Late-Life Depression, Antidepressant Treatment, and Cognition: The Short Haul and the Long Haul

David C. Steffens, M.D., M.H.S.

Late-life depression (LLD) refers to major depression that occurs in older adults regardless of age at onset of the first depressive episode. Thus, LLD includes both early-onset cases, related to higher familial risk and childhood adversity, and late-onset cases, related to later life stressors and apathy. Geriatric psychiatrists and other clinicians caring for older depressed adults have long appreciated that LLD is a complex and quintessentially biopsychosocial disorder. Risks of developing depression include biological and medical factors (e.g., subcortical cerebrovascular disease, cognitive impairment, frailty, sleep disturbance, and the presence of medical comorbidities, especially cardiovascular disease and chronic illnesses), psychological and psychiatric factors (e.g., anxiety, the presence of neuroticism on personality testing, persistent depressive disorder [dysthymia], loneliness, and alcohol and substance use disorders), and social factors (e.g., bereavement, caregiving role, family and relationship stress, and low perceived social support).

The complexity of LLD is also found in the interplay between mood and cognition; clinicians working with older depressed adults have long conceptualized LLD as both a mood disorder and a cognitive disorder. Classically, the cognitive profile of depression across the lifespan, including older age, has been associated with the triad of executive impairment (difficulties in planning, sequencing, and multitasking), difficulties with attention and concentration, and slowing in the processing of information. More recent evidence has shown that among older depressed adults, memory may also be affected and should be assessed (1). Less clear is whether successful treatment of depression in older adults, especially with antidepressants, is associated with improved cognition.

In this issue of the *Journal*, Ainsworth and colleagues (2) present results of a systematic review and meta-analysis of prospective studies of antidepressant pharmacotherapy for older adults with LLD. Among the 22 studies included in the review, 13 showed improvement in one or more cognitive tests, especially tests measuring the domains of memory and learning and processing speed. A meta-analysis of eight studies including 493 participants demonstrated significant improvement in the memory and learning domain but in no other cognitive domain. The authors also found that improvement in depressive symptoms was associated with improvement in cognitive test scores in seven of eight studies. They concluded that antidepressant treatment of LLD appears to improve some domains of cognitive function, particularly memory and learning. The authors note, too, that more studies comparing individuals receiving pharmacotherapy with untreated control participants are needed.

Ainsworth et al. separated tests of memory into two categories: "immediate memory" and "memory and learning." This is an important distinction, because deficits in "delayed memory" or "learning" are linked to cognitive decline associated with neurodegenerative disorders, such as Alzheimer's disease. Most modern memory tests have both immediate and delayed components. For example, in the California Verbal Learning Test (3), the examiner reads a list of 16 nouns (list A) aloud, at about 1-second intervals, over five learning trials. After each trial, patients are asked to recall as many words as they can in any order, which provides a measure of immediate or free recall. An alternate list of words (list B) is then read aloud, which patients are asked to recall. Following this interference task, patients are asked to recall words from list A (short-delay recall) and then again after 20 minutes (long-delay recall). The California Verbal Learning Test ends with a recognition task in which patients are presented with a word list, and they must indicate whether each of the words is a target word or a distractor. Poor recognition is associated with conversion of mild cognitive impairment to Alzheimer's disease (4).

The take-home messages for clinicians are that it is important to treat depression and that patients with depression severe enough to warrant antidepressant treatment are at increased risk of dementia, and thus it is incumbent on the clinician to carefully track cognition over time.

With these distinctions between immediate and delayed recall in mind, another relatively recent systematic review sought to summarize effects of selective serotonin reuptake inhibitors (SSRIs) on all aspects of memory in older adults, including patients with major depression, minor depression, dementia, or alcohol use disorder, and healthy individuals (5). Among the 17 studies with depressed participants in which some type of memory was evaluated, the time from baseline to final assessment ranged from 6 weeks to 1 year,

with most studies reporting results over 6–12 weeks. The results were mixed, with improvement in episodic memory (long-term memory of personal experiences and their context) in eight of 13 studies and improvement in short-term memory in only two of seven studies.

