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## Perspectives on the Management of Vascular Depression

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### Abstract

In the next few years, the youngest of the baby boomers will reach age 65, resulting in the greatest proportion of elderly adults in US history. Concurrent with this demographic change is the growing number of adults living with chronic conditions that increase risk of vascular disease, including hypertension, obesity, hypercholesterolemia, insulin resistance and diabetes mellitus. We address how these conditions contribute to age-related cerebrovascular changes and lead to subsequent effects on mood and cognitive function, with an emphasis on the role of “vascular depression” as a focus of treatment. The case of an elderly gentleman with vascular disease associated with psychiatric symptoms and cognitive changes is presented. We discuss vascular depression in the context of suicide in late life and provide perspectives on treatment that focus not merely on pharmacologic and psychotherapeutic management of depressive symptoms but also emphasize the importance of sleep and health maintenance strategies. Guidelines are offered to help reduce the burden of disability associated with this condition among our older population.

### Case Presentation

An 80-year-old married gentleman presents for his first psychiatric evaluation. He arrives punctually, carrying a manila folder containing documents summarizing his medication history and previous surgical procedures. He reports that this outpatient visit was initiated by a referral from his primary care provider after his wife expressed concerns that her husband appeared to be depressed. The patient denies any previous mental health problems, history of psychotropic medication use, or history of therapy. He reports a period of bereavement after the death of his first wife at age 40, but states that he recovered over time without intervention. He remarried 17 years ago and describes his wife as supportive. He previously worked in an executive position that required substantial travel overseas. The development of angina on these trips ultimately resulted in the placement of multiple cardiac stents and he

retired 12 years ago due to health concerns. He has been less active since retirement, stating “I have no hobbies.” He reports he still ruminates a great deal about past events that occurred during his career.

When asked about depressive symptoms, the patient does not agree that he is depressed and questions the need for the referral. He admits to feeling socially detached with a loss of interest and lack of motivation and states “I know that I should get out more, but I can’t ever get past the first step.” While he denies feeling overtly sad, he reports feeling irritable at times toward his family, which he finds troubling. According to his wife, his irritability is increasing in frequency and tends to arise without substantive provocation. His sleep is suboptimal, with frequent nighttime awakening due to nocturia and difficulty returning to sleep. His appetite is adequate, but his weight has been slowly increasing, which he attributes to his sedentary lifestyle. He feels his memory is “okay,” noting that he occasionally has trouble finding the right word to use, and that it is harder for him to focus when reading or paying the bills. He reports his energy is low, blaming this symptom on his cardiologist’s prescriptions for lisinopril and metoprolol. Overall, he ascribes his difficulties to increased medical problems over the last decade and a corresponding increase in medications. These medications now include atorvastatin for hypercholesterolemia and glipizide for type II diabetes in addition to his antihypertensives, clopidogrel and aspirin. He denies feelings of hopelessness and helplessness but at times feels discouraged at the change in his ability to function relative to his earlier years. He denies suicidal ideation but casually admits to worries that in the future, he could become a burden if he experiences another serious cardiac event.

## Discussion

Here we report a clinical case that reflects the characteristic psychiatric symptoms of vascular depression and its impact on daily life. We then discuss the epidemiology, clinical features and the radiographic markers as well as how it may relate to risk for suicide in later life. Our intention for this summary is to help illustrate the clinical features of age-related vascular disease and how it affects depression and cognition. A range of treatment strategies are then described that may be beneficial for vascular depression and may provide insights to new innovations in the approach to this condition.

Age-related vascular changes have long been observed to be related to depressive syndromes in later life. The insidious role of subcortical microvascular disease was recognized as a critical factor in the development of neurocognitive symptoms initially by Binswanger in 1894 (1) but the prominent role of depressive features in this condition did not become a major focus of study until many decades later (2). In the late 1990s, investigators studying late-life mood disorders proposed the concept of “vascular depression” as a research subtype of late life unipolar depression (3). Two pivotal papers that spurred further studies of vascular depression respectively focused on clinically defined and magnetic resonance imaging (MRI)-defined criteria to operationalize its features (4) (5). Subsequent research testing the “vascular depression hypothesis” (6) leveraged improvements in neuroimaging methods, and the capacity of MRI-based diffusion tensor imaging to examine white matter integrity has allowed for exploration of the relationship between damage to white matter and

development and maintenance of depressive symptoms (7). Despite a large volume of research, vascular depression was not represented in the DSM-5 classification, detracting from clinical recognition and negatively affecting clinically informed systematic study.

