebert 1987; Beskow et al. 1990), and this has been the main method of examining elderly suicides. This approach can be supplemented with access to medical records and records from coroner's inquest (or an equivalent authority). However, there are difficulties in using this approach in older people: inaccuracies may arise because life histories are more remote; histories are given at an emotive time during the bereavement period; informants may be significantly younger than the suicide victim; social circumstances may vary; data collection can be time consuming; sample size may be limited; and there are concerns about the comparison groups (Shah and De 1998; Waern 2011). Moreover, elderly suicide victims often have physical illness, and careful consideration is required for examination of symptoms that are common to physical and mental illness (Shah and De 1998). The main debate, however, has been about the choice of the comparison group, and several different comparison groups, as described in the last section, have been used, but there is lack of consensus on an ideal comparison group (Waern 2011). A further problem has been the differential participation rates for the suicide and the comparison groups (Waern 2011). Also, when the comparison group consists of alive subjects, they have been formally interviewed, resulting in different methods of data ascertainment for the two groups. The difficulty with choosing the correct comparison group can be and has been attenuated by consistent findings across different studies from different countries using different comparison groups and by the findings of large studies using case registers (Waern 2011).

Studies based on large case registers are emerging to complement the traditional psychological postmortem approach. A series of elegant studies based on the Danish national case register have been pioneering (Erlangsen et al. 2004, 2005, 2006, 2008, 2015). Other large suicide series from coroner's courts in Ontario(Juurlink et al. 2004) and vital statistics office in British Columbia (Voaklander et al. 2008) have also complemented the traditional approaches. Another complementary approach was that of a large European multicenter study (De Leo et al. 2001). Additionally, a national English database of all suicides in contact with services was used to study suicides in dementia (Purandare et al. 2009).

Cross-National Comparisons

Large cross-national variations in elderly suicide rates have been repeatedly observed (Shah and Ganesvaran 1994; Shah and De 1998; Shah et al. 2007). A nearly study of all countries listed on the WHO databank observed that elderly suicide rates were the lowest in the Caribbean, Central American, and Arabic countries and the highest in Central and East European, some oriental and some West European countries (Shah et al. 2007); this was replicated in a more recent

study of 97 countries using the same WHO databank (Shah 2011a). Critical examination of potential explanations for this cross-national variation may enable generation of testable hypothesis leading to a better understanding of the etiology of suicide. Studies of different ethnic groups in a single country can be similarly helpful; several studies of elderly suicide rates in the three main ethnic groups in Singapore have enabled development of social and cultural explanatory models (Kua and Ko 1992; Ko and Kua 1995; Kua et al. 2003).

Comparison of suicide rates among first- and second-generation migrants with those in the country of origin may be helpful in segregating the effects of genetics and environment on suicide. However, first-generation migrants may have the added burden of migration and assimilation into the host culture, but the second-generation migrants may be relatively free of these facets. Thus far only first-generation migrants have been examined. An elegant study from Australia reported that suicide rates among older migrants were generally higher in Australia than in the country of their origin and higher in those from countries with a high rate (Burvill 1995). A similar study in England and Wales reported that there was convergence toward the elderly suicide rate in England and Wales, and in men aged 75+ years, the rates were generally higher than those born in England and Wales (Shah et al. 2009). A Swedish study reported that being male, aged 75+ years, and being born in Finland or Eastern Europe significantly increased the risk of suicide.

Time Trends

Trends in elderly suicide rates over time have been studied in individual countries and in comparative studies of clusters of countries; selected examples are described. Suicide rates declined in those aged 65–74 years and 75+ years in both sexes between 1979 and 2002 in the whole of the United Kingdom, England and Wales, and Scotland, but in Northern Ireland, this was only observed in women aged 65–74 years (Shah and Coupe 2009). Three other studies of suicide rates in England and Wales covering the period 1985–2006 reported similar findings (Hoxey and Shah 2000; Lodhi and Shah 2005; Shah et al. 2014a). A further study examined suicide rates between 1985 and 1998 in England and Wales in 5-year age bands after the age of 65 years and illustrated a decline in rates over the four 5-year age bands until 80–84 years, but not in the older groups (Shah et al. 2001). Decline in suicide rates in the elderly has also been observed in Austria between 1970 and 2004 (Kapusta et al. 2006), Beijing between 1987 and 1996 (Yip 2011), Singapore between 1991 and 2000 (Kua et al. 2003, the United States between 1970 and 2002 (McKeown et al. 2006), and New Zealand between 1949 and 1998 (Ferguson 2005). However, in Korea (Shah and Suh 2009; Shah 2009a; Kwon et al. 2009), between 1985 and 2005, and the Philippines (Redaniel et al. 2011), between 1974 and 2005, suicides rates in both genders increased, and in Sweden suicide rates in both genders remained relatively stable between 1970 and 1996 (Wasserman and Ringskog 2001).

A pioneering study, using elegant statistical techniques, demonstrated that suicide rates in elderly men increased in 13 of the 21 Western countries between 1974 and 1987 and in women in ten Western countries (Pritchard 1992). Elderly suicide rates in both sexes were observed to have declined in many countries between 1989/1990 and 1992/1993 (Shah and Ganesvaran 1994). The exceptions were increased rates in both sexes in Denmark, men in Israel, and women in France, Bulgaria, Iceland, and Malta; during the same period, suicide rates did not change in Norway, Poland, and Sweden. A comparative study of elderly suicide rates in selected European countries between 1987 and 1991/1992 reported an increase in men in Denmark, Sweden, and Latvia and in women in Norway, Belarus, and Hungary (Sartorius 1995). A large cross-national comparative study using data from all countries listed in the WHO bank observed that suicide rates either remained unchanged or declined over a variable 10-year period from the 1990s (Shah et al. 2008a). Moreover, the decline was mainly observed in several European countries, but remained unchanged in several South and Central American countries, East European countries, and countries emerging from the former Soviet Union (Shah et al. 2008a).

Age-Associated Trends

Age-associated trends in suicide rates have been studied in individual countries and in comparative studies of clusters of countries; selected examples are described. In England and Wales, female suicide rates increased with age, but in males, there was a peak in young men and a further peak in old age; however, in Scotland and Northern Ireland, suicide rates decreased with aging in men and in women; there was no clear pattern (Shah and Coupe 2009). Studies from the United Kingdom for 1979–2002 (Shah 2007c), the United States for 1970–2002 (McKeown et al. 2006), Taiwan for 1971–2005 (Lin and Ku 2008), Spain for 1959–1991 (Granizo et al. 1996), and Japan for 1985–2006 (Odagiri et al. 2009) have reported an increase in suicide rates with aging in both genders.

Data from the global burden of disease project for the WHO Eastern Mediterranean region observed that suicide rates peaked in women aged 15–29 years and in men 60+ years (Rezaeian 2000). A large cross-national study of 62 countries observed the following patterns: an increase in suicide rates with aging in men in 25 and women in 27 countries; no increase in suicide rates with aging in men in 31 and women in 29 countries; suicide rates were the highest in young men in countries with no increase in male suicide rate with aging; there was regional clustering of countries without an increase in suicide rates with aging in both genders; and in a small number of countries suicide rates declined with aging (Shah 2009b). Another study of Western countries demonstrated similar findings (Pritchard and Hansen 2004). A global analysis using WHO data from 1998 illustrated that suicide rates increased with aging in both genders (Bertolote and Fleischmann 2002). Unfortunately, a number of these studies amalgamated data for 60+, 65+, or 75+ years age groups. However, a recent study demonstrated global suicide rates increased in men in each of the 5-year age bands after the age of

60 years until 95–99 years when they declined (Shah et al. 2015a, b); similar pattern was observed in women except the rates declined at 90–94-year age band (Shah et al. 2015a, b). A further global study of centenarians showed the continuing decline in both genders (Shah et al. 2014b).

Age, Period, and Cohort Effects

Risk factors attributable to age, period, and cohort membership influence suicide rates at any given age, in a given cohort at a given time period. Suicide rates among those born in a particular cohort are peculiar to that cohort – the cohort effect. The individual's age within the cohort at any given age will further influence the suicide rate – the age effect. Environmental factors related to the time period of study will also influence the suicide rates – the period effect. Techniques to partial out the independent effects of age, period, and cohort on suicide rates have emerged (Surtees and Duffy 1989; Carstensen 2006; Smith 2008).

Cohort Effects

A study in England and Wales, covering the period between 1921 and 1980, reported a fall in suicide rate in successive older cohorts (Murphy et al. 1986); it also illustrated a more prolonged cohort effect on suicide rate in middle-aged and elderly men associated with the period effect of the Second World War and detoxification of domestic gas. Furthermore, suicide rates at a given age in the cohort do not predict suicide rates at a later age in the same cohort (Murphy et al. 1986; Lindesay 1993). Another study from the same country, using sophisticated statistical techniques to partial out the independent effects of age, period, and cohort, reported a decline in suicide rates for men in ten successive cohorts from 1871 to 1916; suicide rates in subsequent male cohorts increased and in subsequent female cohorts decreased (Surtees and Duffy 1989). A further study from England and Wales observed that successive male cohorts born after 1940 had a greater risk of suicide as they aged (Gunnell et al. 2003). Suicide rates declined for nonwhite males, white males, and white females in America for cohorts born in the depression years and after the Second World War (Woodbury et al. 1988). Birth cohorts of men in New Zealand born after 1947 showed successively higher rates of suicide at each age, although this was not observed in women despite sharing similar risks (Skegg and Cox 1991). A Spanish study reported that cohort effects were small for cohorts born before 1940, but in cohorts born after 1950, suicide rates increased markedly (Granizo et al. 1996). A cohort-specific effect in a Japanese study was observed in male birth cohorts born after 1926 and female cohorts born after 1956 (Odagiri et al. 2009). A Swiss study observed that male suicide rates peaked in cohorts born in the 1840s, was low in cohorts 60–100 years after that, and began to rise again in cohorts born after the Second World War (Ajdacic-Gross et al. 2006). In women suicide rates were

low in cohorts born in the first half of the nineteenth century and increased in those born in the first half of the twentieth century (Ajdacic-Gross et al. 2006).

Early experience of the cohort may have an important and enduring effect on suicide rates (Murphy and Wetzel 1980). The overall cohort size may influence suicide rates due to competition for scarce resources (Lindesay 1991). Suicide rates generally tend to be higher in age groups which comprise a larger proportion of the population (Haas and Hendin 1983; Lindesay 1991). Thus, it could be argued that suicide rates may increase in the baby boom generation unless health, social care, and social welfare resources are also increased (Blazer et al. 1986; Haas and Hendin 1983; Lindesay 1991). A study of 18 high-income countries reported that large cohort size increases suicide rates in the young and the middle aged but reduces it in the elderly, and these effects are stronger in men than women (Pampel 1996). However, a large Australian study reasoned that most so-called cohort effects were related to environmental changes which may not be a function of the cohort itself (Snowdon and Hunt 2002), but they did not use statistical techniques to partial out the effects of age, period, and cohort. Other studies have questioned the strength of cohort effects (Murphy et al. 1986; Wetzel et al. 1987).

Age Effects

In England and Wales, suicide rates were independently affected by age in both genders; suicide rates, in both genders, increased with age and peaked at 65–79 years (Surtees and Duffy 1989).This was observed consistently for each of the eight 5-year periods between 1946 and 1985. In men aged 65–79, suicide rates declined over the first five 5-year periods and increased for the final three periods. In women of the same age, suicide rates declined in each successive eight 5-year periods. Suicide rates among white American, in Australia, and New Zealand increased with age in men, but in women they increased until menopause and declined thereafter (Skegg and Cox 1991; Snowdon and Hunt 2002; Woodbury et al. 1988). However, suicide rates declined with aging among African Americans and American Indians (Woodbury et al. 1988). Spanish (Granizo et al. 1996), Swiss (Ajdacic-Gross et al. 2006), and Japanese (Odagiri et al. 2009) studies observed an increase in suicide rates with aging independent of cohort and period effects.