Thus, for some older depressed patients, there is evidence that the initial treatment with antidepressant medication may improve short-term or delayed memory and learning. However, when it comes to long-term cognitive outcomes of treatment of depression, one must consider whether these short-term improvements in cognition are sustained. Ainsworth et al. excluded studies reporting cognitive performance 26 weeks and longer after baseline. It is important, however, to consider cognitive outcomes beyond 1 year of successful treatment. For example, we found that among older depressed adults with mild cognitive impairment at baseline, those who achieved remission by 1 year often continued to meet criteria for mild cognitive impairment (6). Moreover, the comorbidity of depression and mild cognitive impairment increases the risk of dementia (1, 7).

It is therefore important to take the long view when caring for individuals with LLD. This perspective incorporates both mood and cognitive outcomes of older depressed adults. Long-term considerations related to mood include high relapse rates over time in individuals with LLD, with evidence suggesting the need for ongoing treatment with antidepressant medication for up to 2 years to avoid relapse (8). In addition to adopting a vigilant stance on the long-term assessment of mood, clinicians must also monitor cognition and function over time. There is abundant evidence that LLD is associated with a variety of negative outcomes over the long term, including increased disability, functional decline, cognitive decline and increased risk of dementia, and premature mortality from medical conditions or suicide (9–11).

Evidence supporting links between depression and the later development of dementia includes older epidemiological studies, summarized well by Jorm in 2001 (12). Other studies have focused on clinical populations of older depressed adults without dementia, seeking to examine factors related to the development of dementia within this population. Alexopoulos et al. followed groups of older depressed patients with and without "reversible" dementia (cognitive impairment in the context of LLD) for an average of 33.8 months and found that irreversible dementia developed significantly more frequently in the depressed group with reversible dementia (43%) than in the group with depression alone (12%) (13). Survival analysis showed that the risk of having developed dementia at follow-up was nearly five times higher in the group with reversible dementia than among the patients with depression alone. Similarly, another study reported that older depressed patients with mild cognitive impairment had a higher risk of developing dementia and Alzheimer's disease than cognitively unimpaired patients (1). Consistent with these findings, depression in the context of mild cognitive impairment has been found to be associated with an increased risk of conversion to Alzheimer's disease (7).

Further complicating this discussion is recent evidence on treatment of depression in mid-to-late life and risk of incident dementia. In one study using data from the UK Biobank, 354,313 participants between 50 and 70 years old were recruited between 2006 and 2010 and followed until 2020; 46,820 participants were diagnosed with depression (14). Depression was associated with a 51% higher risk of dementia, and compared with those who were depressed but untreated, participants receiving treatment for depression had a lower risk of developing dementia (hazard ratio=0.7, 95% CI=0.62–0.77). Another study, based on the U.S. Medical Expenditure Panel Survey from 2010 to 2019, analyzed data from 2,710 participants diagnosed with depression who were treated with an SSRI, a serotonin-norepinephrine reuptake inhibitor (SNRI), or psychotherapy (15). The individuals taking SSRIs or SNRIs had a higher crude incidence of dementia than those receiving psychotherapy (16.1% and 12.7%, respectively). The take-home messages for clinicians are that it is important to treat depression and that patients with depression severe enough to warrant antidepressant treatment are at increased risk of dementia, and thus it is incumbent on the clinician to carefully track cognition over time.

Thus, antidepressants may be helpful in improving short-term delayed memory, but the presence of an impairment in short-term delayed memory in the context of LLD may increase the risk of dementia despite treatment. How does this "short-term treatment is good for memory, but long-term treatment provides no protection" conundrum inform our understanding of LLD and its management? Coupled with several longitudinal studies, the systematic review and meta-analyses of Ainsworth et al. support the notion that the relationship between mood and cognition in LLD is dynamic and may change over time. The sad fact is that for many older adults, particularly those with late-onset depression, the mood disorder may represent a prodromal presentation of a neurodegenerative disorder, such as Alzheimer's disease (16). In this light, the presence of a documented delayed-memory impairment is likely a bad prognostic sign from a cognitive standpoint, even if there is improvement in memory after acute treatment. Despite this depressing assertion, there is evidence that the long-term cognitive outcome for individuals with LLD and cognitive impairment is heterogeneous and does not lead inexorably to dementia. In one study of older depressed patients with cognitive impairment with no dementia, after 2 years, some patients continued to have cognitive impairment, others had progressed to dementia, but many demonstrated normal cognitive performance (17). Hence, for clinicians caring for this population, management should include a healthy mix of persistence, vigilance, and hopefulness.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, University of Connecticut School of Medicine, Farmington.

Send correspondence to Dr. Steffens (steffens@uchc.edu).

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