Medical Comorbidities in Late-Life Depression

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By Abebaw Mengistu Yohannes, PhD [6] and Robert C. Baldwin, MD [7]

Late-life depression is both underrecognized and undertreated, and the impact of medical comorbidity may mask depressive symptoms. Depression further complicates the prognosis of medical illness by increasing physical disability and decreasing motivation and adherence to prescribed medications and/or exercise or rehabilitation programs.

The prevalence of depression is higher in persons with comorbid medical conditions than in those with no comorbidity. Some conditions that are common in older people, such as stroke, cardiac disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, are associated with particularly high rates of depression comorbidity.1,2

Late-life depression is both underrecognized and undertreated, and the impact of medical comorbidity may mask depressive symptoms. Depression further complicates the prognosis of medical illness by increasing physical disability and decreasing motivation and adherence to prescribed medications and/or exercise or rehabilitation programs. In addition, chronic disabling disorders can be a contributory factor to suicide attempts and completions in the elderly, but timely, appropriate treatment of depression can reduce this risk.3

This review provides an update of current evidence in relation to late-life depression and its management in the presence of some common medical conditions: stroke, coronary heart disease, diabetes mellitus, Parkinson disease, and COPD. The relatively new concept of vascular depression is also briefly discussed.4,5

STROKE AND MOOD DISORDER

Depression

Because depression and stroke are common in later life, poststroke depression is also common. Depression develops in 20% to 50% of patients within the first year after a stroke: the peak prevalence of major depression occurs at 3 to 6 months poststroke.6-8 However, the risk may continue for up to 2 or 3 years depending on the effects of disability on the patient’s lifestyle. The variability in prevalence is probably the result of clinical heterogeneity of the sample, the timing of the evaluation, and the lack of a valid disease-specific screening questionnaire for poststroke depression.9

A recent systematic review reported that the predisposing factors for poststroke depression include older age, a history of depressive disorder, the size of infarct, female sex, severity of stroke sequelae, and language impairment.10 Poststroke depression has been shown to be a predictor of impaired quality of life and a risk factor for cognitive decline and poorer functional recovery. It is also associated with an elevated risk of morbidity and mortality.9,10

The literature is inconclusive about whether baseline depressive symptoms predict cerebrovascular events in older age. The Framingham Study examined the risk of developing cerebrovascular events in 2 cohorts of patients: one group was 65 years or younger and the other was older than 65 years.11 The study used the Center for Epidemiologic Studies Depression (CES-D) score of greater than 16 as a cutoff for significant depression.12 Those 65 years and younger who had a CES-D score of 16 or greater were 4 times more likely to experience a stroke or transient ischemic attack as the same age-group without depression, after controlling for risk factors such as smoking status and education. There was no significant difference in the rate at which cerebrovascular events occurred in those who were 65 years or older, with or without depression.

In contrast, findings from another study indicate a positive association between the presence of depression and the risk of stroke across the entire adult age range.13 This study also demonstrated a gradient effect (the greater the depression, the greater the risk of stroke), which was most marked among black racial groups. The exact mechanisms of how depressive symptoms predispose to stroke are not fully known, but depression is known to affect autonomic function and platelet activation. Diagnosing depression after a stroke can be difficult, especially in patients with aphasia. In their review of existing instruments, Bennett and Lincoln14 found the 14-item observer-rated Stroke...
Aphasic Depression Questionnaire Hospital Version (SADQ-H) to be effective. Difficulty in adjusting to major disability may be sufficient to trigger depression. However, the high rate of depression and the inconsistent relationship between severity of stroke and depression has led to a hypothesis based on the site of the lesion. It has been suggested that a stroke in the left front cerebral hemisphere is a major risk factor for depression, possibly caused by the interruption of the monoaminergic routes that connect the brain stem with the cerebral cortex. However, other researchers disagree with the localization hypothesis.

**Treatment**

The principles of treating poststroke depression are the same as the treatment of depression in general. Because spontaneous recovery often occurs within the first 6 weeks, however, watchful waiting may be appropriate. The converse is also true—if a patient remains significantly depressed 6 weeks following a stroke, spontaneous remission is unlikely and somatic treatment should be considered.

A review of the literature provided information on only 10 randomized controlled trials of antidepressants (fluoxetine, citalopram, sertraline, nortriptyline) in poststroke depression. These drugs were shown to be efficacious, although the trials were small and of variable quality. Other antidepressants have been less well studied, although there have been controlled studies of psychostimulants such as methylphenidate at doses of 5 to 10 mg daily. Of historical interest, stimulants may also effectively target stroke-related apathy.

