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Late-life depression: Managing mood in patients with vascular disease

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Initiate preventive strategies to protect your patient's brain and reduce the risk of stroke

Newly diagnosed major depressive disorder (MDD) in patients age ≥65 often has a vascular component. Concomitant cerebrovascular disease (CVD) does not substantially alter the management of late-life depression, but it may affect presenting symptoms, complicate the diagnosis, and influence treatment outcomes.

The relationship between depression and CVD progression remains to be fully explained, and no disease-specific interventions exist to address vascular depression's pathophysiology. When planning treatment, however, one can draw inferences from existing studies. This article reviews the evidence on late-life depression accompanied by CVD and vascular risk factors, the "vascular depression" concept, and approaches to primary and secondary prevention and treatment.

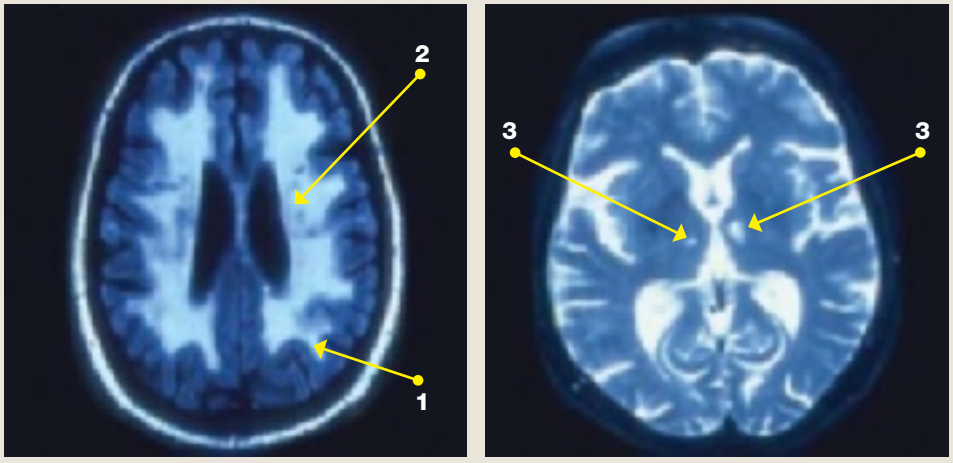
CVD etiology of depression

Vascular depression constitutes a subgroup of late-life depression, usually associated with neuroimaging abnormalities in the basal ganglia and white matter on MRI.[1] The cause of the structural brain changes is thought to be sclerosis in the small arterioles.[2] These end-artery vessels may be particularly susceptible to pulse-wave changes caused by arterial rigidity or hypertension.

Alexopoulos et al[1] and Krishnan et al[3] proposed the concept of vascular depression on the premise that CVD may be etiologically related to geriatric depressive

Figure

Subcortical cerebrovascular disease in late-life depression



Structural MRIs of elderly adults with major depressive disorder consistently show high rates of brain abnormalities. Subcortical white matter abnormalities manifest as (**1**) periventricular hyperintensities [halos or rims adjacent to ventricles] and (**2**) deep white matter hyperintensities [single, patchy, or confluent foci]. Strategic subcortical gray matter infarctions (**3**) are observed, particularly in the basal ganglia, thalamus, and pons.

syndromes. Krishnan et al[3] examined clinical and demographic characteristics of depressed elderly patients with vascular lesions on brain MRI. Those with clinically defined vascular depression experienced greater cognitive dysfunction, disability, and psychomotor retardation but less agitation and guilt feelings than patients with nonvascular depression.

Clinically, vascular depression resembles a medial frontal lobe syndrome, with prominent psychomotor retardation, apathy, and pronounced disability.[4] Depression with vascular stigmata or cerebrovascular lesions on neuroimaging is characterized by poor outcomes, including persistent depressive symptoms, unstable remission, and increased risk for dementia.[5,6] Patients with depression and subcortical vascular lesions have been shown to respond poorly to antidepressants.[6]

Impaired brain function also may predispose to geriatric depression, described by Alexopoulos as "depression-executive dysfunction syndrome of late life."[7] This common syndrome's presentation—psychomotor retardation, lack of interest, limited depressive ideation and insight, and prominent disability—is consistent with its underlying abnormalities.[5] Executive dysfunction also predicts limited response to antidepressants.[8] Thus, the presentation and course of depression-executive dysfunction syndrome are consistent with those of subcortical ischemic depression.

