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Intervention Research in Late-Life Depression: Challenges and Opportunities

Helen Lavretsky, M.D. 

STATE OF THE FIELD

Over the next four decades the number of individuals aged 60 years and older will nearly triple, increasing from 672 million in 2005 to almost 1.9 billion by 2050  <http://www.un.org>). As the global population ages this century to unprecedented levels, the rates of late-life depression (LLD) are also expected to increase in parallel.¹ Late-life mood disorders carry additional risk for suicide, medical comorbidity, disability, and family caregiver burden. Most vulnerable low-income elderly have higher rates of major depression compared with their more fortunate peers (9.5% versus 3.8%). This burden of depressive illness is heightened by the poor response rates to pharmacologic treatments for LLD. Recent meta-analysis of clinical trials in older adults suggests an antidepressant response rate of 48% and a remission rate of 33.7%.² Compounding the problem is the projected shortage of geriatric psychiatrists in the United States, projected to require 4,000–5,000 by 2030. The 2012 Institute of Medicine workforce report³ highlights the need for a diverse team of providers to meet the growing workforce shortages for an aging population.

The expected gold standard of expected treatment response remains the achievement of full remission and a return to wellness. Because of the increasing numbers of older adults with depressive disorders who do not respond well to existing therapies, clinicians need guidance in finding successful treatments for this challenging population. Similarly, more researchers face the issue of inadequate treatment response in the presence of medical and neurologic comorbid disorders and

psychosocial issues like poverty or loneliness that perpetuate the chronic course of depression and suicide.⁴ Because of the slow development of novel antidepressant compounds, attention has turned to building interventions on the basis of pathophysiology of late-life mood disorders.

Advances in delineating the pathophysiology of mood disorders have opened pathways for developing novel interventions that might target different neurotransmitter systems or that might use varied techniques (e.g., pharmacologic, psychosocial, cognitive, device-driven) to modulate the activity of brain circuits that have been identified as hyper- or hypoactive in depression. In recent years a number of drug combination strategies, using drugs with different mechanisms of action, have shown some promise in elderly depressed with improved clinical outcomes.^{4–8} Several studies of a similar nature are still ongoing, testing antidepressant drug combinations with memantine and other compounds. A recently finished relapse prevention trial using Escitalopram (PRIME) has not yet reported the outcomes. The use of novel neuromodulation therapies (e.g., rTMS, tDCS, DBS) in LLD is guided by the emerging understanding of the underlying neurocircuitry but remains limited with very few reported successes.⁹ This proliferation of studies has contributed to increased understanding of the public health impact of late-life mood disorders, including data needed to guide treatment and inform basic research.

Summary of Published Articles

In this issue five published articles reflect on the new approaches to improving efficacy and effectiveness of

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treatment for geriatric depression. Hybels et al.¹⁰ addresses the impact of depression and a known biomarker of cerebrovascular disease (cerebral white matter hyperintensities [WMHs]) measured using structural magnetic resonance imaging on functional decline in older adults with major depression. In the secondary analysis of data collected through the Neurocognitive Outcomes of Depression Study, 381 elderly participants with and without depression were followed for up to 16 years. Those participants who were both depressed and had a higher volume of WMHs at baseline were most at risk for functional decline across all measures of function compared with all others. The notable feature of this study is a long follow-up time of a very well-characterized clinical sample that points to the potential benefits of developing treatments for conditions, depression, and cerebrovascular disease. Although the field has been aware of the relationship between depression and WMHs and disability,^{11,12} we have not been able to develop new interventions addressing this aspect of pathophysiology of LLD.

A prospective treatment study confirmed that the use of selective serotonin reuptake inhibitor antidepressants can be hindered by the presence cerebrovascular disease and executive dysfunction.¹³ However, we do not have interventions targeting cerebrovascular disease comorbid with depression. We could speculate that combining aspirin or lipid-lowering drugs with antidepressants or optimized management of common vascular risk factors like diabetes, heart disease, hyperlipidemia, and sleep apnea should work well in clinical practice. So far, we have not seen research backing such strategies because of the complexity and inter-relationships of various factors (e.g., depression and WMHs). The targets for developing an intervention in this context can include cerebrovascular disease or WMHs, platelet function, lipid profile, hemoglobin A_{1C}, or all of the above. These relationships may not be “broken” into a relatively simple experimental paradigm to justify a target engagement in therapeutic trials as now required by the National Institute of Mental Health (NIMH). The pharmaceutical industry has not been interested in supporting complex studies of risk factors in subpopulations that may show reduced response to the treatment drug. We may never know the answer to this question. On the other hand, an opportunity may be looming from the rapidly increasing interest in imple-

menting lifestyle interventions like diet, exercise, and stress reduction using integrative medicine techniques (e.g., yoga or meditation) that may shed light on these pathophysiologic connections in LLD. The dementia prevention field has been leading the way, using multimodal prevention models¹⁴ that show successful paradigm in treating and preventing cognitive disorders of aging. The geriatric depression research is lagging behind.