Antidepressants are preferred over psychotherapeutic interventions such as cognitive-behavioral therapy (CBT) because of a lack of evidence of efficacy of CBT. However, such trials are methodologically difficult to conduct. A recent study that examined the benefit of integrated care (liaison with a specialist stroke service, primary care physicians, using a telephone tracking system, management of vascular risk factors, and regular screening for depressive symptoms) in stroke survivors revealed fewer depressive symptoms in the integrated care group than in the control group in a 12-month follow-up. The integrated care approach has the potential for detecting and monitoring depressive symptoms in this patient population. It is hoped that future research will clarify the effects of both psychological approaches and stroke rehabilitation in the management of depressed mood.

**CORONARY HEART DISEASE**

There is a strong link between coronary heart disease and depression. In the United States, coronary heart disease affects more than 16 million people and in about 1 of 5 cases can lead to significant symptoms of depression. Nicholson and colleagues investigated the cause(s) and impact of depression as etiological and prognostic indicators in 54 observational studies. In 21 etiological studies the pooled relative risk (RR) of future coronary heart disease events in patients with depression was 1.81 (95% confidence interval [CI], 1.53 - 2.15)—patients with baseline depression were at 81% higher risk for coronary heart disease than patients without depression.
In 34 prognostic studies (among patient populations with an earlier myocardial infarction or coronary artery surgery), the RR of association of depression and prognosis for coronary heart disease was 1.80 (95% CI, 1.50 - 2.15). Of 804 Canadian patients with stable coronary disease, 7.1% met criteria for major depressive disorder and 5.3% for generalized anxiety disorder; both disorders increased the risk of subsequent adverse cardiac effects. This may be a conservative estimate. Depression in patients with acute coronary syndrome is less likely to be recognized (especially in ethnic minorities) in patients with lower educational backgrounds and reduced left ventricular ejection fractions.

**Heart disease progression**

The exact mechanism of the link between depression and coronary heart disease is unclear but includes direct biological mechanisms and behavioral factors. The Table lists the variables associated with depression and coronary heart disease.

The link between depression and coronary heart disease risk may be via autonomic dysfunction that manifests as reduced heart rate variability. Participants in 6 of the 13 studies that looked at depression as it relates to heart rate variability had coronary heart disease. Findings from those studies indicate that depression was associated with reduced heart rate variability. However, the effect sizes were too small to draw firm conclusions and there was much variation between the studies.

Inflammatory markers include C-reactive protein, interleukin-6, tumor necrosis factor, and fibrinogen. In a 2-year follow-up study, Frasure-Smith and colleagues investigated the relationship between depression and inflammatory markers. Elevated depressive symptoms and raised C-reactive protein levels 2 months after an acute event were overlapping risk factors for later cardiac events in men. Carney and colleagues demonstrated that fibrinogen was most highly associated with altered heart rate variability in depressed patients with coronary heart disease and proposed that this could be attributable to deficits in parasympathetic modulation of immunity and coagulation. In contrast, findings from the Heart and Soul Study suggest that major depression is associated with lower levels of C-reactive protein, fibrinogen, and interleukin-6. Differences in assessment scales and sample heterogeneity may have contributed to these disparate findings. Whatever the precise mechanism, untreated depression in cardiac patients is hazardous.

**Treatment for depression**

In the Sertraline Antidepressant Heart Attack Trial (SADHART), a study of 369 patients with a heart attack or unstable angina (mean age, 57), the SSRI sertraline was superior to placebo. Safety data were excellent. In the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, patients with a recent history of heart attack (mean age, 61) benefited from cognitive therapy designed to modify negative thinking that may have contributed to their depression. Neither study showed
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Tricyclic antidepressants (TCAs) are type 1A antiarrhythmics that reduce heart rate variability, 2 factors linked to increased mortality. There is limited evidence on which to judge other antidepressants. Venlafaxine is known to raise blood pressure, although in older patients it can also lead to postural hypotension. It should not be used in patients with a high risk of ventricular arrhythmia. Therefore, the current recommended treatment for depression following an acute cardiac event or with stable heart disease is an SSRI.

**DIABETES MELLITUS**

As with heart disease, there is a 2-way interaction between depression and diabetes, although depression is only a modest risk factor for diabetes once lifestyle factors are accounted for. Other possible factors include activation of neuroendocrine pathways (leading, for example, to hypercortisolemia) and inflammatory responses that result in increased insulin resistance and the metabolic syndrome. In a large follow-up epidemiological study of middle-aged and elderly patients, those with incident type 2 diabetes were most likely to be depressed. This finding suggests that the impact of a new diagnosis is a significant factor for depression. It also suggests that early support might mitigate depression.