Age effects may be due to the experience of aging and the actual process of aging (Lindesay 1991). The latter has been poorly studied. The experience of aging may be linked to the vulnerability hypothesis. Many of the factors listed as individual-level risk factors in the section below are particularly prevalent in old age including physical illness, bereavement, social isolation, loss of income, retirement, and loss of status. Nevertheless, not all elderly who have these characteristics proceed to suicide, and so other factors may be relevant. Personality factors may predispose vulnerable individuals to suicide and are discussed in the section below on individual-level risk factors. Furthermore, the effects of aging may operate in a complex manner. Some risk factors may work in tandem like retirement leading to loss of income. However, older black Americans and American Indians, who are socioeconomically deprived, have lower

suicide rates (McIntosh 1984) because lifelong adversity enables them to better tolerate hardship later in life (Lindesay 1991; Seiden 1981). Studies of societal-level risk factors have demonstrated that societies with early life adversity have lower elderly suicide rates (Shah and Bhat 2009; Shah 2012a).

Cultural factors may also contribute to the vulnerability hypothesis. Suicide rates decline with age among Arabs (Daradekh 1989), Malays in Singapore (Ko and Kua 1995), nonwhite Americans (Seiden 1981), Indian immigrants in the United Kingdom (Raliegh et al. 1990), and some east European groups (Sartorius 1995). This may be because older people are traditionally highly respected and held in high esteem in these groups, and this may offer protection against loneliness and despair, which otherwise may lead to suicide. This may explain increased suicide rates in elderly Japanese (Shimuzu 1990), including those in rural areas (Watanabe et al. 1995), and in two elderly ethnic groups in Singapore (Ko and Kua 1995; Kua and Ko 1992; Kua et al. 2003), who have lost their traditional role in the family. However, about two-thirds of Japanese elderly who commit suicide live in three generation households with a mean of 4.8 persons in the household (Watanabe et al. 1995). Thus, it has been suggested that the concept of emotional proximity (respect and high esteem) from the extended family as opposed to physical proximity (living under the same roof) may be more important (Shah and Ganesvaran 1994; Shah and De 1998). A recent cross-national study challenged this view because elderly suicide rates in both genders increased with reduction in the number of people living in the household, reduction in the percentage of extended families, and an increase in the percentage of single households (Shah 2009c). Perhaps both emotional and geographical proximity are important.

Period Effects

Elderly suicide rates, independent of age and cohort effects, declined during the Second World War (Murphy et al. 1986; Snowdon and Hunt 2002), after detoxification of domestic gas (Murphy et al. 1986; Vecchia et al. 2007) and after restrictions in barbiturate prescribing (Skegg and Cox 1991). Moreover, the effects of world war and detoxification of domestic gas were more pronounced in men and were sustained without replacement by other effects. Economic downturn has also been shown as a period effect (Vecchia et al. 2007; Ajdacic-Gross et al. 2006).The effects of public health campaigns and national suicide prevention policies on suicide rates could and should be critically investigated using statistical methods to partial out the effects of age, period, and cohort (Hoxey and Shah 2000; Shah and Coupe 2009).

Societal-Level Risk and Protective Factors

A linear association was reported between the percentage of Internet users and suicide rates in both genders in a cross-national study (Shah 2010a). Suicide rates in elderly women were linearly associated with the societal prevalence of obesity in a

cross-national study (Shah 2010b). However, increasingly these traditional linear associations have been examined using curve regression analysis because linear correlations can mask curvilinear correlations (Shah 2008a, b; Shah et al. 2012).

Elderly suicide rates in both genders were shown to be have a negative linear correlation with fertility rates in a cross-national study of 81 countries (Shah 2008b), but closer examination of the same data set and careful analysis using curvilinear modeling revealed a curvilinear (U-shaped curve) relationship following the quadratic equation $Y = A + BX + CX^2$, (where Y is the suicide rate; X is the fertility rate; and A, B, and C are constants) (Shah 2008a). This suggests that elderly suicide rates may be high when the fertility rates are either low or high, but low when fertility rates are intermediate. There was also a curvilinear relationship (U-shaped curve) between elderly suicide rates and annual population growth following the quadratic equation $Y = A + BX + CX^2$ (where Y is the suicide rate; X is the annual population growth; and A, B, and C are constants) (Shah 2009d).

A large cross-national study reported that the relationship between elderly suicide rates in both genders and educational attainment was curvilinear (U-shaped curve) following the quadratic equation $Y = A + BX + CX^2$ (where Y is the suicide rate; X is the education index, a measure of educational attainment; and A, B, and C are constants) (Shah and Chatterjee 2008); this was replicated using 5-year data set for suicide rates (Shah 2010c). The specific components of educational attainment sustaining this curvilinear relation included adult literacy rate, percentage of children in the relevant age group enrolled for secondary school, and the youth literacy rate (Shah 2012b). Other studies have also demonstrated nonlinear association between elderly suicide rates and educational attainment and intelligence (Agbayewa et al. 1998; Voracek 2009).

There was a curvilinear (inverted U-shaped curve) relationship between elderly suicide rates in both genders and the Human Development Index (HDI) following the quadratic equation $Y = A + BX - CX^2$ (where Y is the suicide rate; X is the HDI; and A, B, and C are constants) (Shah 2009e); this was replicated using data set of 5 years for suicide rates (Shah 2010d). HDI is a composite index measuring average achievements on three basic dimensions of human development: life expectancy, educational attainment, and socioeconomic status.

A recent cross-national study reported that elderly suicide rates in both genders increased with reduction in the number of people living in the household, reduction in the percentage of extended families, and an increase in the percentage of single households (Shah 2009c). Another large cross-national study reported a positive association between elderly suicide rates in both gender and the elderly dependency ratio (Shah et al. 2008b). The findings of study were replicated using a 5-year data set (Shah 2010e).

Adversity experienced in early life is thought to protect older African Americans and American Indians from suicide due to their improved ability to tolerate adversity later in life (Seiden 1981; Lindesay 1991). Elderly suicide rates in both genders were lower if four of the five proxy measures of adversity in early life were present (Shah and Bhat 2009). These findings were confirmed in another cross-national study using a 5-year data set for suicide rates (Shah 2012c).

There was a curvilinear (inverted U-shaped curve) relationship between elderly suicide rates in men and degree of urbanization following the quadratic equation $Y = A + BX - CX^2$ (where Y is the suicide rate; X is the degree of urbanization; and A, B, and C are constants); this was absent in women (Shah 2010f).

There was a curvilinear (inverted U-shaped curve) relationship between elderly suicide rates in both genders and measures of socioeconomic status including gross national domestic product and income inequality following the quadratic equation $Y = A + BX - CX^2$ (where Y is the suicide rate; X is the measure of socioeconomic status; and A, B, and C are constants) (Shah 2010g; Shah 2011b; Shah et al. 2013).

A large cross-national study reported that elderly suicide rates were higher in countries with a substance misuse policy; greater provision of mental health services including the number of psychiatric beds, psychiatrists, and psychiatric nurses; and availability of training in mental health for primary care professionals (Shah and Bhat 2008a). However, this relationship was complex, whereby the relationships between logarithm of elderly suicide rates and the percentage of the total health budget spent on mental health, the total number of psychiatric beds, and the number of psychiatrists were curvilinear (inverted U-shaped curve) and fitted the quadratic equation $Y = A + BX - CX^2$ (Shah and Bhat 2008b).

The curvilinear associations have been observed in cross-sectional studies, and thus causal links are difficult to establish. Further research is needed to develop explanatory models for these curvilinear relationships. One detailed explanatory model has been developed for the curvilinear relationship between elderly suicide rates and societal socioeconomic status and is described in the next section.

Epidemiological Transition Hypothesis

Societies with low socioeconomic status generally have poorly developed healthcare services (Shah 2007d, 2009f; Jacob et al. 2007; Jacob 2008; Shah et al. 2008c; Shah and Bhat 2008a, b). Poorly developed healthcare services may mediate an increase in child mortality rates by being unable to provide primary preventative measures for diseases in childhood (e.g., immunization programs) and treatment for diseases that are directly related to low socioeconomic status (e.g., infectious diseases) (Suh and Shah 2001). Child mortality rates are higher in countries with low socioeconomic status and higher income inequality (Zhang 1998; Shah et al. 2008c; Shah 2007d). Increased child mortality rates, in turn, reduce life expectancy (Zhang 1998; Shah et al. 2008c; Shah 2007d). Given that suicide rates generally increase with age (Shah 2007b), reduced life expectancy will result in fewer people reaching the age of increased risk for suicide in societies with low socioeconomic status. This, in turn, will result in a reduced number of elderly suicides in countries with low socioeconomic status because there is a positive correlation between elderly suicide rates and elderly population size (Shah et al. 2008a) and elderly dependency ratios (Shah et al. 2008b). Also, selective survival of those at reduced risk of suicide in old age due to genetic or constitutional factors may further compound this trend (Suh and Shah 2001). Moreover, in societies with low socioeconomic status, those who do survive

into old age may be at reduced risk of suicide because they may be able to better tolerate additional hardship in old age due to lifelong exposure to adversity (Lindesay 1991; Seiden 1981; McIntosh 1984). This situation could be labeled as a low elderly suicide rate-low socioeconomic society stage.

With improvement in the socioeconomic status of countries, the degree of development of healthcare services will also improve (Zhang 1998; Shah 2007d, 2009f; Jacob et al. 2007; Shah et al. 2008c; Shah and Bhat 2008a, b). Improvement in healthcare services may facilitate reduction in child mortality rates because of improved ability to provide primary preventative measures for diseases in childhood (e.g., immunization programs) and treatment for diseases that are directly related to low socioeconomic status (e.g., infectious diseases) (Suh and Shah 2001). Reduction in child mortality rates, in turn, increases life expectancy (Zhang 1998; Shah 2007d; Shah et al. 2008c). This, in turn, will result in greater number of subjects reaching the age of increased risk of suicide and an increase in elderly suicide rates (Shah et al. 2008c). This will lead to a gradual transition from low elderly suicide rate-low socioeconomic society stage to a high elderly suicide rate-low socioeconomic society stage.

As societies develop, they are likely to change from being socioeconomically less developed to being socioeconomically more developed. Further improvement in healthcare services may facilitate further reductions in child mortality rates because of improved ability to provide primary preventative measures for diseases in childhood (e.g., immunization programs) and treatment for diseases that are directly related to low socioeconomic status (e.g., infectious diseases) (Suh and Shah 2001). Further reductions in child mortality rates, in turn, further increases life expectancy (Zhang 1998; Shah 2007d; Shah et al. 2008c). This, in turn, will result in increasing number of subjects reaching the age of increased risk of suicide (Shah et al. 2008c). Reduced child mortality rates and increased life expectancy will also lead to reduction in selective survival of those at reduced risk of suicide in old age due to constitutional or genetic factors. Furthermore, the protective effects of lifelong adversity on elderly suicide rates (McIntosh 1984; Seiden 1981; Lindesay 1991) may be absent in countries with higher socioeconomic status. The composite effect of these changes would be an increase in the number of individuals at increased risk of suicide in old age in socioeconomically more developed societies. This will lead to a gradual transition from the high elderly suicide rate-low socioeconomic society stage to a high elderly suicide rate-high socioeconomic society stage.

Theoretically, in socioeconomically well-developed societies, due to further reduction in child mortality rates and increase in life expectancy, greater number of people would reach the age of increased suicide and consequently lead to higher elderly suicide rates. However, in many socioeconomically well-developed countries (e.g., Italy, the Netherlands, Norway, the United Kingdom, and the United States), elderly suicide rates were comparatively low (Shah et al. 2007) and have declined over time (Shah et al. 2008a). In socioeconomically very well-developed societies, elderly suicide rates may progressively decline over many years due to improved efforts to control the risk factors for elderly suicides and enhance protective factors for elderly suicides, advances in medical care, prompt resuscitation of

those who attempt suicide, and better provision of healthcare (including mental health) services and public health initiatives to reduce suicide rates (Gunnell et al. 2003; Lodhi and Shah 2004, 2005; Shah and Coupe 2009; Shah 2009g). Ultimately, this will lead to a gradual transition from a high elderly suicide rate-high socioeconomic society stage to a low elderly suicide rate-high socioeconomic society stage.