Neuroimaging support

The vascular depression hypothesis is supported by observations related to MRI hyperintensities (HI):

- CT and MRI studies identify HI in persons with late-life depression.
- HI are associated with age and cerebrovascular risk factors.
- Pathophysiologic evidence indicates that HI are associated with widespread diminution in cerebral perfusion.[9]

Neuropathologic correlates of HI are diverse and represent ischemic changes, together with demyelination, edema, and gliosis.[9-11] The putative link between HI and vascular disease is central to the vascular theory of depression.

In a study of 56 patients age ≥50 meeting DSM-III-R criteria for MDD, Fujikawa et al[12] reported "silent cerebral infarctions" on MRI in 60% of patients. High rates of

Clinical Point

With psychomotor retardation, apathy, and pronounced disability, vascular depression looks like a medial frontal lobe syndrome

Vascular depression

Clinical Point

Patients with depression and subcortical vascular lesions have been shown to respond poorly to antidepressants

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Table 1

Shared risk factors for depression and heart disease

Decreased heart rate variability
Vascular inflammation (increased interleukin-6 and C-reactive protein)
Endothelial dysfunction
Platelet dysfunction
Atherosclerosis
Dyslipidemia
Smoking

Source: References 26-29

abnormalities consistently have been observed on MRIs of older adults with MDD,[10,11] and these can be classified into 3 types (***Figure, page 21***):

- Periventricular HI are halos or rims adjacent to ventricles that in severe forms may invade surrounding deep white matter.
- Deep white matter HI are single, patchy, or confluent foci observed in subcortical white matter.
- Deep gray matter HI may be found, particularly in the basal ganglia, thalamus, and pons.[9]

These leukoaraiosis (or encephalomalacia) occur more frequently in patients with geriatric depression than in normal controls[13] or patients with Alzheimer's disease[14] and may be comparable to the rate associated with vascular dementia.[15] Observations in older adults[11] suggest that diminished brain volume (especially in frontal regions) and HI may provide additive, albeit autonomous, pathways to late-life MDD. Vascular and nonvascular medical comorbidity contribute to HI, which in turn facilitate MDD.

Bidirectional relationship

The relationship between depression and cardiovascular disease appears to be bidirectional:

- Depression may be the first clinical expression of an underlying cardiovascular disease, which is expressed as an increased risk for ischemic events.
- Depression itself, whether or not contributed by a silent cardiovascular disease, increases the risk of vascular damage, which in turn further promotes depression.
- Vascular pathogenesis affecting heart and brain is likely to increase the risk for depression through a variety of mechanisms.

Post-stroke depression (PSD) occurs within 12 to 24 months after a cerebrovascular accident.[13] DSM-IV-TR categorizes PSD as a "mood disorder due to a general medical condition with the specifiers of (a) depressive features, (b) major depressive-like episodes, or (c) mixed features."

Although important in depression's pathophysiology, the location of stroke lesions is not the exclusive etiologic factor. Personal diathesis for depression, psychosocial factors, and physical and social impairment related to post-stroke neurologic deficits also may contribute to PSD.[16]

PSD patients with right-sided lesions often have family histories of depressive illness.[17] Different serotonergic mechanisms might be responsible for depressive illness associated with right-sided vs left-sided lesions. This notion is supported by observed lateralized changes in serotonin type-2 (5-HT2) receptors[18] and the influence of lateralized lesions on prolactin responsivity to d-fenfluramine challenge in PSD.[19] Damage closer to the frontal lobes is likely to affect catecholamine-mediated brain activity.

