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Management of Late-Life Depression: Focus on Comorbid Conditions

By Warren D. Taylor, MD, and K. Ranga Rama Krishnan, MB, ChB

ABSTRACT ~ *Depression, a heterogeneous disease often accompanied by significant medical and psychiatric comorbidity, is common among the elderly. Clinicians caring for depressed elders should look for comorbidities, as they may affect management of the patient. For example, comorbid anxiety may represent a more difficult to treat syndrome, while inadequately treated depression with comorbid cardiovascular disease has a greater risk of cardiovascular-associated mortality. Comorbidities such as Alzheimer's dementia and cerebrovascular disease may provide insight into the pathogenesis of late-life depression. This review highlights these comorbid conditions as they occur in depressed elders. Recommended directions for future research in the area of late-life depression are provided.*
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Introduction

Depression is a common illness among the elderly population. Not only does it cause significant suffering for the afflicted patient, but its association with disability, medical comorbidity, and increased risk of mortality makes it a significant public health concern. Over the last few decades, late-life depression has been the focus of much research, predominantly for two reasons. First, the population >65 years of age is expected to double in the next 30 years, with a comparable increase in the population >85 years of age. Second, there is increasing evidence for the biological basis of late-life depression, including the contribution of cerebrovascular disease and neurodegenerative disorders. This provides an opportunity for a better understanding of the disease process and opportunities to develop more effective and better tolerated treatments.

This article will provide a brief overview of the prevalence, clinical presentation, and treatment issues generally associated with late-life depression. It will then focus on pertinent medical and psychiatric comorbidities and potential etiologies of this disorder, particularly evidence supporting neurodegenerative and cerebrovascular pathologies.

Dr. Taylor is clinical associate in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center in Durham, NC. Dr. Krishnan is chair of the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center.

To whom correspondence should be addressed: Warren D. Taylor, MD, Duke University Medical Center, DUMC Box 3903, Durham, NC 27710; Tel: 919-684-3746; Fax: 919-681-7668; E-mail: Taylo066@mc.duke.edu

EPIDEMIOLOGY

The prevalence of depression in the elderly depends on the definition of depression and the population studied. For community-dwelling elders, up to 15% will endorse some depressive symptoms. The incidence of major depressive disorder (MDD), according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[1] is 1% to 4%.[2-5] These rates increase when studying populations in medical environments, including ambulatory, acute, and long-term care facilities. Depression is most prevalent in the long-term care setting, where 30% to 40% of elders experience depressive symptoms and 12% to 16% meet MDD criteria.[6-8] In both community and long-term care settings, these rates appear comparable between black and white elders.[9,10]

CLINICAL PRESENTATION

A critical issue affecting clinical presentation is the age of depression onset. A significant amount of research has examined the validity of distinguishing between early- and late-onset depression, typically using an age of 50–60 as the dividing line between the two groups. While early-onset depression has a larger female predominance, late-onset depression has a more equal distribution between men and women.[2,11,12] Genetic factors appear to play less of a role, as there is a lower incidence of family history of affective disorders in the late-onset group.[13,14] Clinical differences in the presentation between the two groups have been described[15] but the characterization of these differences is plagued by conflicting results.[12,15-19] Apathy may be the most consistent clinical difference seen in late-onset depression.[12] Anxiety, psychosis, guilt, and pessimism may not be significantly different between the early- and late-onset groups.[12]

ANTIDEPRESSANT THERAPY IN THE ELDERLY

Several changes associated with aging should impact how we prescribe antidepressant agents (Table). Decreases in hepatic clearance and reduction in cytochrome P450 3A4 activity can result in prolonged elimination half-life and increased plasma levels. Elders also exhibit increased receptor sensitivity and are particularly sensitive to anticholinergic effects. For both of these reasons, antidepressants should be started at lower doses in the elderly and may require a more cautious titration. Finally, comorbid medical conditions need to be considered as there may be contraindications to the use of specific agents, or at least the requirement of more intensive monitoring. The other side of this coin is polypharmacy: elders with comorbid conditions are typically on several medications at the same time.[20,21]