Individual-Level Risk and Protective Factors

Complex interactions between several different factors may contribute to elderly suicides, although such factors may be absent in up to a third of cases (Cattell 1988).

Gender

Suicide rates are generally higher in men than women worldwide (Shah et al. 2007; Shah 2011a). However, a gender difference was absent in some case-control studies (Chiu et al. 2004; Preville et al. 2005), perhaps because of selection artifact for the comparison group.

Social Factors

Older suicide victims often lived alone (Duberstein et al. 2004), particularly women (Heikkinen and Lonnqvist 1995); may be lonely(Waern et al. 2003) with a limited social network (Beautrais 2002); meet family members at a lower frequency (Preville et al. 2005); were likely to spend their free time alone (Preville et al. 2005); and had low levels of social interaction (Beautrais 2002). Social isolation, by depriving individuals of emotional support and reducing the opportunity for therapeutic intervention, may aggravate suicidal intent (Waern et al. 2003). Furthermore, widowed, single, or divorced individuals were overrepresented among older suicide victims (Erlangsen et al. 2004; Preville et al. 2005). Additionally, bereavement may be an important precipitant for suicide, particularly in those aged 80+ years (Erlangsen et al. 2004). As majority of bereaved spouses do not commit suicide, other factors, including quality and nature of marital relationship and post-bereavement social support, may play a role, but data are lacking. Marital and family discord has been suggested as another risk factor (Beautrais 2002; Waern et al. 2003; Duberstein et al. 2004; Preville et al. 2005).

Income and Employment

Employment change, lower socioeconomic status, and financial strain may be important risk factors (Duberstein et al. 2004; Voaklander et al. 2008).

Mental Disorder

Mental disorder is more prevalent among older suicide victims than in the comparison groups of various case-control studies (Beautrais 2002; Preville et al. 2005). Many older victims have a previous history of attempted suicide (Beautrais 2002; Voaklander et al. 2008). Such studies have consistently reported that depression is more prevalent, up to 86%, among older suicide victims (Conwell et al. 2000; Beautrais 2002; Waern et al. 2002a, 2003; Chiu et al. 2004; Juurlink et al. 2004; Preville et al. 2005; Erlangsen et al. 2006; Voaklander et al. 2008). The first episode of depression is a particularly vulnerable period (Erlangsen et al. 2006), although up to 43% of victims have had a previous episode (Cattell 1988). The duration of the index episode is usually prolonged, between 6 and 12 months (Barraclough 1971; Cattell 1988; Conwell et al. 1990).

Alcohol or substance abuse or dependence is present in up to 44% of older suicide victims (Conwell et al. 2000; Beautrais 2002; Waern et al. 2002a, 2003; Voaklander et al. 2008), particularly the young-old compared to the old-old (Waern et al. 2003). Although there was no difference in alcohol dependence between older suicide victims and a comparison group of accidental deaths, but the latter group may involve accidents related to alcohol use leading to death (Cattell 1988). Up to 30% of older suicide victims have significant amount of alcohol in their blood (Cattell 1988; Conwell et al. 1990; Cattell and Jolley 1995). Alcohol may be the main intoxicating agent, may potentiate other lethal agents like barbiturates, or may be taken for "Dutch courage" leading to disinhibition (Cattell 1988; Shah and De 1998).

A smaller, but significant, proportion of older victims have schizophrenia and related psychotic disorders (Chiu et al. 2004; Waern et al. 2002a). Up to 19% of older suicide victims have anxiety disorders with overrepresentation in some, but not all, case-control studies (Beautrais 2002; Waern et al. 2002a, 2003; Chiu et al. 2004; Juurlink et al. 2004; Preville et al. 2005). Anxiety disorders were overrepresented among inpatient older suicide victims (Erlangsen et al. 2006).

The relationship between suicide in older people and dementia is less well established and controversial. A Finnish study reported the prevalence of organic mental disorders, without specification of the precise diagnosis, to be 3% (Henriksson et al. 1995). A national case-register study of untoward deaths reported that 1.1% all suicide victims in contact with mental health services had dementia (Purandare et al. 2009). However, in case-control studies, despite the prevalence of dementia in older suicide victims being up to 3.5%, there was no preponderance of dementia in the suicide group (Waern et al. 2002a, 2003; Chiu et al. 2004; Voaklander et al. 2008). However, a large Danish national case-register study of 50+ year olds diagnosed to have dementia in hospital reported an increased suicide risk in men and women with dementia, particularly in the period after diagnosis, but it persisted even 3 years after diagnosis (Erlangsen et al. 2008).

Mental illness may be absent in up to 13% of older suicide victims (Barraclough 1971; Cattell 1988; Henriksson et al. 1995), but the retrospective nature of the studies may have reduced the sensitivity in identifying mental illness. Moreover, some suicides may be "rational" suicides. However, personality factors may be

important in this context, but have been sparsely studied. Up to 13% of older suicide victims may have personality disorder (Henriksson et al. 1995). Suicides in older people were associated with the personality traits of lower openness to experience and high neuroticism (Costa and McCrae 1988; Duberstein 1995). Another study reported that 48% of suicide victims over the age of 60 years had marked personality traits or disorder, particularly with anxious and anankastic traits (Harwood et al. 2001). Older suicide victims without psychiatric disorder in a larger case-control study had lower scores on measures of traits of extraversion and agreeableness and higher on neuroticism (Draper et al. 2014). Those with psychiatric disorders had higher scores on measures of the traits of openness and neuroticism, but for mood disorders, only neuroticism scored higher (Draper et al. 2014). These findings collectively suggest that there may be interactions between personality traits, age, and psychiatric disorder leading to suicide (Draper et al. 2014). The personality traits amounting to rigidity, inflexibility, and neuroticism may make it difficult for older people to adapt to age-associated changes, including physical ill-health, leading to suicide (Draper et al. 2014). Other personality factors include an inability to tolerate change and loss of control (Bonnewyn et al. 2014a); feeling of loneliness, despair, and dependence on others (Bonnewyn et al. 2014a); fear of death and escape acceptance (Bonnewyn et al. 2015); and life attitudes and purposelessness in life (Bonnewyn et al. 2014b).

Physical Factors

The relationship between suicide in older people and serious physical illness has been well established. Up to 82% of older suicide victims have a physical illness (Conwell et al. 2000; Beautrais 2002; Waern et al. 2002a, b, 2003; Duberstein et al. 2004; Erlangsen et al. 2005), often prolonged (Heikkinen and Lonnqvist 1995) and sufficiently severe to cause discomfort, pain, and interference with activities of daily living (Juurlink et al. 2004). Up to 23% of older suicide victims would have received inpatient care for their physical illness in the preceding 2 years (Beautrais 2002; Juurlink et al. 2004; Erlangsen et al. 2005).

Pain is an important risk factor for suicide in older people (Juurlink et al. 2004) and was present in up to 27% of older suicide victims (Cattell 1988; Cattell and Jolley 1995). Such pain can be divided into three categories: severe and associated with definite organic pathology such as ischemic heart disease, less severe and chronic associated with musculoskeletal system, and pain as a hypochondriacal symptom (Cattell 1988). Post-herpetic neuralgia has been reported to precede suicide in the elderly (Cattell 1988). Pain may act as a precipitant through several mechanisms including altered self-perceptions, impairing capacity for enjoyment and fostering dependence (Cattell 1988).

A range of physical illnesses have been shown to be associated with suicide in older people including chronic dyspnea associated with chronic obstructive lung disease, heart failure, and cancer; neurological disorders, including seizure disorder; urinary incontinence; cancer in various different organs; stroke; liver disease; and

sensory impairment (Horton-Deuth et al. 1992; Waern et al. 2002b, 2003; Juurlink et al. 2004; Preville et al. 2005; Erlangsen et al. 2015). Disorders of all major organ systems have been associated with suicide in older people (Waern et al. 2002b). Postmortem data provides further evidence of a link between cancer and suicide in older people (Barraclough 1971; Cattell 1988).

A model has been developed to explain the complex relationship between physical illness and suicide (Cattell 1988; Shah and De 1998; Waern et al. 2002b). The two main considerations are the actual physical disability and the victim's perception of this disability (Waern et al. 2002b; Duberstein et al. 2004; Juurlink et al. 2004; Erlangsen et al. 2005; Preville et al. 2005). In this context, four overlapping scenarios are identified. Suicide may occur, in the absence of any other factor, to relieve continued physical problems, when the victim is clear about undoubted prognosis. Second, physical illness may interact with other psychological and social variables to promote suicide. Thus, a mild or moderate physical illness may interact with depression leading to suicide. Third, physical illness in the elderly can lead to depression and influence its prognosis. Relapses may lead to hopelessness and despair which may precipitate suicide. Finally, physical symptoms may be hypochondriacal symptoms of depression or some other mental disorder, which in turn may lead to suicide.

Hospitalization and Nursing Home Placement

Up to two-thirds of older suicide victims were hospitalized for medical illness within 2 years of the suicide (Chiu et al. 2004; Erlangsen et al. 2005). Up to 20% of elderly victims have had a psychiatric admission in the preceding year (Cattell 1988; Cattell and Jolley 1995; Beautrais 2002). The highest risk period for suicide was a week after psychiatric admission or a week after discharge from such an admission (Erlangsen et al. 2006). Discharge from hospital may lead to hopelessness in patients who perceive persistent physical or psychological illness despite inpatient care, anger, and a return to social isolation (Cattell 1988). The thought of hospitalization may increase any existing feelings of hopelessness and helplessness and lead to suicide (Shah and De 1998). Anticipation of being placed into a care home has been associated with suicide in older people, particularly married couple (Loebel et al. 1991; Finkel and Rosman 1995), in whom this may be a life event of separation and severance of mutual support. Also, the presence of pre-existing depression may color the patient's view about care home.

Medical Contact

Older suicide victims often contact health service professionals prior to death. Up to 90% consult their general practitioner in the preceding 3–6 months, up to 77% in the preceding month, and up to 50% in the preceding week (Barraclough 1971; Cattell 1988; Conwell et al. 1991; Vassilas and Morgan 1994; Cattell and Jolley 1995; Chiu

et al. 2004; Juurlink et al. 2004); case-control studies confirmed this as excess consultation in the suicide group (Chiu et al. 2004; Juurlink et al. 2004). Nevertheless, up to 12% may not have seen their general practitioner in the last 6 months (Cattell and Jolley 1995).

Up to 20% of older suicide victims would have seen a psychiatrist in the preceding 6 months (Cattell 1988; Vassilas and Morgan 1994; Cattell and Jolley 1995). Up to half would have a lifetime history of psychiatric service contact, and up to a quarter would have had contact with psychiatric services in the last week (Conwell et al. 1990; Vassilas and Morgan 1994; Waern et al. 2002a, b; Chiu et al. 2004; Juurlink et al. 2004); case-control studies confirmed this excess contact in the suicide group (Chiu et al. 2004; Juurlink et al. 2004). In one study, ten subjects committed suicide on the same day as consulting a psychiatrist (Juurlink et al. 2004).

Data on the last consultation with the doctor (or other healthcare professionals) are limited. In a Finnish study of all age group suicides, up to 22% of victims had discussed suicide during their final consultation (Isometsa et al. 1995), and 21% had seen a doctor on the same day as their death (Isometsa et al. 1995). A discussion about suicide was more likely if the patient was seen in a psychiatric setting, had a previous history of self-harm, and was male (Isometsa et al. 1995); in a study of older suicide victims, consultation with a physician prior to suicide was not accompanied by ominous diagnoses (Juurlink et al. 2004). Several explanations have been offered for the low rate of discussion of suicide (Isometsa et al. 1995): patients may have been unable to, or did not wish to, communicate suicidal intent, perhaps because of depression, hopelessness, or ambivalence; professionals may have missed evidence of suicidal intent; those expressing suicidal intent may have received care and treatment preventing suicide, whereas those who die may have not communicated their suicidal intent; and, patients may not have intended to kill themselves at the time of the consultation.