“Late life depression” is diagnosed when a major depressive episode occurs in older adults, (3,8). This is a heterogeneous group, including individuals with “early onset” depression that arose in adolescence or early adulthood, and “late onset” depression where the initial depressive episode occurs after age 50 to 55 years. Like other variants of late-life depression, vascular depression has unique characteristics that distinguish it from early-onset depression. Notably, vascular depression frequently develops after the age of 60 – 65 years in the absence of a prior history of affective illness. Further, there is often an absence of a family history of affective disorder. From a practical perspective, patients with vascular depression may have less insight into their mood symptoms and may be less aware of and less comfortable with mental health services. Also, the nature of depression related to vascular aging does not follow a path of clearly delineated episodes with recovery in the same way as early onset depressive disorders. In vascular depression, there is often a more persistent character to the mood and cognitive symptoms that may fluctuate over time without discrete episodes. This insidious and often chronic course tends to delay the recognition and necessary assessments considerably. A recent consensus report on vascular depression specified key symptoms of low energy, lack of insight, anhedonia, deficits in self-initiation, psychomotor retardation and reduced processing speed (9). As noted in the clinical case above, patients with vascular depression may not perceive themselves to have a depressive disorder. Initial evaluation often occurs at the insistence of family members who observe a change in daily function and perhaps an increase in irritability or apathy.

## Epidemiology of Vascular Depression

Vascular Depression is not a distinct diagnosis in DSM-5 (10) and has different operational definitions in various classifications, leading to variance among estimates of its frequency. One U.S. study used a national probability sample of 16,423 adults to examine the population prevalence using survey assessments. Vascular depression was defined by applying DSM-IV criteria for an episode of major depressive disorder within the preceding 12 months in older adults with cardiovascular or cerebrovascular disease or major cardiovascular risk factors (11). In this national sample of adults 50 years or older, the prevalence of major depression without vascular disease was 12.2%, and the population prevalence of vascular depression was 3.4%. Among those affected with depression, over one-fifth (22.1%) of those with a lifetime history of major depressive episodes met study criteria for vascular depression. These rates were higher than in a Korean two-stage epidemiological study of older adults age 65 years or greater, using a MRI-based definition of vascular depression (12). In that population-based survey of 783 subjects, the prevalence of major depression without MRI-defined vascular disease was 2.36%, while the prevalence of major depression with MRI-defined vascular disease was 2.40%. Importantly, rates of MRI-defined vascular depression increased with advanced age, so in the cohort aged 75 years or older with a diagnosis of major depression all patients met radiographic criteria for vascular depression.

## Cognitive Features of Vascular Depression Affecting Clinical Management

Vascular depression is often characterized as a disorder of executive dysfunction, including difficulty with task completion and decision-making, both of which may increase the likelihood of experiencing irritability and social withdrawal. Additional cognitive features of vascular depression include slowed speed of information processing and impairments in concentration and attention. It is not uncommon for these cognitive complaints, rather than depressive symptoms, to be the trigger for a clinical evaluation. Given the common nature of cognitive concerns in older adults, patients and families may be more amenable to engaging in the assessment process when discussing problems with attention, concentration, reasoning and memory. In contrast, discussing one's mood or emotions may be more difficult for an older patient. When the treatment plan and assessment is couched in seeking to improve attention, concentration, planning and engagement in life, the therapeutic relationship can be enhanced substantially. Further, an awareness of the type of cognitive deficiencies associated with vascular depression can help in finding ways to increase social engagement and understand some of the limitations that patients may be experiencing. This approach is at the heart of Problem-Solving Therapy (PST), a form of cognitive-behavioral therapy that has been adapted for older depressed patients with executive impairment (13,14). Given the predominance of difficulties with psychomotor slowing, poor initiation of thought and movement, and reduced processing speed, as well as relative impairment in insight into mood symptoms, it is not uncommon for the depressive symptoms associated with vascular depression to fail to meet criteria for DSM-5 major depressive disorder. However, in older adults even subthreshold depressive disorders can have a very large impact on functional status, quality of life, and mortality (15).

Along these lines, it has also been recognized that depressive symptoms may at times be a less prominent component within vascular depression, which may be characterized as a "Depression-Executive Dysfunction Syndrome" or DED as proposed by Alexopoulos and colleagues (16). This conceptualization focuses on executive and information processing deficits often observed in late life depression, with an emphasis on these deficits in the diagnostic evaluation. The DED syndrome is associated with a range of clinical symptoms, including reduced fluency, impaired visual naming, psychomotor retardation, loss of interest in activities, and paranoia. In contrast, other depressive symptoms were comparatively milder. Notably, among depressed patients without the DED syndrome, depressive symptoms appeared to have less of a disabling effect than in patients with executive dysfunction. Consequently, vascular depression and DED may be conceptualized along the same spectrum of illness, with cognitive features being particularly pronounced in DED. Depending on methods used for diagnostic evaluation, many patients may meet criteria for both disorders, reflecting their considerable clinical and diagnostic overlap.

Given the prominent cognitive features in both DED and vascular depression, it is unsurprising that depressed elders are at increased risk for progression to a major neurocognitive disorder. Multiple studies have examined populations with late-life depression (of which vascular depression is one subtype) and demonstrated an increased longitudinal risk for dementia. A meta-analysis examining 23 population-based prospective studies reported that late life depression was associated with a 2-fold increased risk for

dementia of any type and that the increased risk for vascular dementia exceeded that for dementia of the Alzheimer's type (17). A parallel longitudinal study of late-life depression further demonstrated that WMH volume was independently associated with time to dementia (18).