How well do elders respond to treatment? Contrary to common perception, the remission rate may be comparable to younger patients, but as many as 18% of depressed elders may meet criteria for treatment resistance.[22] Reynolds and colleagues[23] analyzed data from two controlled studies of nortriptyline maintenance therapy for recurrent major depression in elderly and midlife subjects. During acute-phase therapy, 71.4% of the elderly subjects and 69.6% of midlife subjects experienced remission, defined as a Hamilton Depression Rating Scale (HAM-D)[24] score ≤7. Although the two groups had comparable remission rates, midlife subjects had a faster reduction in the rating scores. This study provides crucial information about response in elders, but does not necessarily translate into clinical care. Steffens and colleagues[25] recently reported results from an algorithm-based treatment study for late-life depression where all antidepressant therapies, including electroconvulsive therapy, were available. They demonstrated that over an 18-month period, 88.6% of elderly subjects responded (response was defined as a Montgomery-Asberg Depression Rating Scale (MADRS)[26] score ≤15) and 65.4% of elderly subjects remitted (remission was defined as a MADRS score ≤7). This study's results are comparable to previous studies[27] and demonstrates the importance of persisting with antidepressant therapy in elderly patients who do not respond to the first trial of treatment.

Acute-phase clinical trials have examined the ability of specific antidepressant agents to achieve short-term remission in depressed elders. Several factors limit these data. Currently published trials are of

TABLE

CONSIDERATIONS FOR TREATMENT OF DEPRESSION IN THE ELDERLY

CONSIDERATION	POTENTIAL CONSEQUENCE
Changes in metabolism and impact of aging on cytochrome P450 system	Prolonged drug half-life and higher blood levels
Increased receptor sensitivity	Increased medication side effects
Medical contraindications to antidepressant use	Increased risk of medical morbidity; need for frequent monitoring and evaluations
Drug-drug interactions	Increased side effects, particularly when drugs have common effects (eg, QTc prolongation, anticholinergic side effects)
Dosing regimen complexity and polypharmacy	Patients may miss or repeat doses
Cost of treatment	Nonadherence

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varying length (between 6 and 12 weeks) and use the term "elderly" for different ages, with the lower limit ranging from 50–65 years of age. Different investigators also use different measures of depression severity, response, or remission. This is more than just differences in depression rating scales (such as the HAM-D or MADRS); different studies use different scale cutoffs to define remission. One study may define remission as a HAM-D score of ≤7; another may define it as ≤10. This makes a direct comparison of remission rates across studies difficult. There are also cross-study differences in antidepressant doses and, with tricyclic antidepressants (TCAs), differences in blood levels. Finally, not all antidepressants have been well studied in the elderly.

Placebo-controlled trials exemplify this last problem. Placebo-controlled trials with TCAs have largely focused on nortriptyline[28-30] and imipramine.[31-33] These studies are particularly limited by small sample sizes. Published selective serotonin reuptake inhibitor (SSRI) placebo-controlled trials in the elderly are limited to studies of fluoxetine[34,35]; the largest study of 671 elderly outpatients showed that fluoxetine is more effective than placebo.[35] Phenelzine, a monoamine oxidase inhibitor,[28] and bupropion[32] are also more effective than placebo. Many agents have not been studied in the elderly, but these studies indicate that antidepressants are generally more effective than placebo in the treatment of geriatric depression. A more complete review of this topic is available as a Cochrane Systematic Review.[36]

Beyond placebo-controlled trials, there are a number of head-to-head acute-phase trials comparing the efficacy of various antidepressants in the elderly. These studies suffer from many of the same problems as the placebo studies: small numbers of subjects, differing trial lengths, and different definitions of remission. Additionally, because of the high placebo response rate seen in depression trials, it is difficult to say many of these agents are more effective than placebo. The larger scale studies typically show no difference in the remission rates between agents.[37-39] Smaller studies may demonstrate significant differences between agents, although findings between drug classes are mixed. For example, one study demonstrated that nortriptyline was more likely to achieve remission than citalopram,[40] while another group found that sertraline was more effective than nortriptyline[41] or fluoxetine.[42] These findings may be due to small sample sizes: currently there is no consistent, convincing evidence that one agent is more effective than another in treating late-life depression.