Another article in this issue, by Pimontel et al.,¹⁵ addresses the second conundrum in geriatric depression, the role of executive dysfunction, by trying to understand what aspects of executive dysfunction are more likely to predict treatment outcomes. The authors used meta-analytical strategy to examine treatment response in those with depression and executive dysfunction. They addressed different aspects of executive dysfunction to identify the most sensitive domain predictive of poor response. Six domains were identified on the basis of 25 measures from eight studies: cognitive flexibility, planning and organization, response inhibition, selective attention, verbal fluency, and the Dementia Rating Scale Initiation/Perseveration composite score. The domain of planning and organization (but not others) was meaningfully associated with poor antidepressant treatment response in LLD. These findings suggest that therapies that focus on planning and organization (e.g., problem-solving therapy [PST] or an individualized cognitive training protocol) may provide effective augmentation strategies for antidepressant nonresponders with LLD. This finding lends itself to the next step of investigation of devising a computerized cognitive training protocol that addresses individual profile of cognitive impairment or developing an “app,” as many researchers and businesses are investing in these days. This line of inquiry will continue to grow with the advances in computerized and adaptive learning technology for the aging population, including those with depression.

The two other articles from two collaborating groups led by George Alexopoulos and Patricia Arean examine the use of PST in impoverished older adults and in those with suicidal ideations, executive dysfunctions, and major depression. Alexopoulos et al.¹⁶ compared 12-week clinical case management integrated with PST (CM-PST) with clinical case management alone (CM) in reducing depressive symptoms in 171 depressed, disabled, impoverished patients. The

researchers hypothesized that the development of problem-solving skills would be related to improvement of depression. However, they found that CM was as effective in reducing depression and in the remission rates as CM-PST (31% versus 37.9%). Development of problem-solving skills did not mediate treatment outcomes. Although these results may be disappointing for researchers who were hoping to find greater effects of the PST, the results of the study are really “good news” for the implementation scientists and for our patients because CM is offered across the nation. Social workers and nurses and social organizations providing CM can improve outcomes of depression management in millions of disabled low-income older adults with depression. However, the second article focused on the PST interventions that can identify a target population to benefit from this intervention. Gustavson et al.¹⁷ compared 12 weekly PST sessions to supportive therapy in reducing suicidal ideation in older adults with major depression and executive dysfunction using secondary data analysis in 221 older adults with major depression. The PST group had a higher rate of improvement in suicidal ideation (60.4%) after 12 weeks compared with the supportive therapy group (44.6%), indicating that PST is a promising intervention for older depressed adults, even in the presence of executive dysfunction.

Finally, Hoeft et al.¹⁸ gives a futuristic view of priorities for health services research based on identified gaps and projected needs in the community care for LLD. The results of this selective review supplemented by more recommendations from national experts identified three areas of gaps in the community care for LLD: older men, racial and ethnic minority groups, or in those with comorbid medical or mental disorders. The study highlights three priority research areas to improve health services for LLD: focusing on the unique needs of the patient through patient-centered and culturally sensitive care, involving caregivers outside the traditional clinical care team (e.g., religious leaders, outreach community workers), and involving alternate settings of care (e.g., nursing home). An additional recommendation that emerged from the expert interviews focused on the importance of prevention of depression in the populations at risk for depression or in those with treatment-resistant depression. Such research involving community partnerships and community outreach through patient-centered outcomes research holds

considerable promise for broadening access to effective depression care for an increasingly diverse aging population.