In most studies only a small number of older suicide victims, between 19% and 39%, were on antidepressants, often in inadequate doses, despite depression being the most prevalent diagnosis (Barraclough 1971; Cattell 1988; Conwell et al. 1991; Cattell and Jolley 1995). However, a Swedish study, reviewing case notes and postmortem toxicology data, reported that 53% of older suicide victims were receiving antidepressants in the preceding 6 months, but data on dosage, compliance, and efficacy were absent (Waern et al. 1996). A subsequent Swedish study demonstrated that 74% of those with major depressive disorder had received antidepressants during the final 6 months of life, and the prescribed doses were at the level recommended for the elderly or higher (Waern et al. 2002a). A significant number of older suicide victims were on sedatives and hypnotics (Conwell et al. 1986; Cattell and Jolley 1995; Voaklander et al. 2008).

Methods of Suicide

With increasing age, violent methods are used more frequently, particularly in men (Conwell et al. 2002; Chiu et al. 2004; Juurlink et al. 2004; Abrahams et al. 2005; Voaklander et al. 2008; Shah and Buckley 2011). Hanging, jumping from a height,

drowning, and suffocation are used commonly in many countries including the United Kingdom (Shah and Buckley 2011), Canada (Juurlink et al. 2004; Voaklander et al. 2008), Hong Kong (Chiu et al. 2004), Japan (Watanabe et al. 1995), India (Abrahams et al. 2005), Finland (Henriksson et al. 1995), New Zealand (Beautrais 2002), and Australia (Burvill 1995). Death with use of firearms is more prevalent in the United States (Conwell et al. 2002), Canada (Juurlink et al. 2004; Voaklander et al. 2008), New Zealand (Beautrais 2002), Australia (Burvill 1995), and Finland (Henriksson et al. 1995) compared to the United Kingdom, Japan, and Singapore (Kua and Ko 1992; Ko and Kua 1995; Shimuzu 1990; Shah and Buckley 2011) due to tighter firearms regulation. Suicide by car exhaust fumes is prevalent in the United Kingdom (Shah and Buckley 2011), New Zealand (Beautrais 2002), and Australia (Burvill 1995) and has been observed in Hong Kong (Chiu et al. 2004). Moreover, in the Unitec States, older people with firearms at home, particularly hand guns, and those who kept hand guns loaded were at higher risk of suicide (Conwell et al. 2002).

Self-poisoning was generally more common in older women (Cattell and Jolley 1995; Burvill 1995; Shah and Buckley 2011), although in India drowning and burning were more common in women (Abrahams et al. 2005). Self-poisoning has declined in several countries (Juurlink et al. 2004; Voaklander et al. 2008) and may be related to decline in barbiturate poisoning in some countries (Skegg and Cox 1991). Suicides due to analgesics and benzodiazepines have increased in older people, particularly women (Shah and Buckley 2011), and analgesics are the commonest drugs taken in overdose, particularly aspirin and paracetamol (Cattell and Jolley 1995; Shah and Buckley 2011).

Suicide Note

Suicide notes can provide valuable insight into the victim's thinking and are usually considered a serious measure of suicidal intent (Shah and De 1998), but have been sparsely studied in older people (Leenaars 1992; Salib et al. 2002a, b). About 43% of older suicide victims left a note in one study, and this was at a lower frequency than younger victims (Salib et al. 2002a). This may be because many older suicide victims are isolated, may have no one to leave a note for, and may be unable to write a note because of poor vision or limb dysfunction (Shah and De 1998; Salib et al. 2002a, b). Suicide notes tend to be brief and self-reproachful (Salib et al. 2002a). An absence of suicide note should not be seen as less serious suicidal intent (Salib et al. 2002a, b).

Overlap with Attempted Suicides

Epidemiology

Deliberate self-harm is less common in older people, accounting for up to 15% all attempted suicide (Pierce 1987; Hawton and Fagg 1990; Merrill and Owens 1990; Upadhyaya et al. 1989; Nowers 1993; Draper 1994; Lawrence et al. 2000). Older

people are overrepresented in suicides with a ratio of 1:4 compared to 1:200 for young people (De Leo et al. 2001). Suicide attempts in older people are less impulsive then in younger people, and suicidal intent is generally high in older attempters (Pierce 1987, 1996; Merrill and Owens 1990; Upadhyaya et al. 1989; Hawton and Fagg 1990; Nowers 1993; Draper 1994; Hepple and Quinton 1997). Moreover, the severity of intent has a linear relationship with age: highest in the old, then the young-old, and lowest in the young (Pierce 1987; Merrill and Owens 1990). Thus, attempted suicide has been considered to be similar to completed suicide in the elderly (Shulman 1978; Lindesay and Murphy 1987; Draper 1996) and that careful examination with direct interview of suicide attempters has been used as an opportunity of study elderly suicides (Shah and De 1998).

Older men are more likely to commit suicide and older women are more likely to make a serious nonfatal attempt (Beautrais 2002). The sex ratio is around 2:3 with a range from 3:2 to 2:5 (Takahashi et al. 1995; Chiu et al. 1996; Pierce 1996; Schmidtke et al. 1996; Szanto et al. 1998; Lawrence et al. 2000; De Leo et al. 2002a; Marriott et al. 2003). Attempted suicides are associated with not being married, being divorced, being widowed, or being single (Nowers 1993; Hawton and Fagg 1990; Lawrence et al. 2000; De Leo et al. 2001), However, this is not a universal finding as those self-harming were more likely to be married in two studies (Chiu et al. 1996; Beautrais 2002), and there was no difference in a third study (Takahashi et al. 1995), but these findings may be contingent on local cultural factors (Chan et al. 2007). Living alone (Pierce 1987; Nowers 1993; Draper 1994; Takahashi et al. 1995), lower levels of social contact (Beautrais 2002), perceived lower level of social support (Szanto et al. 1998), relationship difficulties (Draper 1994; Beautrais 2002), financial difficulties (Draper 1994), and unresolved grief (Upadhyaya et al. 1989; Draper 1994) have all been associated with older attempters.

Mental Disorders

Older suicide attempters were more likely to have a previous psychiatric history and hospitalization (Chiu et al. 1996; Takahashi et al. 1995; Lawrence et al. 2000; Beautrais 2002; Marriott et al. 2003).

Up to 90% of older suicide attempters have depression (Merrill and Owens 1990; Chiu et al. 1996; Pierce 1987, 1996; Hepple and Quinton 1997; Lawrence et al. 2000; De Leo et al. 2001, 2002a; Beautrais 2002; Suominen et al. 2004; Kato et al. 2013). Adjustment disorders (Takahashi et al. 1995; Chiu et al. 1996) and high levels of somatization (Takahashi et al. 1995) were also present in some studies.

The role of schizophrenia and related disorders is unclear with the prevalence among older suicide attempters being only up to 6.3% (Takahashi et al. 1995; Chiu et al. 1996; Pierce 1996; Lawrence et al. 2000; De Leo et al. 2001, 2002a), although a Finnish study reported a higher prevalence of 20% (Suominen et al. 2004). However, no difference was found in a case-control study (Barak et al. 2004).

Alcohol misuse and consumption of alcohol before the attempted suicide are common (Hawton and Fagg 1990; Upadhyaya et al. 1989; Draper 1994), particularly in men and those who are depressed (Hawton and Fagg 1990). Both alcohol and substance misuse have been linked to suicide attempts in older people (Szanto et al. 1998; Beautrais 2002). Moreover, in Japan and Hong Kong, older suicide attempters have a low rate of alcohol misuse (Chiu et al. 1996; Takahashi et al. 1995), but this may be due to cultural factors (Chan et al. 2007).

Dementia occurs at a lower prevalence, up to 10%, in older people attempting suicide (Pierce 1987; Nowers 1993; Chiu et al. 1996; Takahashi et al. 1995; Osvath et al. 2002). Frontal lobe dysfunction for impulsive episodes and depression are important factors (Pierce 1987; Draper 1994), but the evidence is limited (King et al. 2000).

Up to 26% have a secondary diagnosis of personality disorder (Draper 1994), but recent studies have reported lower prevalence of up to 7% (Takahashi et al. 1995; Chiu et al. 1996; Hepple and Quinton 1997; Lawrence et al. 2000; De Leo et al. 2001; Beautrais 2002; Suominen et al. 2004). Personality factors associated with a lifetime history of suicide attempts in older people include high levels of hopelessness, including low positive emotions facet (Szanto et al. 1998; Duberstein et al. 2001; Seidlitz et al. 2001; Useda et al. 2004) and low extraversion (Duberstein et al. 2000); higher neuroticism, including high impulsiveness and low self-consciousness (Duberstein et al. 2000); and low openness to experience (Duberstein et al. 2000). It has been suggested that older people with a lower preference for social interaction coupled with an inability to experience positive emotions and an inability to seek help from others may become hopeless during adversity promoting suicidal behavior (Chan et al. 2007). However, another study of those with lifetime history of attempts, a number of attempts, and serious attempts failed to show an association with neuroticism component of self-consciousness (Useda et al. 2004). Lower levels of anger and hostility were associated with higher intent and greater lethality and lower guilt with greater lethality (Seidlitz et al. 2001).

Physical Illness

Serious physical illness and pain, leading to demoralization, as a cause of attempted suicide is not uncommon (Pierce 1987; Upadhyaya et al. 1989; Nowers 1993; Draper 1994; Takahashi et al. 1995). Chronic physical illness is more common in men and the old in both genders (Nowers 1993; Draper 1994; Takahashi et al. 1995). Acute physical illness is more common in women and the old (Nowers 1993; Draper 1994). It is possible that many attempted suicides in old age are genuine bids for suicide, which have failed due to confusion from physical illness, overmedication, or alcohol misuse (Sendbeuhler and Goldstein 1977). Nevertheless, individuals with organic brain disease made impulsive and hazardous attempts, often by several means, in a state of confusion, depression, and cerebral disinhibition (Pierce 1987).

Methods

Violent attempts were found more often in earlier studies, but more recent studies report self-poisoning, in up to 89% of cases, as the most prevalent method (De Leo et al. 2001, 2002a; Hepple and Quinton 1997; Upadhyaya et al. 1999; Beautrais 2002; Lykouras et al. 2002; Marriott et al. 2003). Psychotropic drugs are commonly used including benzodiazepines (Chiu et al. 1996; De Leo et al. 2001; Ticehurst et al. 2002). Other drugs used include hypnotics, antidepressants, and analgesics, including paracetamol and paracetamol-containing preparations (Pierce 1987; Hawton and Fagg 1990; Nowers 1993; Draper 1994; Takahashi et al. 1995); barbiturates are rarely used nowadays. Women were more likely to take overdoses, whereas men were more likely to use violent methods (De Leo et al. 2001; Osvath et al. 2002). Drug overdose was also uncommon in Japan and Hong Kong (Chiu et al. 1996; Takahashi et al. 1995). Self-injury from wrist cutting, stabbing, attempted asphyxiation, attempted drowning, hanging, and jumping from a height are also not uncommon (De Leo et al. 2001, 2002; Hepple and Quinton 1997; Upadhyaya et al. 1999; Lykouras et al. 2002; Chiu et al. 1996; Takahashi et al. 1995).

Possible Pathways to Suicide

Suicide is considered an outcome of both distal and proximal risk and protective factors (Hawton and Van Heeringen 2009). Moreover, it may constitute a pathway starting with a wish to die and eventually leading to suicide (Caine and Conwell 2001; Bonnewyn et al. 2014a). A model describing pathways to suicide (Shah and Ganesvaran 1994), based on the concept of preparatory and trigger factors and their role in the development of suicidal intent (Shimuzu 1990), the concept of proximal and distal risk factors (Moscicki 1995), and Shulman's (1978) permissive model of suicide, has been described. Shimuzu's (1990) preparatory and trigger factors are similar to Moscicki's (1995) distal and proximal factors, respectively. The preparatory state has been hypothesized to be a state of preparedness for suicidal intent, and this usually develops insidiously (Shah and Ganesvaran 1994). Age, period, and cohort effects; personality and constitutional factors; and early life adversity may contribute to this state. The suicidal intent may be high or low and may be contingent on the frequency and intensity of these factors. However, other factors are likely to operate because not everyone in this stage of preparedness proceeds to suicide. These additional factors are the trigger factors. Trigger factors are generally more acute in onset and may be of high or low intensity in successful suicides depending upon the intensity of suicidal intent in the preparedness state (Shimuzu 1990). Social adversity, cultural factors, and physical illness may act as both trigger and preparatory factors. The combination of these trigger and preparatory factors may lead to the development of mental illness, particularly depression. Moreover, in the presence of mental illness, these two states will lead to the formation of suicidal intent and subsequent suicide. However, this pathway may be interrupted at any stage and may fluctuate, making it difficult for professionals to identify those at risk of suicide (De Leo et al. 2005).