A small number of well-designed trials use the same definition of remission—a HAM-D score of ≤7. A 6-week placebo-controlled trial of fluoxetine 20 mg/day in 671 elderly outpatients reported a remission rate of 21% for fluoxetine compared with a 13% remission

rate in placebo (P=.008).[35] An unpublished 8-week trial in 300 elders taking flexible dose venlafaxine 37.5–225 mg/day found a response rate of 42%, but this response was not statistically different than what was seen in fluoxetine (response rate=29%, dose range 20–60 mg/day) or placebo (response rate=38%).[43] A 12-week trial of flexible dose sertraline 50–150 mg/day in 104 elders found a remission rate of approximately 30% at 6 weeks and 55% at 12 weeks.[37] These data highlight several issues: (1) increased time on medication may lead to improved response rates; (2) the response rate for elders may be relatively low; and (3) placebo continues to have a significant effect in geriatric depression trials.

There are relatively few antidepressant maintenance studies in the elderly. Studies by Reynolds and colleagues[44] demonstrate that maintenance therapy with nortriptyline or interpersonal psychotherapy (IPT) is superior to placebo in preventing or delaying recurrence of symptoms. A combination of nortriptyline and IPT may be more effective than either treatment alone. They have also demonstrated that recurrence is associated with advanced age and lower nortriptyline plasma levels.[44-46] Additionally, smaller studies have shown that paroxetine and venlafaxine may have good efficacy as maintenance agents.[47-49] These studies have found that 20% to 40% of subjects will experience a relapse or recurrence of symptoms over a period of 18–24 months.

As there is no compelling evidence that one antidepressant medication is superior to another, treatment decisions should be based on considerations of anticipated tolerability and side effects. This is particularly important in the elderly, who may be more sensitive to medications and require slower titrations to therapeutic antidepressant doses. Similar to clinical experience, research shows that SSRIs have fewer side effects than TCAs,[50] and higher, more therapeutic TCA blood levels are associated with greater side effects.[45] SSRIs are a reasonable first-line treatment, although they may have side effects and doses should be titrated upward cautiously. However, many individuals may not respond to an SSRI, so TCAs remain an important part of our armamentarium, along with novel agents such as bupropion, mirtazapine, and venlafaxine.

Depression and Comorbid Anxiety Disorders

Late-life depression is frequently comorbid with anxiety. Although anxiety disorders are the most common psychiatric disorders in the United States, they appear to be less prevalent in older age groups.[51] In contrast, 25% to 47% of elders with MDD also meet criteria for various anxiety disorders.[52-54] In these depressed and anxious individuals, the diagnoses of panic disorder, social phobia, or specific phobia have comorbid rates of less than 10%; generalized anxiety disorder (GAD) is more common at 27.5%.[53]

Why is this comorbid syndrome important? Similar to what is seen in younger populations, comorbid depression and anxiety are associated with more severe overall psychopathology.[54] Patients with this comorbid syndrome are more likely than nonanxious depressed elders to have severe somatic complaints[53]; if this is associated with greater medication side effects, it may lead to increased treatment dropout rates.[55] Moreover, this comorbid syndrome may be associated with poorer social functioning,[53] greater disability,[56] and higher suicide rates.[53,57]

There is some evidence that a comorbid depressive-anxiety syndrome has a different course than depression alone. Higher baseline levels of anxiety may predict a poorer response in depressed elders.[58] Additionally, this population takes longer to respond to antidepressant treatment than do individuals with nonanxious depression[55,59] and is more likely to require augmentation of their antidepressant regimen.[60] While higher baseline anxiety may not predict relapse,[61] relapse is more likely if residual anxiety symptoms persist.[62]

As treatment options for this syndrome have not been well studied in the elderly, we cannot confidently make treatment recommendations. Assuming that elders share a common pathophysiology with younger individuals who exhibit comorbid anxiety and depression, practitioners may want to consider using antidepressants that have shown efficacy in anxiety disorders such as GAD (eg, venlafaxine).[63] As cognitive-behavioral therapy is also efficacious in many anxiety disorders, a psychotherapeutic intervention should also be considered. However, this intervention may be problematic if there are concomitant cognitive deficits.