The 8-year Framingham study[20] examined the risk of developing cerebrovascular events in persons age ≤65 vs those age >65. Subjects age ≤65 with significant depressive symptoms—Center for Epidemiologic Studies Depression scale score >16[21]—were 4 times more likely to develop stroke or transient ischemic attack compared with the same age group without depression. Another study found a link between depression and stroke risk across the adult age range.[22] Mechanisms by which depressive symptoms may predispose to stroke are not fully known, but depression has been shown to affect autonomic function and platelet activation.[23]

CHD and depression. In the United States, approximately 20% of coronary heart dis-

Table 2

Clinical management of late-life vascular depression

Decision point	Assessment/intervention
Diagnosis	Apply DSM-IV-TR diagnostic criteria based on results of comprehensive assessment (neuropsychiatric, neuropsychological, structural neuroimaging, vascular and genetic risk factors)
Prevention	Identify and treat modifiable risk factors for the development or worsening of cerebrovascular disease, especially in high-risk populations (***Table 4, page 29***)
Treatment goals	**Target 1**: Achieve remission of depressive symptoms, improved cognition and function **Target 2**: Maintain remission and prevent relapse
Managing psychological and behavioral symptoms	**Step 1:** Consider psychotherapy addressing existing stressors and environmental management in patients with mild-to-moderate depression **Step 2:** If depression is severe or Step 1 is ineffective, an antidepressant trial* is highly recommended (***Table 3, page 24***); consider ECT or TMS in severe cases

*Avoid medications that could worsen cognition or motor functioning, such as tricyclic antidepressants or neuroleptics
ECT: electroconvulsive therapy; TMS: transcranial magnetic stimulation

ease (CHD) patients have clinically significant depressive symptoms.[24] A history of depression also has been shown to increase the relative risk of developing CHD by >80%.[25]

The association between depression and CHD is unclear but likely includes:

- direct biological mechanisms such as autonomic dysfunction and dysregulated inflammation

continued

Clinical Point

A history of depression has been shown to increase the relative risk of developing coronary heart disease by more than 80%

Vascular depression

Clinical Point

CT or MRI may not be necessary for diagnosis when depression onset is associated with strong physical evidence of a stroke

Table 3

Recommended antidepressant dosing for elderly patients with vascular depression*

Drug	Starting daily dosage (usual therapeutic range)	Side effect profile (patient characteristics)
SSRIs		
Escitalopram	5 mg (10 to 20 mg)	Nausea, headaches, GI upset, insomnia, anxiety
Fluoxetine	10 mg (10 to 60 mg)	
Paroxetine	10 mg (10 to 30 mg)	
Sertraline	25 mg (50 to 150 mg)	
Others		
Bupropion	75 mg (75 to 300 mg)	GI upset, anxiety (may be useful for patients with high apathy)
Mirtazapine	7.5 mg (15 to 45 mg)	Sedation, weight gain (may be useful for patients with severe insomnia or anorexia)
Venlafaxine	37.5 mg (75 to 300 mg)	Nausea, headaches, anxiety, blood pressure elevation, insomnia (may be useful for patients with chronic pain)
Duloxetine	20 mg (30 to 120 mg)	

*Avoid medications that could worsen cognition or motor functioning, such as tricyclic antidepressants or neuroleptics
GI: gastrointestinal; SSRIs: selective serotonin reuptake inhibitors

- behavioral factors such as smoking or poor self-care (***Table 1, page 22***).

A recent analysis of 13 cross-sectional studies[26] suggests that reduced heart rate variability (HRV) related to autonomic dysfunction may be the link between depression and CHD risk. The studies' effect sizes were small, however, and their methodologies varied considerably.

C-reactive protein (CRP), interleukin-6, tumor necrosis factor-α (TNF-α), and fibrinogen are inflammatory markers. In a 2-year follow-up study, Frasure-Smith et al[27] investigated the relationship between depression and inflammatory markers in 741 patients (602 male) with acute coronary syndrome. Two months after an acute coronary event, depressive symptoms and elevated CRP levels were overlapping risk factors for future cardiac events in men.

Carney et al[28] showed that fibrinogen was most associated with altered heart rate variability in depressed CHD patients and proposed deficits in parasympathetic modulation of immunity and coagulation as the cause. In contrast, Whooley et al[29] found no association between major depression and inflammatory markers—including CRP, fibrinogen, and interleukin-6—in 984 outpatients with CHD. Differences in assessment scales and sample heterogeneity may have contributed to these disparate findings.