Prevention

Prevention of suicide can be seen at three overlapping levels: in those at immediate risk of suicide, in those potentially at high risk, and in society generally.

Immediate Risk of Suicide

Individuals demonstrating suicide risk behaviors, including suicidal ideation and intent with or without a suicide attempt, require preventative help (Shah and De 1998). Firstly, any older person with a recent suicide attempt or with suicidal ideation requires careful assessment of the current risk of suicide (Shah and De 1998). This assessment should be threefold: the assessment of the severity of the intent of the recent attempt, the assessment of the severity of the current intent, and the assessment of potential risk factors including the presence of mental illness. Avenues to treat the mental illness and to keep the individual safe from a fresh suicide attempt should be planned. If the patient cannot be managed outside the hospital setting because of the severity of intent, severity of mental illness, lack of social support, and lack of appropriate community mental health services, admission should be immediate and involuntary if necessary (Shah and De 1998). The patient should be carefully observed on the ward and a careful management plan, agreed with all clinical team members and the patient and the family, should be formulated. An important risk period for suicide is immediately after discharge. It may be possible to reduce this risk by careful and appropriate discharge planning and close monitoring after discharge, as advocated by the care program approach in the United Kingdom, but has not been formally evaluated in this context.

Once a suicide has occurred, all members of the clinical team should carefully review the case and consider any reports from the coroner or an equivalent, to identify future preventative factors (Alexopoulos 1991; Rosowsky 1993). All psychiatric centers should have procedures and policies that automatically invoke an audit of suicides and involve multidisciplinary staff, including practice-based staff, social services, home care agencies, and voluntary organizations (Cattell and Jolley 1995; King and Barraclough 1990). The National Confidential Inquiry into Homicides and Suicides in the United Kingdom collects detailed data on every suicide, and they may have an important role in identifying preventative factors also (Shah and De 1998).

Prevention in High-Risk Groups

A large number of older suicide victims have seen a doctor shortly before death. It is not clear if evidence of mental illness and suicidal intent is missed or such evidence was subtle or absent (Isometsa et al. 1995). It is important to recognize mental illness and suicidal intent because majority of older suicide victims have a potentially treatable mental illness (Shah and De 1998). Although it would be difficult for a

general practitioner to predict such an uncommon event (Diekstra and Van Egmond 1989), it may be possible to target those with some of the risk factors discussed earlier, and the presence of these factors should alert the doctor to assess the risk of suicide. Those general practitioners with superior interview skills, good previous knowledge of their patients, and a favorable attitude toward mental illness are better able to detect mental illness, and this ability can be improved by training (Morriss 1992; Gask 1992). Moreover, a postgraduate training program, directed at general practitioners, to improve detection and treatment of depression, reduced suicide rates on the Swedish island of Gotland (Rutz et al. 1989, 1992, 1997).

Depression is common among geriatric medicine patients and is poorly recognized and treated, often with inadequate doses of antidepressants (Ames et al. 1994; Koenig et al. 1997; Shah and Hoxey 2001). Thus, the same issues as for general practitioners need to be addressed with doctors in geriatric medicine. As a significant number of older victims would have had recent contact with a psychiatrist or other professionals in psychiatric services, the same issues as for general practitioners need to be addressed, including education, but have not attracted similar criticisms. Training all professionals in primary and secondary care and social services in the recognition of mental illness and suicide risk in older people may prove to be invaluable (Shah and De 1998).

Should the general practitioner or geriatrician feel out of depth in treating the mental illness, then the patient should be referred to specialist mental health services (Shah and De 1998). Specialist community psychiatric services can reduce suicide rates (Walk 1967). The use of community psychiatric nurse to treat and coordinate the treatment of mental illness can bridge the gap between primary and secondary care (Michel and Valach 1992). Close collaboration is needed between psychiatrists, geriatricians, general practitioners, and social services when dealing with mentally ill patients with physical disorders (Shah and De 1998). Although only a small number of older suicide victims were on antidepressants and often at inadequate doses, there is emerging evidence that suicide rates in older people decrease with increased prescription of antidepressants (Hall et al. 2003; Lodhi and Shah 2004).

The IMPACT (Unutzer et al. 2002, 2006) and PROSPECT (Alexopoulos et al. 2009; Bruce et al. 2004) randomized controlled trials examined the effect of the relevant intervention program, compared to care as usual, on depression in older people in primary care. In both studies, those in the intervention group received support from care managers (nurses, psychologists, and social workers), including education about treatment options, interpersonal or behavioral brief psychotherapy, monitoring of depressive symptoms and side effects, and follow-up. In the IMPACT study, individuals were randomized into the intervention and care as usual groups. In the PROSPECT study, individual primary care practices were randomized into the intervention and care as usual groups. In the IMPACT study, participants in the intervention group had significantly lower levels of depression and suicidal ideation at 6, 12, 18, and 24 months of follow-up (Unutzer et al. 2002, 2006). In the PROSPECT study, suicidal ideation was only significantly reduced in those with major depression at 4, 8, and 24 months (Alexopoulos et al. 2009). However, these studies were not designed to examine suicide itself as an outcome measure.

A pooled analysis of three intervention studies of depression evaluating 12 weeks of pharmacotherapy with or without interpersonal psychotherapy reported resolution of suicidal ideation in all groups (Szanto et al. 2003). Those with higher suicide risk required 6 weeks for this improvement compared to 3 weeks for those with lower risk. However, these studies were not designed to examine suicide itself as an outcome measure.

A group of retirees having difficulty in adapting to retirement received intervention program of an 11-week workshop using a cognitive behavioral approach (Lapierre et al. 2007). This resulted in 80% of those in the intervention group demonstrating absence of suicidal ideation compared to 36% of the control group after 6 months. Another study of 16-week interpersonal psychotherapy, for adults with elevated risk of suicide, to improve social functioning and skills and enhance social support and satisfaction of interpersonal needs, showed reduction before and after treatment of the severity of depressive symptoms and suicidal ideation (Heisel et al. 2009). Again, both these studies were not designed to measure suicide itself as an outcome measure.

None of the above intervention studies of potentially high-risk groups measured suicide as an outcome. Demonstrating reduction in suicidal ideation is not the same as reduction in the number of suicides. National suicide prevention policies in various countries have focused on high-risk groups, but their effectiveness has not been formally evaluated as a period effect independent of age and cohort effect by gender.

Prevention at a Societal Level

Although there are several studies of telephone counseling outreach services for older people, only one study has formally examined its impact on suicide (De Leo et al. 2002b). After 11 years of a telephone service, offering a 24-h emergency service to older people to call for help and a twice weekly telephone support service, there was a significant reduction in mortality due to suicide. Over 80% of users of the telephone service were women, and the main benefits were in women. Such telephone services are available in other countries.

A series of Japanese cohort studies implemented community-based outreach programs in rural areas where the rate of suicide was elevated in both genders (over 150 per 100, 000 person years) (Oyama et al. 2004, 2005, 2006a, b, c). The interventions included mental health workshop for older people conducted to promote awareness of depression and suicide risk. Additionally, there was annual screening for depression, and those with depression received interventions from psychiatrists or general practitioners coupled with follow-up by mental health nurses. The overall program in one of the cohorts was different including absence of screening, but participants were encouraged to self-assess for depression with a short questionnaire. A meta-analysis of these studies reported that the incidence rate ratio (number of suicides divided by the population size) was significantly reduced after the intervention (Oyama et al. 2008). This was mainly in women with risk reduction of 70% (Oyama et al. 2008).

Removal of the means of suicide by detoxification of domestic gas and barbiturates resulted in reduction in suicide rates (Lindesay 1991). This may also apply to removal of other methods including reduced rates due to exhaust fumes in the United States following exhaust emission laws (Clarke and Lester 1987). Although it would be difficult to control the prescription of drugs like aspirin and paracetamol, which can be purchased over the counter in most countries, the quantity that can be purchased can be regulated as in the United Kingdom. This is important for older people who may be physically ill with pain. Suicides due to benzodiazepines could be reduced by limiting or eradicating their prescription in older people as they are only of limited value in older people.

Society as a whole, including friends, family, and neighbors, should be made aware that mental illness and suicidal behavior in the elderly can be recognized and treated. This can be achieved by public education campaign (Shah and De 1998). The Defeat Depression Campaign in the United Kingdom may have had this effect, but has not been formally examined as a period effect. Elderly people may be more likely to turn to the clergy rather than the doctor when they or someone they know are contemplating suicide. Thus, it is important that the clergy are trained to recognize mental illness and suicidal behavior and are aware of locally available relevant services. Organizations promoting suicide and assisting people in identifying methods of suicide, many easily accessible via the Internet, should all be banned.

Conclusions

Suicide in older people is an important public health concern and is potentially preventable. Although a lot is known about the epidemiology and potential risk and protective factors at an individual and societal level, there is only limited evidence from evaluative studies pertaining to strategies to reduce suicides. There is a clear need to examine the relative impact of both individual and societal-level risk and protective factors on suicides and develop multifaceted preventative strategies. It is necessary to evaluate these strategies with suicide as the outcome measure rather than suicidal ideation, as the latter may not always translate to suicide. As suicide is a comparatively rare event, any such intervention study would require large numbers for adequate statistical power (Pokorny 1983) and may need to not only be multicenter but truly cross-national.

References

Abrahams VJ, Abrahams S, Jacob KS (2005) Suicide in the elderly in Kaniyambadi block, Tamil Nadu, South India. Int J Geriatr Psychiatry 20:953–955

Agbayewa MO, Marion SA, Wiggins S (1998) Socioeconomic factors associated with suicide in elderly populations of British Columbiia: an 11-year review. Can J Psychiatr 43:829–836

Ajdacic-Gross V, Bopp M, Gostynski M, Lauber C, Gutzwiller F, Rossler W (2006) Age-period-cohort analysis of Swiss data, 1881–2000. Eur Arch Psychiatry Clin Neurosci 256:207–214