Depression and Comorbid Medical Problems

Just as anxiety symptoms need to be considered in any discussion of late-life depression, so do comorbid medical problems. Many patients and clinicians alike believe that depression is inevitable or even appropriate with aging and chronic medical illness.[64] Older patients may be reluctant to report depressive symptoms or may attribute them to physical ailments. Depression is not inevitable; it is a disease state. Depression is not a normal part of aging.[65]

Depression in the elderly often coexists with one or more medical problems and is associated with worse medical outcomes. Cardiovascular and cerebrovascular disease outcomes in particular are tightly linked to depression; in depression, hypothalamic-pituitary-adrenal axis hyperactivity and enhanced sympathetic tone can increase platelet activity and vulnerability to arrhythmia, thus increasing the risk of stroke or myocardial infarction.[66,67]

Depression is common in individuals with cerebrovascular or cardiovascular disease. MDD occurs in 22% to 30% of individuals recovering

from stroke; untreated, it interferes with rehabilitation and resumption of activities.[68-70] Likewise, MDD occurs in 15% to 20% of patients with postmyocardial infarction and congestive heart failure, and up to one third may have depressive symptoms.[67,71-74] The presence of depression in these populations is associated with higher mortality rates,[70-73] and higher mortality rates may be associated with greater severity of depression.[74]

Depression is also associated with nonvascular diseases. Eleven percent of the population with diabetes have MDD.[76] Depression is more common in patients with acquired immunodeficiency syndrome and cancer and may result in worse outcomes.[77]

The association between depression and poor medical outcomes may be even greater in nursing home patients. A study by Rovner and colleagues[7] examined the prevalence of MDD and depressive symptoms in nursing home patients and how depressive symptoms are related to mortality over 1 year. They found that MDD was an independent risk factor for 1-year mortality; the likelihood of death was increased by almost 60% in patients with MDD compared to those with no depressive disorder.[7]

The concept that depression increases the risk of medical morbidity and mortality raises the question of whether appropriate antidepressant therapy will improve these poor outcomes. Acute psychological interventions in individuals with coronary artery disease are associated with reduced risk of recurrent cardiovascular events[78] and increased rates of long-term survival.[79-81] Interestingly, more recent larger, longer-term home-based psychotherapeutic interventions have been found to offer little if any benefit.[82-84] The Montreal Heart Attack Readjustment Trial found that psychotherapeutic interventions may even increase mortality in some populations.[82]

Pharmacological interventions are another viable approach. There are safety concerns using older agents such as the TCAs in this population; the cardiac toxicity of these agents limits their use in patients with coronary artery disease. In contrast, the SSRIs are generally safe and effective in this population,[85,86] but this does not mean that they improve cardiac outcomes. This question is being investigated, and preliminary evidence favors this hypothesis. In a small study of depressed postmyocardial infarction subjects, sertraline appeared to increase heart rate variability, a predictor of improved cardiac clinical outcome[87]; this increase paralleled changes seen in a nondepressed control population.

Treatment of poststroke depression may also improve functional outcomes. Recent research demonstrates that patients who receive effective treatment of depression enjoy better functional recovery than individuals who are not treated or do not respond.[88-90] However, this may have limits, as other researchers have found that individuals with treated poststroke depression may still not improve as well as individuals without depression.[91]

POTENTIAL CAUSES OF DEPRESSION IN THE ELDERLY

Specific medical comorbidities—the presence of cerebrovascular disease or neurodegenerative diseases that result in dementia—may provide clues to the pathogenesis of depression. Cognitive deficits and magnetic resonance imaging (MRI) abnormalities are common in depressed elders. As each of these issues is a discussion unto itself, our overview of the involvement of cerebrovascular disease and Alzheimer's disease in the pathogenesis of late-life depression will necessarily be brief.

DEPRESSION AND CEREBROVASCULAR DISEASE: THE VASCULAR DEPRESSION HYPOTHESIS

The earliest work in this field stemmed from the observation that individuals with stroke were at increased risk for depression. Investigators recognized that individuals who had strokes involving the frontal lobe or the caudate, particularly in the left hemisphere, were at highest risk of developing depression.[92-95] Similar findings were also seen in neurological diseases affecting the basal ganglia, such as Parkinson's disease or Huntington's disease.