In patients aged 70 to 79 years there was a 30% increased risk of incident depression (odds ratio [OR], 1.31; 95% CI, 1.07 - 1.61), which was attenuated after adjustment for diabetes-related comorbidities (OR, 1.20; CI, 0.97 - 1.48); this still represents a significantly increased risk. Some studies suggest a link between depression and diabetic complications and poorer glycemic control. Painful neuropathy may be another causal factor. Diabetes can cause small-vessel pathology in the brain that leads to subcortical encephalopathy, not unlike that seen in vascular depression. This may lead to both cognitive impairment and depressed mood.

TCAs are more likely to impair diabetic control than SSRIs. Fluoxetine should be used with caution, however, because as it can cause hypoglycemia. TCAs can be effective for painful neuropathy. Mirtazapine may cause weight gain (a risk factor for diabetes), lithium toxicity is increased if there is nephropathy, and valproate may give a false-positive result on urine testing for glucose. There is increasing interest in alternative and complementary medicine to improve glycemic control and mood in diabetic patients, including Ayurvedic medicine, exercise, yoga, and acupuncture.

There are also reports of the benefits of CBT. However, as with the treatment of depression in heart disease, it has yet to be demonstrated that such interventions actually are disease modifying (as measured by glycated hemoglobin levels).

**PARKINSON DISEASE**

Parkinson disease is characterized by slowness of movement, rigidity, resting tremor, shuffling gait, and postural instability. The reported prevalence of depressive symptoms varies widely from 7% to 76%, with an average of 40%. The cause of depression in Parkinson disease is multifactorial, but there is evidence linking it to neurodegeneration with an associated reduction in the neurotransmitter level not only of dopamine but other catecholamines important in mood regulation. However, 3,4-dihydroxy- l-phenylalanine (l-dopa) does not seem to improve mood in Parkinson disease patients. Serotonin and noradrenaline are probably more important.

In Parkinson disease with comorbid depression, there is more involvement of dopaminergic and noradrenergic pathways and reduced frontal metabolism than in Parkinson disease without depression. Other causal factors include social isolation, cognitive impairment, severity of disease, and duration of illness, although there is no consistent relationship between the last 2. Untreated depression in patients with Parkinson disease is associated with increased physical disability, impaired quality of life, and decreased social interaction. Ravina and colleagues found that more than 40% of their Parkinson disease patients had clinically significant depression that might benefit from intervention.

Treatment options for Parkinson disease with comorbid depression include antidepressants, electroconvulsive therapy, exercise, and CBT. Support groups and self-help programs are also encouraged. Well-controlled clinical trials in the treatment of depression in Parkinson disease are scarce. SSRIs are most frequently prescribed. Although there are concerns that SSRIs can cause emergent extrapyramidal effects, this is controversial. The combination of an SSRI and selegiline can lead to the potentially fatal serotonin syndrome (altered level of consciousness, myoclonus, sweating, hyperreflexia, tremor, diarrhea, shivering, uncoordination, and fever). TCAs are not recommended because of anticholinergic effects. Tianeptine (which increases the presynaptic recapture of 5-hydroxyindole acetic acid) and moclobemide (a reversible and selective inhibitor of monoamine oxidase A) are most frequently prescribed. Although there are concerns that SSRIs can cause emergent extrapyramidal effects, this is controversial.
Evidence from a small study suggests that the use of the dopamine receptor agonist mirapex combined with l-dopa may improve not only motor activity, daily activities, quality of life, and dyskinesias but also anxiety and depression in patients with Parkinson disease.\textsuperscript{46} Modafinil, used to counteract sleepiness, has been used in Parkinson disease; in at least 1 antidepressant drug trial (not of Parkinson disease patients) it modestly diminished fatigue and sleepiness in patients with partially responsive SSRI-treated depression.\textsuperscript{47} Lastly, deep brain stimulation is a treatment for both Parkinson disease and severe depression. To what extent this treatment may exert a specific antidepressant effect in patients with Parkinson disease is unknown, however.\textsuperscript{48}

### CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is projected to be the third leading cause of death by 2020.\textsuperscript{49} A recent review of depression comorbid with COPD in the elderly identified a prevalence of 40% (95% CI, 36% - 44%).\textsuperscript{50} Untreated depression in patients with COPD is associated with increased physical disability, impaired quality of life, increased health care use, and increased mortality.\textsuperscript{51-53} The mechanisms that link depression to patients with COPD is unclear. Possibilities include factors related to COPD (level of physical disability and fluctuating mood because of dyspnea), smoking (which increases the risk of vascular brain disease), and behavioral factors (lack of exercise, limited activity, and concomitant social isolation). Social factors are important and include the level of perceived and actual support and disruption to life caused by repeated hospital admissions (those with moderate to severe COPD are likely to have 3 or 4 admissions per year) or becoming housebound either through worsening disability or the need for continuous oxygen treatment.\textsuperscript{51}