Alexopoulos GS (1991) Psychological autopsy of an elderly suicide. Int J Geriatr Psychiatry 6:45–50
Alexopoulos GS, Reynolds CF, Bruce ML, Katz IR, Raue PJ, Mulsant BH, the PROSPECT group (2009) Reducing suicidal ideation and depression in older primary care patients: 24-month outcomes of the PROSPECT study. Am J Psychiatr 166:882–890
Ames D, Flynn E, Harrigan S (1994) Prevalence of psychiatric disorders amongst inpatients of acute geriatric hospitals. Aust J Ageing 13:8–11
Barak Y, Knobler CY, Aizenberg D (2004) Suicide attempts among elderly schizophrenia patients: a 10-year case-control study. Schizophr Res 71:77–81
Barraclough BM (1971) Suicide in the elderly. Br J Psychiatry 6:87–97
Beautrais AL (2002) A case control study of suicide and attempted suicide in older adults. Suicide Life-Threat Behav 32:1–9
Bell P, Shah AK (1999) Suicidal ideation amongst functionally ill psychogeriatric inpatients. Int J Psychiatry Clin Pract 3:253–256
Bertolote JM, De Leo D (2012) Global suicide mortality rates: a light at the end of the tunnel? Crisis 33:249–253
Bertolote JM, Fleischmann A (2002) A global perspective in the epidemiology of suicide. Suicidologi 7:6–8
Beskow J, Runeson B, Asgard U (1990) Psychological autopsies: methods and ethics. Suicide Life Threat Behav 20:307–323
Blazer DG, Bachar JR, Manton KG (1986) Suicide in late life-review and commentary. J Am Geriatr Soc 13:743–749
Bonnewyn A, Shah A, Bruffaerts R, Demyttenaere K (2014a) Are gender and life attitudes associated with the wish to die in older psychiatric and somatic inpatients? An exploratory study. Int Psychogeriatr 26:1693–1702
Bonnewyn A, Shah A, Bruffaerts R, Schoevaerts K, Rober P, Van Parys H, Demyttenaere K (2014b) Reflections of older adults on the process preceding their suicide attempt: a qualitative approach. Death Stud 38:612–618
Bonnewyn A, Shah A, Bruffaerts R, Demyttenaere K (2015) Are religious and death attitudes associated with the wish to die in older people. Int Psychogeriatr 28:397
Bruce M, Ten Have TR, Reynolds CF, Katz II, Schulberg HC, Mulsant BH, Alexopoulos GS (2004) Reducing suicidal ideation and depressive symptoms in depressed older primary care patients. J Am Med Assoc 291:1081–1091
Burvill PW (1995) Suicide in the multi-ethnic population of Australia. 1979–1990. Int Psychogeriatr 7:319–333
Caine E, Conwell Y (2001) Suicide in the elderly. Int Clin Psychopharmacol Suppl 2:S25–S30
Carstensen B (2006) Age-period-cohort models for the Lexis diagram. Stat Med 26:3018–3045
Cattell H (1988) Elderly suicides in London: an analysis of coroner's inquests. Int J Geriatr Psychiatry 3:251–261
Cattell H, Jolley D (1995) One hundred cases of suicide in elderly people. Br J Psychiatry 166:451–457
Chan J, Draper B, Banerjee S (2007) Deliberately self-harm in older adults: a review of the literature from 1995–2004. Int J Geriatr Psychiatry 22:720–732
Chang SS, Sterne JAC, Lu TH, Gunnell D (2010) 'Hidden' suicides among deaths certified as undetermined intent, accident by pesticide poisoning and accident by suffocation in Taiwan. Soc Psychiatry Psychiatr Epidemiol 45:143–152
Chiu HFK, Lam LCW, Pang AHT et al (1996) Attempted suicide by Chinese elderly in Hong Kong. Gen Hosp Psychiatry 18:444–447
Chiu HFK, Yip PS, Chi I, Chan S, Tsoh J, Kwan CW, Li SF, Conwell Y, Caine E (2004) Elderly suicide in Hong Kong: a case controlled study. Acta Psychiatr Scand 109:299–305
Christensen K, Doblhammer G, Rau R, Vaupel JW (2009) Ageing populations: the challenges ahead. Lancet 374:1196–1208
Clarke RV, Lester D (1987) Toxicity of car exhaust and opportunity for suicide: comparison between Britain and United States. J Epidemiol Community Health 41:114–120

Conwell Y, Pearson J, DeRenzo EG (1986) Indirect self-destructive behaviour among elderly patients in nursing homes: a research agenda. Am J Geriatr Psychiatry 4:152–163
Conwell Y, Rotenberg M, Caine ED (1990) Completed suicides aged 50 and over. J Am Geriatr Soc 38:640–644
Conwell Y, Olsen K, Caine ED, Flannery C (1991) Suicide in later life. Psychological autopsy findings. Int Psychogeriatr 3:59–66
Conwell Y, Lyness JM, Duberstein P, Cox C, Seidlitz L, DiGiorgio A, Caine ED (2000) Completed suicide among older patients in primary care practices: a controlled study. J Am Geriatr Soc 48:23–29
Conwell Y, Duberstein PR, Connor K, Eberly S, Cox C, Csine E (2002) Access to firearms and risk of suicide in middle-aged and older adults. Am J Geriatr Soc 10:407–416
Costa PT, McCrae RR (1988) Personality in adulthood: a six-year longitudinal study of self-reports and spouse ratings on NEO personality inventory. J Pers Soc Psychol 54:853–863
Daradekh TK (1989) Suicide in Jordan 1980–1985. Acta Psychiatr Scand 79:241–244
De Leo D (2015) Australia revises its mortality data on suicide. Crises 31:169–173
De Leo D, Padoani W, Scocco P et al (2001) Attempted and completed suicide in older subjects: results of the WHO/EURO multicentre study of suicidal behaviour. Int J Geriatr Psychiatry 16:300–310
De Leo D, Padoani W, Lonnqvist J et al (2002a) Repetition of suicidal behaviour in elderly Europeans: a prospective longitudinal study. J Affect Disord 72:291–295
De Leo D, Dello Buono L, Dwyer J (2002b) Suicide among elderly: the long term impact of of a telephone support and assessment intervention in Northern Italy. Br J Psychiatry 181:226–229
De Leo D, Cerin E, Spanthonis K, Burgis S (2005) Lifetime risk of suicide ideation and attempts in an Australian community: prevalence, suicidal process and help-seeking behaviour. J Affect Disord 86:215–224
Dennis M, Read S, Andrews H et al (2001) Suicide in a single health district: epidemiology and audit of the involvement of psychiatric services. J Ment Health 6:673–682
Diekstra RFW, Van Egmond M (1989) Suicide and attempted suicide in general practice, 1976–1986. Acta Psychiatr Scand 79:268–275
Draper B (1994) Suicidal behaviour in the elderly. Int J Geriatr Psychiatry 9:655–661
Draper B (1996) Attempted suicide in old age. Int J Geriatr Psychiatry 11:577–587
Draper B, Kolves K, De Leo D, Snowdon J (2014) A controlled study of suicide in middle-aged and older people: personality traits, age and personality disorders. Suicide Life Threat Behav 44:130–138
Duberstein PR (1995) Openness to experience and completed suicide across the second half of life. Inernational Psychogeriatr 7:183–198
Duberstein PR, Conwell Y, Seidlitz L et al (2000) Personality traits and suicidal behaviour and ideation in depressed inpatients 50 years of age and older. J Gerontol 55:18–26
Duberstein PR, Conner KR, Conwell Y, Cox C (2001) Personality correlates of hopelessness in depressed patients 50 years of age and older. J Pers Assess 77:380–390
Duberstein PR, Conwell Y, Conner KR, Eberly S, Caine ED (2004) Suicide at 50 years of age and older: perceived physical illness, family discord and financial strain. Psychol Med 34:137–146
Ebert BW (1987) Guide to conducting psychological autopsy. Prof Psychol: Res Pract 58:775–782
Erlangsen A, Jeune B, Bille-Brahe U, Vaupel JW (2004) Loss of partner and suicide risks among oldest old: a population-based register study. Age Ageing 33:378–383
Erlangsen A, Vach W, Jeune B (2005) The effect of hospitalisation with medical illnesses on suicide risk in the oldest old: a population-based register study. J Am Geriatr Soc 53:771–776
Erlangsen A, Zarit SH, Tu X, Conwell Y (2006) Suicide among older psychiatric inpatients: an evidence-based study of high risk group. Am J Geriatr Psychiatr 14:734–741
Erlangsen A, Zarit SH, Conwell Y (2008) Hospital diagnosed dementia and suicide: a longitudinal study using prospective, nationwide register data. Am J Geriatr Psychiatr 16:220–228

Erlangsen A, Stenager E, Conwell Y (2015) Physical diseases as predictors of suicide in older adults: a nationwide, register-based cohort study. Soc Psychiatry Psychiatr Epidemiol 50:1427–1439
Etzersdorfer E, Fischer P (1993) Suicide in the elderly in Austria. Int J Geriatr Psychiatry 8:727–730
Ferguson S (2005) Suicide rates in New Zealand. Exploring associations with social and economic factors. Report 2: social explanations for suicide in New Zealand. Wellington, Ministry of Health.
Finkel SI, Rosman M (1995) Six elderly suicides in a one-year period in rural midwestern community. Int Psychogeriatr 7:221–230
Ganesvaran T, Rajarajeshwaran R (1988) Fatal deliberate self-harm seen in a Sri Lankan hospital. Br J Psychiatry 152:420–423
Gask L (1992) Training general practitioners to detect and treat emotional disorders. Int Rev Psychiatry 4:293–300
Granizo JJ, Guallar E, Rodrigeuz-Artalejo F (1996) Age-period-cohort analysis of suicide mortality rates in Spain, 1959–1991. Int J Epidemiol 25:814–820
Gunnell D, Middleton N, Whitley E, Dorling D, Frankel S (2003) Influence of cohort effects on patterns of suicide in England and Wales, 1950–1999. Br J Psychiatry 182:164–170
Haas AP, Hendin H (1983) Suicide among older people: projections for older people. Suicide Life Threat Behav 13:147–154
Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P (2003) Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. Br Med J 327:289
Harwood DM, Hawton K, Hope T, Jacoby R (2001) Psychiatric disorders and personality factors associated with suicide in older people: a descriptive and case-control study. Int J Geriatr Psychiatry 16:155–165
Harwood DM, Hawton K, Hope T, Harriss L, Jacoby R (2006) Life problems and physical illness as risk factors for suicide in older people: a descriptive and case-control study. Psychol Med 36:1265–1274
Hasegawa K, Finkel SI, Bergerner M et al (1992) Late life suicide. Int Psychogeriatr 4:163
Hawton K, Fagg J (1990) Deliberate self-poisoning and self-injury in older people. Int J Geriatr Psychiatry 5:367–373
Hawton K, Van Heeringen K (2009) Suicide. Lancet 373:1372–1381
Heikkinen ME, Lonnqvist JK (1995) Recent life events in elderly suicide: a nationwide study. Int Psychogeriatr 7:287–300
Heisel M, Duberstein P, Talbot N, King D, Tu X (2009) Adapting interpersonal psychotherapy for older adults at risk of suicide: preliminary findings. Prof Psychol: Res Pract 40:156–164
Henriksson MM, Martunnen MJ, Isometa ET et al (1995) Mental disorders in elderly suicides. Int Psychogeriatr 7:275–286
Hepple J, Quinton C (1997) One hundred cases of attempted suicide in the elderly. Br J Psychiatry 171:42–46
Holding TA, Barraclough BM (1975) Psychiatric morbidity in a London Coroner's open verdicts. Br J Psychiatry 127:133–143
Horton-Deuth SL, Clark DC, Farran CJ (1992) Chronic dyspnea and suicide in elderly men. Hosp Comm Psychiatry 43:1198–1203
Hoxey K, Shah AK (2000) Recent trends in elderly suicide rates and methods in England and Wales. Int J Gertiatr Psychiatr 15:274–279
Isometsa ET, Heikkinen ME, Martunnen MJ et al (1995) The last appointment before suicide. Is intent communicated? Am J Psychiatr 152:919–922
Jacob KS (2008) The prevention of suicide in India and the developing world: the need for population-based strategies. Crisis 29(2):102–106
Jacob KS, Sharan P, Mirza I, Garrido-Cumbrera M, Seedat S, Mari JJ, Sreen V (2007) Global mental health 4. Mental health systems in countries: where are we now? Lancet 370:1061–1077