Although reduced volumes of specific regions may be seen in late-life depression, research focusing on links between depression and cerebrovascular disease has focused on the severity and location of cranial MRI hyperintense lesions. These are bright areas in the brain parenchyma as seen on T2-weighted MR images; they have been variously termed unidentified bright objects, hyperintensities, leukoaraiosis, and when extensive, leukoencephalopathy. They are typically classified into three major groups by location: periventricular hyperintensities, deep white matter hyperintensities (DWMH), and subcortical gray matter hyperintensities (SCH). Hyperintensities are associated with advanced age[96-99] and greater medical comorbidity.[99-102] Examining the literature, there are several persistent, relevant clinical associations for DWMH and SCH. These include older age, diagnosis of depression, older age at onset of depression, presence of cerebrovascular risk factors (particularly hypertension and diabetes), and more severe current medical comorbidity.[103]

What is the etiology of these hyperintensities? Postmortem examination of DWMH shows white matter necrosis, arteriosclerosis, gliosis, and axon loss.[104,105] Further, functional imaging studies demonstrate reduced blood flow in DWMH regions,[106] while diffusion imaging demonstrates changes suggestive of ischemia.[107] This suggests that ischemia contributes to their pathogenesis. Such injury, occurring in specific regions, may interrupt anatomical tracts involved in emotion regulation.

Hyperintensities are associated with depression in the elderly. There are both uncontrolled and controlled studies demonstrating increased severity of DWMH[108-113] and SCH[111,114-117] in elderly patients with late-

onset depression when compared with early-onset depressed elders, nondepressed elders, or younger subjects. More recent studies have attempted to localize hyperintensities associated with depression. SCH in the caudate and putamen[114,117,118] and frontal lobe DWMH are particularly associated with depression.[118,119] Recent efforts to further localize depression-associated DWMH have implicated lesions in the orbital frontal cortex.[120] The evidence supporting this presumably vascular cause of depression is so strong that diagnostic criteria for a vascular depression subtype have been proposed.[121]

It is unclear whether these abnormalities influence antidepressant treatment response: results for the few trials addressing this question are mixed. Researchers have demonstrated that greater severity of subcortical hyperintensities[122-124] and DWMH[125] are associated with treatment-resistant depression. Other researchers have not found such an association.[126,127] A more robust finding is that greater subcortical hyperintensity severity is associated with a greater likelihood of adverse reactions to antidepressant therapies.[124,128-131]

Methodological issues plagued these trials. Hyperintense lesion severity was measured using visual rating scales rather than more accurate volume measurements. Just as importantly, more specific localization of the occurrence of these hyperintensities was not recorded. If hyperintensities contribute to depression by disrupting circuits involved in mood regulation and are then associated with poor treatment response, global measures of lesion severity may have limited usefulness.

If brain abnormalities are ultimately associated with treatment resistance, clinicians should not abandon hope. Simpson and colleagues[122] demonstrated that although subcortical lesions may be associated with resistance to acute 12-week therapy, some patients may benefit from adjunctive therapy. Persistence with various treatment options may be the key for this population.

Depression and Alzheimer's Disease: Evidence for a Common Pathway

Unfortunately, depression commonly accompanies Alzheimer's disease (AD). Epidemiological studies report the prevalence of major or minor depression in AD as ranging between 30% to 50%, although some estimates are significantly lower.[132-135] This variability reflects differences in definitions, assessment measures, and who reports the symptoms. Patients may experience impairment in insight, thus resulting in underreporting of depressed mood,[136] but caregivers may overestimate depression and even provide information that is inconsistent from what is provided by the patient.[137-140] One study reported that depression becomes increasingly more common as individuals progress from mild cognitive

impairment to moderate dementia, but the prevalence of depression decreases in severe dementia[141]; this finding is complicated by the difficulty of diagnosing depression in severely demented individuals.