There are no good trials of antidepressant medication in COPD but given the association of COPD depression with marked anxiety, a more sedating SSRI such as paroxetine or the non-SSRI mirtazapine can be tried. Benzodiazepines should be avoided because they depress respiration. Pulmonary rehabilitation based on activation and physical conditioning along with an antidepressant may be an effective approach compared with medication alone.\textsuperscript{54} Although there are limited data, in 1 study a 2-hour CBT session reduced both depression and anxiety.\textsuperscript{55} Furthermore, in a recent randomized controlled study, 8 weeks of group educational therapy was found to be as effective as CBT in alleviating depression and anxiety symptoms and improving quality of life in patients with COPD.\textsuperscript{56} It is worth replicating the findings of this study in other settings.

### VASCULAR DEPRESSION

Vascular depression is a subgroup of late-onset depression symptoms that present with reduced depressive ideation, greater psychomotor disturbance, apathy, executive dysfunction (slow, inefficient thinking, difficulty in switching mental set), and neuroimaging abnormalities in the basal ganglia and white matter on MRI in older patients.\textsuperscript{4,5} It may account for 50% of newly diagnosed cases of major depressive disorder in later life.\textsuperscript{57} The cause of the structural brain changes is thought to be atheromatous damage to small penetrating arterioles deep within the brain.\textsuperscript{4,5,57} These vessels are end arteries and may be particularly susceptible to pulse-wave changes (pulse-wave encephalopathy) caused by factors such as arterial rigidity and/or hypertension. Many older adults have evidence of microvascular disease on brain imaging but not all of them have vascular depression or executive dysfunction. Hence, it is important to recognize the interplay of personal predisposition (from genetics or development), cognitive reserve, and cerebral lesion localization as well as overall lesion burden.\textsuperscript{58,59}

Standard antidepressant treatment is less effective in patients with microvascular disease than in nonvascular cases. One recent study demonstrated the benefits of augmenting fluoxetine treatment with nimodipine in patients with vascular depression.\textsuperscript{60} Nimodipine is a calcium channel drug used to lower blood pressure, and it may also dampen the systolic pulse wave to the brain. Such studies require replication but raise a question about what would be truly innovative depression-based treatment paradigms for halting vascular damage in those with vascular depression. For example, it is known that drugs such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have vasoprotective properties that extend beyond their primary role. Until this research is carried out, it is as important to address vascular risk factors rigorously in late-onset depression as it is to treat depression.

Another approach is to target symptoms, such as apathy, linked to subcortical brain disease and hence vascular depression. No trials have been undertaken, but it has been suggested that dopamine-acting agents may be effective in depressed patients with frontostriatal impairment that leads to low motivation. In addition, antidepressants and other psychotropic agents with a-blocking action may inhibit behavioral recovery following ischemic lesions, whereas psychotropic drugs that
increase catecholaminergic activity may promote recovery. Such concepts may guide future treatment. Low motivation or apathy has been treated with problem-solving treatment and behavioral activation with some encouraging results.

**CONCLUSION**

Several medical conditions that are prevalent in later life are associated with increased rates of depression. The extent to which the link is biological is debatable because, particularly in older people, the causes of depression are multifactorial. There is increasing evidence that depression itself is associated with the development of several diseases, especially those that involve the blood vessels. It is interesting to see if future research is able to identify whether vasoprotective drugs can improve the prognosis for vascular depression.

There is every reason to be optimistic about treating depression in older adults with medical comorbidity. There are effective psychological and antidepressant drug treatments, both for the immediate management and to keep the patient well after recovery from depression.

**References: Drugs Mentioned in This Article**

Citalopram (Celexa)
Fluoxetine (Prozac, Sarafem)
Lithium (Eskalith, Lithane, Lithobid)
Methylphenidate (Ritalin LA)
Mirapex (Pramipexole)
Mirtazapine (Remeron)
Moclobemide (Aurox, Manerix)
Modafinil (Provigil)
Nimodipine (Nimotop)
Nortriptyline (Aventyl, Pamelor)
Paroxetine (Paxil)
Selegiline (Emsam, Atapryl, Carbex, others)
Sertraline (Zoloft)
Tianeptine (Stablon)
Valproate/valproic acid (Depakote, others)
Venlafaxine (Effexor)

**References**


Evidence-Based References