Diabetes and depression. As with CHD, a bidirectional relationship exists between depression and diabetes mellitus, although depression is only a modest risk factor for diabetes.[30] Possible explanations include hypercortisolemia and increased inflammation resulting in increased insulin resistance and metabolic syndrome.

Diagnosis of vascular depression

Vascular depression is characterized by a clinical diagnosis of DSM-IV-TR-defined MDD, dysthymia, or depression not-otherwise-specified, accompanied by:

- evidence of CVD or
- known vascular risk factors (hypertension, diabetes, hyperlipidemia, stroke, heart failure, etc.).

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Table 4

Preventing vascular causes of late-life depression

Decision point	Assessment/intervention	Comment
Primary, secondary prevention of stroke, vascular depression, and cognitive impairment	Identify and treat modifiable risk factors (hypertension, alcohol use, smoking, hyperlipidemia, diabetes mellitus), especially in high-risk patients	Consider as high-risk patients having ≥1 of these features: age >50; male gender; Asian, Hispanic, or African-American heritage; low educational achievement; concurrent vascular risk factors
Tertiary prevention of worsened illness in patients with established vascular disease	Intensively treat vascular risk factors	Collaborate with primary care physician to manage arterial hypertension, myocardial infarction, atrial fibrillation, coronary heart disease, diabetes, atherosclerosis, hyperlipidemia, obesity, and smoking
	Rapidly identify and treat acute stroke to limit ischemic brain changes and promote recovery	
	Prevent stroke recurrence by aggressively treating vascular risk factors	Let CVD etiology guide treatment

CVD: cerebrovascular disease
Source: Adapted from Lavretsky H. Diagnosis and treatment of vascular dementia. Directions in Psychiatry. 2006;26(1):49-68

In performing thorough neurologic, neuropsychiatric, and neuropsychological examinations, look for soft neurologic signs with regional weakness, apathy, and executive dysfunction. Useful bedside scales include the clock-drawing test, word list generation, brief dementia screens, and the Apathy Evaluation Scale.[31]

CT or MRI can provide supportive evidence by demonstrating signs of subcortical or cortical stroke. Neuroimaging studies may not be necessary, however, when depression onset is temporally associated with strong physical evidence of a stroke (such as falling, peripheral muscle weakness, or incontinence).

Treating depression symptoms

When treating vascular depression, clinical goals are to ameliorate affective symptoms, improve quality of life, and help patients perform activities of daily living (***Table 2, page 23***).

Psychosocial interventions. When depression is less than severe, consider psychosocial interventions as first-line treatment. Investigate environmental factors such as financial and marital problems or loneliness in patients' depressive symptoms, and develop corresponding interventions—such as education, nutrition, exercise, socialization, or pain and stress management. Cognitive rehabilitation training and cognitive-behavioral therapy can reduce cognitive impairment and associated depression.

Antidepressants. A trial of antidepressant therapy is advisable for moderate-to-severe, chronic vascular depression, even though comorbid CVD may diminish the antidepressant response. In elderly patients, start with one-third to one-half the usual adult antidepressant dosage and increase while balancing efficacy and tolerability.

Match the medication's side-effect profile with the patient's target symptoms (such as anxiety vs apathy).[32] Selective serotonin reuptake inhibitors are probably first-line, but bupropion, venlafaxine, duloxetine, or mirtazapine may be more appropriate for some patients (***Table 3, page 24***).

In PSD, nortriptyline has shown a

Clinical Point

Methylphenidate, 5 to 20 mg/d, may improve apathy and social withdrawal, but evidence for its use in vascular depression is lacking

Vascular depression

Clinical Point

ECT appears to be quite safe in depressed older patients, especially if not used in the first 6 months after a stroke

significantly greater response rate than fluoxetine or placebo in improving anxiety symptoms and recovery of activities of daily living.[33] Tricyclic antidepressants' anticholinergic properties are a safety concern in patients with heart disease, however. In general, avoid agents with substantial anticholinergic effects in elderly patients to minimize the risk of cognitive impairment and other side effects, such as urinary retention or worsening of glaucoma.

Because of the substantial risk of postural hypotension, nonselective monoamine oxidase inhibitors are probably appropriate only for geriatric patients with highly treatment-refractory depression. Dopaminergic agents such as methylphenidate in a relatively moderate dose (such as 5 to 20 mg/d) may improve apathy and social withdrawal, but research into their use in vascular depression is lacking.