Jeune B, Skytthe A (2001) Centenarians in Denmark. In the past and the present. Popul: An Engl Sel 13:75–94
Juurlink DN, Herrman N, Szalai JP, Kopp A, Redelmeier DA (2004) Medical illness and the risk of suicide in the elderly. Arch Intern Med 164:1179–1184
Kapusta ND, Etzersdorfer E, Sonneck G (2006) Trends in suicide rates of the elderly in Austria, 1970–2004: an analysis of changes in terms of age groups, suicide methods and gender. Int J Geriatr Psychiatry 22:438–444
Kapusta ND, Tran US, Rockett IR, De Leo D, Naylor CP, Niederkrotenthaler T, Voracek M, Etzersdorfer E, Sonneck G (2011) Declining autopsy rates and suicide misclassification: a cross-national analysis of 35 countries. Arch Gen Psychiatry 68:1050–1057
Kato K, Akama F, Yamada K, Maehara M, Saito M, Kimoto K, Takahashi Y et al (2013) Frequency and clinical features of suicide attempts in elderly patients in Japan. Psychiatry Clin Neurosci 67:119–122
King E, Barraclough B (1990) Violent death and mental illness. A study of single catchment area over eight years. Br J Psychiatry 156:714–720
King DA, Conwell Y, Cox C et al (2000) A neuropsychological comparison of depressed suicide attempters and non-attempters. J Neuropsychiatry Clin Neurosci 12:64–70
Kjolseth I, Ekeberg O, Strethaug S (2009) "Why do they become vulnerable when faced with the challenges of old age". Elderly people who committed described by those who knew them. Int Psychogeriatr 21:903–912
Ko SM, Kua EH (1995) Ethnicity and elderly suicide in Singapore. Int Psychogeriatr 7:309–317
Koenig HG, George LK, Meador KG (1997) Use of antidepressants by nonpsychiatrists in the treatment of medically ill hospitalised depressed elderly patients. Am J Psychiatr 154:1369–1375
Kua EH, Ko SM (1992) A cross-cultural study of suicide in the elderly in Singapore. Br J Psychiatry 160:558–559
Kua EH, Ko SM, Ng TP (2003) Recent trends in elderly suicide rates in a multi-ethnic Asian city. Int J Geriatr Psychiatry 18:533–536
Kwon JW, Chun H, Cho SI (2009) A closer look at the increase in suicide rates in South Korea 1986–2005. BMC Public Health. http://www.biomedcentral.com/1471.2458/9/72 Viewed 8 Nov 2015
Lapierre S, Dube M, Bouffard L, Alain M (2007) Addressing suicidal ideations with the realisation of meaningful personal goals. Crisis 28:16–25
Lawrence D, Almeida O, Hulse GK et al (2000) Suicide and attempted suicide among older adults in Western Australia. Psychol Med 30:813–821
Leenaars AA (1992) 5 Suicide notes of older adults. Suicide Life Threat Behav 22:62–69
Lin JJ, Ku TH (2008) Suicide mortality by sex, age and method in Taiwan, 1971–2005. BMC Public Health. doi:10.1186/1471-2458-8-6. http://www.biocentral.com/1471.2458/8/6 Viewed 10th November 2015
Lindesay J (1991) Suicide in the elderly. Int J Geriatr Psychiatry 6:355–361
Lindesay J (1993) Age, sex and suicide rats within birth cohorts in England and Wales. Soc Psychiatry Psychiatr Epidemiol 24:249–252
Lindesay J, Murphy E (1987) Suicide in old age. Int J Geriatr Psychiatry 2:71–72
Linsley KR, Schapira K, Kelly TP (2001) Open verdict v suicide – importance to research. Br J Psychiatry 178:465–468
Lodhi L, Shah AK (2004) Psychotropic prescriptions and elderly suicide rates. Med Sci Law 44:236–244
Lodhi L, Shah AK (2005) Factors associated with the recent decline in suicide rates in the elderly in England and Wales. 1985–1998. Med Sci Law 45:115–120
Loebel JP, Loebel JS, Dager SR et al (1991) Anticipation of a nursing home placement may be a precipitant of suicide among the elderly. J Am Geriatr Soc 39:407–408
Lykouras L, Gournellis R, Fortos A et al (2002) Psychotic (delusional) major depression in the elderly and suicidal behaviour. J Affect Disord 69:225–229

Marriott R, Horrocks J, House A, Owens D (2003) Assessment and management of self-harm in older adults attending accident and emergency: a comparative cross-sectional study. Int J Geriatr Psychiatry 18:645–652
McIntosh JL (1984) Components of the decline in elderly suicides: suicide in young old and old old by race and sex. Death Educ 8:113–124
McIntosh JL, Hubbard RW (1988) Indirect self-destructive behaviour among the elderly. A review with case examples. J Gerontol Soc Work 13:37–48
McKeown RE, Cuffe SP, Schulz RM (2006) US suicide rates by age group, 1970–2002. An examination of recent trends. Am J Public Health 96:1744–1751
Merrill J, Owens J (1990) Age and attempted suicide. Acta Psychiatr Scand 82:385–388
Michel K, Valach I (1992) Suicide prevention. Spreading the gospel to general practitioners. Br J Psychiatry 160:757–760
Modestin J (1989) Completed suicides in psychogeriatric inpatients. Int J Geriatr Psychiatry 4:209–214
Morriss RK (1992) Interviewing skills and detection of psychiatric problems. Int Rev Psychiatry 4:287–292
Moscicki EK (1995) North American perspectives: epidemiology of suicide. Int Psychogeriatr 7:137–148
Murphy GE, Wetzel RD (1980) Suicide risk by birth cohorts in the United States, 1949–1974. Arch Gen Psychiatry 37:519–523
Murphy E, Lindesay J, Grundy E (1986) 60 years of suicide in England and Wales: a cohort study. Arch Gen Psychiatry 43:969–976
Nelson FL, Farberow NL (1980) Indirect self-destructive behaviour in the elderly nursing home patient. J Gerontol 35:949–957
Nowers M (1993) Deliberate self-harm in the elderly: a survey of one London Borough. Int J Geriatr Psychiatry 8:609–614
O'Donnell I, Farmer R (1995) The limitations of official suicide statistics. Br J Psychiatry 166:458–461
Odagiri Y, Uchida H, Nakano M (2009) Gender differences in age, period and birth-cohort effect on suicide mortality rate in Japan 1985–2006. Asia Pac J Public Health 23:581–587
Oeppen J, Vaupel JW (2002) Broken limits to life expectancy. Science 296:1029–1031
Osvath P, Fekete S, Voros V (2002) Attempted suicide in late life – review of results of PECs centre in WHO/EURO multicentre study of suicidal behaviour. Psychiatrica Danubina 14:3–8
Oyama H, Koida J, Sakashita T, Kudo K (2004) Community-based prevention for suicide in elderly by depression screening and follow-up. Community Ment Health J 40:249–263
Oyama H, Watanabe N, Ono Y, Sakashita T, Takenoshita Y, Taguchi T, Kumagai K (2005) Community-based suicide prevention through group activity for the elderly successfully reduced the high suicide rate for females. Psychiatry Clin Neurosci 59:337–344
Oyama H, Fujita M, Goto M, Shibuya H, Sakashita T (2006a) Outcome of community-based screening of depression and suicide prevention among Japanese elders. Gerontologist 46:821–826
Oyama H, Goto M, Fujita M, Shibuya H, Sakashita T (2006b) Preventing elderly suicide through primary care by community-based screening for depression in rural Japan. Crisis 27:58–65
Oyama H, Ono Y, Watanabe N, Tanaka E, Kudoh S, Sakashita T, Yoshimura K (2006c) Local community intervention through depression screening and group activity for elderly suicide prevention. Psychiatry Clin Neurosci 60:110–114
Oyama H, Sakshita T, Ono Y, Goto M, Fujita M, Koida J (2008) Effect of community-based intervention using depression screening on elderly suicide risk: a meta-analysis of the evidence from Japan. Community Ment Health J 44:311–320
Pampel FC (1996) Cohort size and age-specific suicide rates: a contingent relationship. Demography 33:341–355
Pierce D (1987) Deliberate self harm in the elderly. Int J Geriatr Psychiatry 2:105–110
Pierce D (1996) Repeated deliberate self-harm in the elderly. Int J Geriatr Psychiatry 11:983–986

Pokorny AD (1983) Prediction of suicide in psychiatric patients. Arch Gen Psychiatry 40:249–257
Preville M, Hebert R, Boyer R, Bravo G, Seguin M (2005) Physical health and mental disorder in elderly suicide: a case control study. Ageing Ment Health 9:576–584
Pritchard C (1992) Changes in elderly suicides in the USA and the developed world 1974–1987: comparison with current homicide. Int J Geriatr Psychiatry 7:125–134
Pritchard C, Hansen L (2004) Comparison of suicide in people aged 65–74 and 75+ by gender in England and Wales and the major western countries 1979–1999. Int J Geriatr Psychiatry 20:17–25
Purandare N, Oude Voshaar RC, Rodwat C, Bickley H, Burns A, Kapur N (2009) Suicide in dementia: 9-year national clinical survey in England and Wales. Br J Psychiatry 184:175–180
Raliegh VS, Bulusu L, Balarajan R (1990) Suicides among immigrants from the Indian subcontinent. Br J Psychiatry 156:46–50
Redaniel MT, Lebanan-Dalida MA and Gunnell D (2011) Suicide in the Philippines: time trend analysis (1974–2005) and literature review.BMC Public Health. http://www.biomedcentral.com/1471-2458/11/536. Viewed 8 Nov 2015
Rezaeian M (2000) Age and sex suicide rates in the Eastern Mediterranean region based on global burden of disease estimates for 2000. East Mediterr Health J 13:953–960
Rosowsky E (1993) Suicidal behaviour in a nursing home and a post-suicidal intervention. Am J Psychother 47:127–142
Rutz W, Von Knorring L, Wallinder J (1989) Frequency of suicide in Gotland after systematic postgraduate education of general practitioners. Acta Psychiatr Scand 80:151–154
Rutz W, Von Knorring L, Wallinder J (1992) Long-term effects of an educational programme for general practitioners given by the Swedish Committee for prevention and treatment of depression. Acta Psychiatr Scand 85:83–88
Rutz W, Wallinder J, Von Knorring L et al (1997) An update on the Gotland study. Martin Dunitz, London
Salib E, Cawley S, Healy R (2002a) The significance of suicide notes in the elderly. Ageing Ment Health 6:186–190
Salib E, El-Nimr G, Yacoub M (2002b) Their last words: a review of suicide notes in the elderly. Med Sci Law 42:334–338
Sartorius N (1995) Recent changes in suicide rates in selected eastern European and other European countries. Int Psychogeriatr 7:301–308
Schmidtke A, Bille-Brahe U, De Leo D et al (1996) Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989–1992: results of the WHO/EURO multicentre study on parasuicides. Acta Psychiatr Scand 93:327–338
Seiden RH (1981) Mellowing with age: factors influencing the non-white suicide rate. Int J Ageing Human Dev 13:265–284
Seidlitz L, Conwell J, Duberstein P et al (2001) Emotional traits in older suicide attempters and non attempters. J Affect Disord 66:123–131
Sendbeuhler JM, Goldstein S (1977) Attempted suicide among the aged. J Am Geriatr Soc 25:245–248
Shah AK (2007a) Demographic changes among ethnic minority elders in England and Wales. Implications for development and delivery of old age psychiatry services. Int J Migr, Health Social Care 3:22–32
Shah AK (2007b) The relationship between suicide rate and age: an analysis of multinational data from the World Health Organisation. Int Psychogeriatr 19(6):1141–1152
Shah AK (2007c) Elderly suicide rates in the United Kingdom: trends from 1979 to 2002. Med Sci Law 47:56–60
Shah AK (2007d) The importance of socio-economic status of countries for mental disorders in old age: a development of an epidemiological transition model. Int Psychogeriatr 19:785–787
Shah AK (2008a) A non-linear relation of fertility and suicide rates in elderly people. Psychol Rep 103:943–946