OPPORTUNITIES FOR INTERVENTION DEVELOPMENT IN GERIATRIC DEPRESSION

We need better treatments for our complex patients. It is demoralizing for a clinician to observe only partial improvement in depression and function achieved with the currently available tools. Incremental improvements by administering similar drugs are not enough to provide professional satisfaction with progress. We need real breakthroughs and innovative approaches to healthcare and disease prevention. These breakthroughs may be coming from some unexpected sources of inspiration and innovation, including the new cohorts of young researchers fostered by our field, such pioneering training programs as the Summer Research Institute (just celebrated 20 years of funding from the NIMH), and the Advanced Research Institute that trained cumulatively 618 junior investigators who will provide the workforce for geriatric mental health research in the decades to come.¹⁹

We are also witnessing some exciting societal shifts accompanied by the increased understanding of globalization and interconnectedness of mental health and aging that can lead to important insights, transdisciplinary innovation, and global cooperation. The growth of the industry that would support the global aging population is developing new technologies for early detection and prevention of aging-related diseases, including depression and dementia. Focusing on cognitive and emotional resilience of the population will likely lead in the new direction of intervention development that will not be disease but will be wellness and resilience oriented.^{20,21}

NEW GOVERNMENT-NATIONAL INSTITUTES OF HEALTH INITIATIVES RELEVANT FOR GERIATRIC MENTAL HEALTH FIELD

The convergence of geroscience and mental health is a novel concept in organizing science^{22,23} in the geriatric mental health field that is focused on optimizing

psychological, emotional, and physical health and well-being through transdisciplinary integration of clinical practice with research and innovations from nonclinical fields (e.g., molecular biology, business, information technology, computer science, digital media, engineering, entrepreneurship, finance, law, management, mathematics, and politics). Geroscience is an interdisciplinary field that aims to understand the relationship between aging and aging-related diseases.²² “Compression of morbidity” and prevention of aging-related diseases are major focuses of geroscience research. A number of mechanisms of aging are tested and include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, and chronic inflammation. Geroscience is supported by the Trans-NIH GeroScience Interest Group with some 20 National Institutes of Health institutes and centers participating.

The BRAIN Initiative

The Brain Research through Advancing Innovative Neurotechnologies, or BRAIN 2025 initiative announced by President Obama is another example of convergence neuroscience that can be easily applied to geriatric mental health. The goal of the BRAIN initiative is to accelerate the development and application of new technologies to enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought. Lifespan understanding of the neural processes is imperative for this initiative.

Precision Medicine Initiative

A recent commentary by Collins and Varmus²⁴ reviewed the Precision Medicine initiative that was announced by President Obama in January of 2015. The focus of this initiative is to offer large-scale biologic databases such as the human genome sequence; novel molecular techniques such as proteomics, metabolomics, genomics, cellular assays; and computational tools like machine learning for analyzing large datasets. Although it was initially developed for cancer research, it is highly applicable for the geroscience and mental health fields.

NIMH: Research Domain Criteria Project

The NIMH-sponsored Research Domain Criteria, or RDoC, project²⁵ is an experimental approach to the classification of mental disorders that incorporates multiple dimensions and levels of analysis: behavior, thought patterns, neurobiologic measures, and genetics. An immediate aim of the project is to develop a diagnostic system that departs from reliance on phenomenology and embraces matrix-spanning genetic, molecular, cellular, brain circuit individual, family environment, and social levels that could lead to innovation in diagnostic approaches and, ultimately, to developing new interventions.

CONCLUSION

Despite a slow progress in the development of new interventions for LLD, we anticipate a rapid shift in research priorities that will address immediate needs of the aging population based on the development of new technologies and global cooperation in mental health and aging. Future research will also seek to translate findings into clinical practice and community care to improve the well-being of older adults with depression. Given increasing economic globalization, international efforts in mental health research will focus on alleviation of the global burden of depression and associated disability and are likely to use simple algorithm-based approaches to the management and prevention of common mental disorders in primary care and other alternative care settings. We are hopeful and optimistic about the future of our field and anticipate the following next steps:

- Development of new classes of therapeutic agents and interventions for LLD based on the known underlying mechanisms of biologic and cognitive aging.
- Development of partnerships among the research community, healthcare providers, and healthcare payers such as the Centers for Medicare & Medicaid Services to design economically sustainable models of mood disorder care in the general medical sector and to further effectiveness and cost-effectiveness studies of evidence-based clinical disease management models.

- Development of partnerships between researchers and other community agencies for outreach to underserved and minority elderly people.
- Development of international collaborations for global mental health initiatives to enhance resilience and well-being in older adults.

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