Other options. Clinical experience suggests that electroconvulsive therapy (ECT) is effective for patients who do not respond to antidepressants. ECT appears quite safe in older patients, especially if not used in the first 6 months post-stroke. Strategies to reduce the risk of cognitive side effects include:

- 2 rather than 3 weekly treatments
- unilateral or bifrontal rather than bilateral treatments
- frontal lead placement.[34]

In the only study of transcranial magnetic stimulation (TMS) for geriatric patients with depression (N=92), those with treatment-resistant vascular depression showed higher remission rates with TMS (27.3%) compared with sham TMS (3.5%). Response rates to TMS were negatively correlated with advancing age and positively correlated with higher frontal gray matter volumes.[35]

Fish oil or vitamin B complex may be used to manage hyperlipidemia or nutritional deficiencies.[36] Herbal preparations such as St. John's wort (*Hypericum perforatum*) or S-adenosyl-L-methionine (SAMe) have shown some efficacy in adults with MDD, but further study is needed.

Treating vascular factors

In addition to treating your patients' depressive symptoms, collaborate with their primary care physicians to modify physiologic and behavioral factors that increase the risk for vascular injury—such as hypertension, diabetes mellitus, cigarette smoking, and hyperlipidemia. All can be controlled in presymptomatic or mildly symptomatic stages (***Table 4, page 29***).

Anticoagulation. In appropriate patients, anticoagulation can prevent thromboembolic strokes, although risks such as increased hemorrhagic complications must be considered.[37] In elderly adults, base treatment decisions on individual risk factors, goals of treatment, and quality-of-life expectancy. In a study of low-dose aspirin (81 mg/d) and low-intensity oral anticoagulation in men at risk of cardiovascular disease, verbal fluency and mental flexibility were significantly better in men taking antithrombotic medications (especially aspirin) than in those taking placebo.[38]

Antihypertensives and statins. Patients with vascular depression may benefit from calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors for hypertension and HMG-CoA reductase inhibitors (statins) for hyperlipidemia. Statins seem to decrease the generation of amyloid precursor protein, the neuronal secretion of β-amyloid, and cholesterol synthesis.[39] Some epidemiologic studies suggest an association between statin use for cholesterol reduction and reduced prevalence of Alzheimer's disease and vascular dementia.[40]

Potential preventive strategies are not without controversy, however:

- Beta blockers and ACE inhibitors have been linked to depression, although the evidence has been conflicting.
- Lipid-lowering therapies and calcium-channel blockers have been linked to an increased risk of suicide.[41]
- A more recent population-based study did not support an association between an increased risk of suicide and cardiovascular drugs (except perhaps for angiotensin-receptor antagonists).[42]

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Related Resources

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Drug Brand Names

Bupropion • Wellbutrin
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Methylphenidate • Ritalin, Concerta, others
Mirtazapine • Remeron
Nortriptyline • Aventyl, Pamelor
Paroxetine • Paxil
Sertraline • Zoloft
Venlafaxine • Effexor

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Clinical Point

Collaborate with patients' physicians to modify risks for vascular injury, such as hypertension, diabetes, smoking, and hyperlipidemia

Bottom Line

Prominent psychomotor retardation, apathy, and pronounced disability are hallmarks of late-life vascular depression. First-line treatments for many patients are psychosocial interventions or selective serotonin reuptake inhibitors. Other antidepressants, methylphenidate, ECT, or TMS may be appropriate for others. Collaborate with medical providers to modify cerebrovascular risk factors such as hypertension, diabetes mellitus, smoking, and hyperlipidemia.

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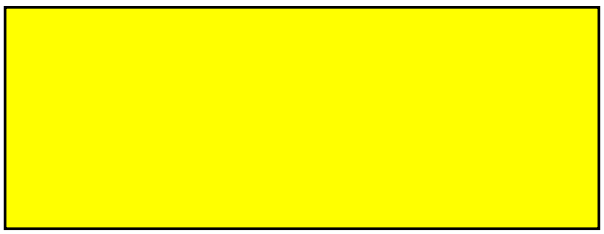

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