Shah AK (2008b) Association of suicide rates in elderly persons with fertility rates. Psychol Rep 102:369–376
Shah AK (2009a) Time trends in elderly suicide rates and age-associated trends in suicide rates: a comparison between Korea and the United Kingdom. J Chin Clin Med 4(9):503–511
Shah AK (2009b) The relationship between suicide rates and age: an analysis of multinational data from the World health organisation. Int Psychogeriatr 19:1141–1152
Shah AK (2009c) The relationship between elderly suicide rates, household size and family structure: a cross national study. Int J Psychiatry Clin Pract 13:259–264
Shah AK (2009d) The relationship between population growth and elderly suicide rates: a cross-national study. Int Psychogeriatr 21:379–383
Shah AK (2009e) The relationship between elderly suicide rates and the human development index: a cross-national study of secondary data from the World Health Organisation and the United Nations. Int Psychogeriatr 21:69–77
Shah AK (2009f) The relationship between socio-economic status and mental health funding, service provision and national policy: a cross-national study. Int Psychiatry 6:44–46
Shah AK (2009g) Attempted suicide in the elderly in England: age-associated rates, time trends and methods. Int Psychogeriatr 21:889–895
Shah AK (2010a) The relationship between elderly suicide rates and the internet: a cross-national study. Int J Soc Psychiatry 56:214–219
Shah AK (2010b) The relationship between obesity and elderly suicide rates: a cross-national study. J Inj Violence Res 2:105–109
Shah AK (2010c) A replication of a non-linear association of educational attainment and suicide rates in the elderly using five-year data. Int Psychogeriatr 22:339
Shah AK (2010d) A replication of the relationship between elderly suicide rates and the Human Development Index in a cross-national study. Int Psychogeriatr 22:727–732
Shah AK (2010e) A replication of the relationship between elderly suicide rates and elderly dependency ratios: a cross-national study. J Inj Violence Res 2:19–24
Shah AK (2010f) A cross-national study of the relationship between elderly suicide rates and urbanisation. Suicide Life Threat Behav 38:714–719
Shah AK (2010g) The possible evidence for an epidemiological transition hypothesis for elderly suicides. Int Psychogeriatr 22:219–226
Shah AK (2011a) Elderly suicide rates: a replication of cross-national comparisons and association with sex and elderly age-bands using five year suicide data. J Inj Violence Res 3(2):80–84
Shah AK (2011b) Further evidence for epidemiological transition hypothesis for elderly suicides. J Inj Violence Res 3:29–34
Shah AK (2012a) A replication of the relationship between adversity earlier in life and elderly suicide rates using five years cross-national data. J Inj Violence Res 4:7–9
Shah AK (2012b) The relationship between elderly suicide rates and different components of education: a cross national study. J Inj Violence Res 4:52–57
Shah AK (2012c) A replication of the relationship between adversity earlier in life and elderly suicide rates using five years cross-national data. J Inj Violence Res 4:7–9
Shah AK, Bhat R (2008a) The relationship between elderly suicide rates and mental health funding, service provision and national policy: a cross-national study. Int Psychogeriatr 20:605–615
Shah AK, Bhat R (2008b) Are elderly suicide rates improved by increased provision of mental health service resources? Int Psychogeriatr 20:1230–1237
Shah AK, Bhat R (2009) Does adversity earlier in life affect elderly suicide rates? Cross-national study. Int J Psychiatry Clin Pract 13:273–277
Shah AK, Buckley L (2011) The current status of methods used by the elderly for suicides in England and Wales. J Inj Violence Res 3:68–73
Shah AK, Chatterjee S (2008) Is there a relationship between elderly suicide rates and educational attainment? A cross-national study. Ageing Mental Health 12:795–799
Shah AK, Coupe J (2009) A comparative study of elderly sucides in England and Wales, Scotland and Northern Ireland: trends over time and age-associated trends. Int Psychogeriatr 21:581–587

Shah AK, De T (1998) Suicide in the elderly. Int J Psychiatry Clin Pract 2:3–17
Shah AK, Erlangsen A (2015) Suicide in older people. Crisis 35:365–367
Shah AK, Ganesvaran T (1994) Suicide in the elderly. In: Functional psychiatric disorders of the elderly (Eds. Chiu E, Ames D). Cambridge, Cambridge University Press. Pgs 221–244.
Shah AK, Ganesvaran T (1997a) Psychogeriatric inpatient suicides in Australia. Int J Geriatr Psychiatry 12:15–19
Shah AK, Ganesvaran T (1997b) Inpatient suicides in an Australian hospital. Aust New Zealand J Psychiatry 31:291–298
Shah AK, Hoxey K (2001) Depression in medically ill elderly inpatients: prevalence, correlates and longitudinal stability. Int J Methods Psychiatr Res 10:147–156
Shah AK, Suh GK (2009) Elderly suicides in Korea: time trends and age-associated trends. J Chin Clin Med 4:274–281
Shah AK, Elanchenny N, Collinge T (2001) Trends in age band-specific suicide rates in the elderly. Med Sci Law 41:102–106
Shah AK, Bhat R, MacKenzie S, Koen C (2007) Elderly suicide rates: cross-national comparisons and association with sex and elderly age-bands. Med Sci Law 47:244–252
Shah AK, Bhat R, MacKenzie S, Koen C (2008a) Elderly suicide rates: cross-national comparisons of trends over a 10-year period. Int Psychogeriatr 20:673–686
Shah AK, Padayatchi M, Das K (2008b) The relationship between elderly suicide rates and elderly dependency ratios: a cross-national study using data from the WHO data bank. Int Psychogeriatr 20:596–604
Shah AK, Bhat R, MacKenzie S, Koen C (2008c) A cross-national study of the relationship between elderly suicide rates and life expectancy and markers of socio-economic status and healthcare status. Int Psychogeriatr 20:347–360
Shah AK, Lindseay J, Dennis M (2009) Comparison of elderly suicide rates among migrants in England and Wales with their country of origin. Int J Geriatr Psychiatry 24:292–299
Shah AK, Bhat R, Zarate-Escudero S (2012) Elderly suicide rates: the importance of a non-linear relationship with distal risk and protective factors. Int Psychogeriatr 24:1363–1367
Shah AK, Bhat R, Zarate-Escudero S (2013) Further evidence for epidemiological transition in elderly suicides. In: Wilson AS, Schenider MS (eds) Mental health and psychiatry. Nova Publishers, New York, pp 53–70
Shah AK, Zinchin G, Zarate Escudero S, Somayaji M (2014a) The relationship between the prescription of psychotropic drugs and suicide rates in older people in England and Wales. Int J Soc Psychiatry 60(1):83–88
Shah AK, Zarate-Escudero S, Bhat R, De Leo D, Erlangsen A (2014b) Suicide in centenarians: the international landscape. Int Psychogeriatr 26:1703–1708
Shah AK, Bhat R, Zarate-Escudero S, De Leo D, Erlangsen A (2015a) S.uicide rates in five-year age-bands after the age of 60 years: the international landscape. Ageing Ment Health. doi:10.1080/1367863.2015.1055552
Shah AK, Zarate-Escudero S, Bhat R, De Leo D, Erlangsen A (2015b) Suicide rates in five-year age-bands after the age of 60 years: the international landscape. Ageing Ment Health 20:1
Shimuzu M (1990) Depression and suicide in late life. In: Hasegawa K, Homma A (eds) Psychogeriatrics: biomedical and social advances. Excerpta Med, Amsterdam, pp 330–334
Shulman K (1978) Suicide and parasuicide in old age. Age Ageing 7:201–209
Skegg K, Cox B (1991) Suicide in New Zealand 1957–1986: the influence of age, period and birth-cohort. Aust New Zealand J Psychiatry 25:181–190
Smith HL (2008) Advances in age-period-cohort analysis. Sociol Methods Res 3:287–296
Snowdon J, Hunt GE (2002) Age, period and cohort effects on suicide rates in Australia, 1919–1999. Acta Psychiatr Scand 105:265–270
Stengel E (1977) Suicide and attempted suicide. Penguin, Ringwood
Suh GH, Shah AK (2001) A review of the epidemiological transition in dementia – cross-national comparisons of the indices related to Alzheimer's disease and vascular dementia. Acta Psychiatr Scand 104:4–11

Suominen K, Isometsa E, Lonnqvist J (2004) Elderly suicide attempts with depression are often diagnosed only after the attempt. Int J Geriatr Psychiatry 19:35–40
Surtees P, Duffy JC (1989) Suicide in England and Wales 1946–1985: an age period cohort analysis. Acta Psychiatr Scand 79:216–223
Szanto K, Reynolds CFIII, Conwell Y et al (1998) High levels of hopelessness persist in geriatric patients with remitted depression and a history of attempted suicide. J Am Geriatr Soc 27:194–206
Szanto K, Mulsant BH, Houck P, Drew MA, Reynolds CFIII (2003) Occurrence and course of suicidality during short-term treatment of late-life depression. Arch Gen Psychiatry 60:610–617
Takahashi Y, Hirasawa H, Koyama K et al (1995) Suicide and ageing in Japan: an examination of treated elderly suicide attempters. Int Psychogeriatr 7:239–251
Ticehurst S, Carter GL, Clover KA et al (2002) Elderly patients with deliberate self-poisoning treated in an Australian general hospital. Int Psychogeriatr 14:97–105
Unutzer J, Katon W, Callahan C, Williams J, Hunkeler E, Harpole L, the IMPACT investigators (2002) Collaborative care management of late-life depression in the primary care setting: a randomised controlled trial. J Am Med Assoc 288:2836–2845
Unutzer J, Tang L, Oishi S, Katon W, Williams J, Hunkeler E, Harpole L, the IMPACT investigators (2006) Reducing suicidal ideation in depressed older primary care patients. J Am Geriatr Soc 54:1550–1556
Upadhyaya AK, Warbuton H, Jenkins JC (1989) Psychiatric correlates of non fatal deliberate self harm in the elderly: a pilot study. J Clin Exp Gerontol 11:131–143
Upadhyaya AK, Conwell Y, Duberstein PR et al (1999) Attempted suicide in older depressed patients. Am J Geriatr Psychiatr 7:317–320
Useda JD, Duberstein PR, Conner KR, Conwell Y (2004) Personality and attempted suicide in depressed adults over the age of 50 years and older: a facet level analysis. Compr Psychiatry 45:353–361
Vassilas CA, Morgan HG (1994) Elderly suicides' contact with general practitioners before death. Int J Geriatr Psychiatry 9:1008–1009
Vecchia CL, Bollini P, Imazio C, Decarli A (2007) Age, period of death and birth cohort on suicide mortality in Italy 1955–1979. Acta Psychiatr Scand 74:137–143
Voaklander DC, Rowe BH, Dryden BM, Pahal J, Saar P, Kelly KD (2008) Medical illness, medication use and suicide in seniors: a population-based case control study. J Epidemiol Community Health 62:138–146
Voracek M (2009) Suicide rates, national intelligence estimates and differential K theory. Percept Mot Skills 109:733–736
Waern M (2011) Risk factors for suicide in the elderly: what do we know? What do we need to find out? Suicidologi 16:3–8
Waern M, Beskov J, Runeson B et al (1996) High rate of antidepressant treatment in elderly people who commit suicide. Br J Psychiatry 313:1118
Waern M, Runeson B, Allebeck P, Beskow J, Rubenowitz E, Skoog I, Wilhelmson K (2002a) Mental illness in elderly suicides: a controlled study. Am J Psychiatr 159:450–455
Waern M, Rubenowitz E, Runeson B, Skoog I, Wilhelmson K, Allebeck P (2002b) Illness burden in elderly suicides: a controlled study. Br Med J 324:1355–1358
Waern M, Rubenowitz E, Wilhelmson K (2003) Predictors of suicide in the old elderly. Gerontology 49:328–334
Walk D (1967) Suicide and community care. Br J Psychiatry 105:1381–1391
Wasserman D, Ringskog S (2001) Suicide among the elderly in Sweden. National Centre for Suicide Research and Prevention of Mental Ill-Health, Stockholm
Wasserman D, Cheng Q, Jiang GX (2005) Global suicide rates among young people aged 15–19. World Psychiatry 4:114–120
Watanabe N, Hasegawa K, Yoshinaga Y (1995) Suicide in later life in Japan: urban and rural differences. Int Psychogeriatr 7:253–261

Wetzel RD, Reich T, Murphy GE et al (1987) The changing relationship between age and suicide rates: cohort effects, period effects or both. Psychiatr Dev 3:179–218
Woodbury MA, Manton KG, Blazer D (1988) Trends in US suicide mortality rates 1968–1982: race and sex differences in age, period and cohort components. Int J Epidemiol 17:356–362
Yip PSF (2011) An epidemiological profile of suicides in Beijing, China. Suicide Life Threat Behav 31:62–70
Zhang J (1998) Suicide in the world: toward a population increase theory of suicide. Death Stud 22:525–539

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H. Chiu, K. Shulman (eds.), *Mental Health and Illness of the Elderly*, Mental Health and Illness Worldwide, DOI 10.1007/978-981-10-2414-6