Although the exact mechanism remains unclear, AD pathology may contribute to the development of depression in a variety of ways. At a genetic level, AD and depression may share common susceptibility genes.[141] Neurochemically, depression in AD is associated with the selective loss of noradrenergic and serotonergic nuclei.[108,143-146] There may also be neuroanatomic correlates: Smaller hippocampi volumes are seen both in AD[147-149] and late-life depression.[150-152] This finding in depressed subjects is supported by metabolic deficits found on functional imaging.[153] It is unclear if this finding represents common or independent pathologic processes, as smaller hippocampal volumes in depressed elders have been associated with the subsequent development of dementia.[154]

Provisional diagnostic criteria for depression of AD have recently been developed by Olin and colleagues.[135] This proposal arose from the observation that depressive symptoms are common in AD but may not meet criteria for a major depressive episode. Depression of AD is more associated with social isolation, withdrawal, irritability, dysphoria, and anhedonia than with sleep or appetite disturbances.[135,155] Of note, the prevalence of depressive symptoms varies widely across studies, which necessitates further research. The development of these provisional criteria is a step toward better characterization of this syndrome.

There are only limited data on the course of depression in AD. Most research suggests that it may be difficult to treat and may have increased risk of morbidity and mortality. Even with treatment, the recurrence rate for depressive symptoms over a 12-month period may be as high as 85%.[156] Moreover, depressive symptoms in the elderly may presage cognitive impairment and, to a slight extent, increase mortality.[157] Although there is no evidence that this increase in mortality risk is due to suicide, a recent postsuicide autopsy study found that AD pathology was overrepresented in their sample.[158]

Clinical trials for dementia of AD exhibit design problems similar to the trials in the general elderly population, such as different methodological designs, different trial lengths, and small sample sizes. Interpretation of the results for this syndrome is further complicated by varying severity of cognitive impairment. All of the trials are heterogeneous in design and do not provide support for specific treatment recommendations, although expert recommendations for treatment are available.[159]

Many of the systematic, placebo-controlled published trials in depression with AD demonstrate that TCAs and SSRIs are more effective than placebo[160-164]; this finding is not universal as there are negative studies demonstrating an important placebo response.[165,166] There are two

studies comparing an SSRI with a TCA[167,168]: Both of these studies found no difference in response between the tested agents but did note that the SSRI was better tolerated. There is also limited evidence suggesting that both electroconvulsive therapy[169] and behavioral interventions aimed at either the patient or the caregiver may also be effective.[170]

Questions for Future Research

This brief review only touches the surface of comorbid conditions in late-life depression, but it raises several important points that should be considered for future research. The first question should focus on how different etiologies of depression may affect prognosis. Depression is not a homogeneous disease: a depressed individual with MRI lesions and complicated medical history may be different from a depressed individual with early signs of cognitive impairment and a strong family history of AD. One might expect that the naturalistic clinical course for these two individuals would be quite different. But how does it impact treatment? Based on risk factors, do certain individuals have a poorer chance of responding to an antidepressant? If so, can we use our burgeoning understanding of the pathologic processes to guide the development of better interventions?

Such understanding would be invaluable as we become more savvy about the underlying causes of late-life depression, and it raises the possibility of preventive therapy. Could there be a role for future cognitive enhancers in treating depression that is felt to be a foreshadowing symptom of AD? Could cardiovascular interventions affect the development of vascular depression? Although better treatments are crucial, preventive treatments may potentially be even more important as the geriatric population continues to grow.

Another consideration is the development of clinical trials. The methodology used for many trials is as heterogeneous as depression itself. Standardizing lengths of trials and determining clear, uniform response and remission criteria are but two issues facing the research community. Fortunately, this community is asking itself these very questions. A recent consensus statement focused on the role of placebo in depression trials[171]; although the participants believed that placebo arms were critical in solid research, we need better means to limit the risk to research subjects.

There is also the question of how to define antidepressant response. Although remission of depressive symptoms is the goal in clinical treatment, most published trials have used measures of remission or response that are less relevant in clinical practice. Many trials use measures of depression severity, such as the HAM-D[24] or the MADRS,[26] but these scales may not provide the best measure of remission. As remission may

mean different things to different patients, we may need to consider more personalized measurements.

This discussion distills down to the simple issue that we are still short of providing optimal treatments for all patients. Much work needs to be done in geriatric depression, examining these questions and many others. It is certain that these issues will only become more important with time and the increased number of elderly. ✤

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