This complex interplay between late-life mood symptoms and cognitive deficits has been difficult to capture within diagnostic nosology, particularly if both are related to cerebrovascular pathology. However, the new criteria for the cognitive disorders in the DSM-5 which include the classification of "mild" neurocognitive disorder now permit the specification of cognitive symptoms as being due to vascular disease when they have passed the threshold of severity to qualify for mild NCD, in the same manner that "mild cognitive impairment" was previously termed to represent the transition phase at risk for a dementia syndrome (10). As cognitive symptoms other than concentration deficits are not included in diagnostic criteria for major depressive disorder, we propose that mood and cognitive symptoms be evaluated and diagnosed separately according to the respective criteria. For example, if criteria are met for both Mild Vascular Neurocognitive disorder as well as a DSM-5 mood disorder diagnosis such as major depressive disorder, then both disorders should be recognized for the greatest diagnostic clarity.

### **Clinical Assessment and Radiographic Markers of Vascular Depression**

The assessment for this disorder ideally includes not only a review of vascular risk factors and history of vascular disease, but also evidence demonstrating subcortical white matter disease. Such findings are observed on an MRI brain scan as periventricular or deep white matter hyperintensities (WMH). In the clinical setting, it is not uncommon for these findings to be noted within the narrative text of the radiology report, with the overall impression often reading as unremarkable for age. This may lead to a reduced awareness, clinically, of the potential relationships of these findings with the clinical syndrome. For example, one study of healthy community-dwelling adults aged 44–48 reported that WMH were found in 50.9% of individuals (7). However, in most cases WMH severity is mild and MRI-based definitions of vascular depression require a minimum threshold of WMH severity for diagnosis (19)

Given the overwhelming frequency with which the clinical radiologists see WMH, it may be difficult for them to raise clinical concerns unless the white matter changes are particularly severe or there is a clinical background describing cognitive changes or motor impairment. The burden may fall on the psychiatrist to bring together imaging information with the clinical features of vascular depression to help educate individual patients as to the range of symptoms experienced, their underlying causes, and the rationale for treatment. Despite the lack of clarity in general clinical practice regarding the relevance of WMH on MRI scans, there have been numerous neuroimaging studies that have demonstrated that a greater burden of white matter hyperintensities correlates with poor treatment response (9,20). Consequently, the best approach for incorporating WMH into clinical decision-making may be to consider the presence of WMH as a risk factor for symptoms of vascular depression as well as potentially a prognostic factor when particularly severe evidence for WMH is observed in the context of depression. However, the ability to quantify their precise impact on risk and outcome remains to be clarified in future research due to the multiple factors that

interact in late life disorders. Data from relatively new techniques such as diffusion tensor imaging that utilize fractional anisotropy as a more sensitive measure of white matter degradation may offer new ways to better understand white matter changes in relation to depression, although studies to date remain mixed.

### **Treatment Issues: Suicide Risk**

As suicide risk increases in later life, it is important to consider how the presence of vascular depression may affect this risk. While there is no clear evidence to date linking vascular depression specifically to suicide mortality, there is good support that increased mortality from all causes occurs in the context of vascular depression attributable to accelerated frailty, general morbidity, and cardiac death (10,22). Recent mortality data from the U.S. Census Bureau highlight a concern over increasing “deaths of despair” in middle age individuals, relating to both suicide as well as “poisonings” associated with complaints of poor health (22,23). A study examining suicide risk factors using data from Veterans Health Administration (VHA) system (24) observed that the presence of chronic pain, sleep impairment, and traumatic brain injury were associated with a greater suicide risk, attesting to the impact of medical comorbidity. While this study did not directly compare risk between younger versus older Veterans, the impact of medical comorbidity is an important addressable risk factor that is highly relevant to older adults with depression. A separate VHA study similarly observed that older veterans who completed suicide had a greater predominance of medical health problems (25). It further noted that nearly all of the elderly decedents used firearms. A noteworthy study used the National Violent Death Reporting System from the years 2005–2014 to identify N=16,924 suicide decedents over the age of 65 years. The study noted that “Physical health problems were recorded as a suicide precipitant for 50% of the older decedents.” For those decedents who disclosed intent, concerns centered around pain, cancer, fear of dementia-related decline, fear of burdening others, nursing homes and loss of independence (26). Finally, the cognitive symptoms of late-life depression also increase risk. Older depressed patients with executive impairment such as poor cognitive control are at increased risk for suicidal attempts. Of note, PST can reduce suicidal ideation in older depressed adults with executive dysfunction (14).

### **Treatment Issues: Management**

Vascular depression increases the likelihood of not only poor response to antidepressant treatment and persistent depressive symptoms, but also may contribute to poor self-management of medical comorbidities and greater impairments in daily function (27,28). Further, there may be cumulative disability associated with impaired sleep, chronic pain, and use of analgesic medications as well as complex conditions such as peripheral neuropathy and impaired mobility, all of which add to the likelihood of poor treatment outcomes and vascular depression. Response to treatment is significantly attenuated in the context of vascular depression (9), so typical treatment strategies are often unsatisfactory and do not result in full remission of depressive symptoms. For example, one of the few randomized controlled pharmacological treatment trials of vascular depression observed a low rate of remission at 33% (29), even with careful titration of the SSRI sertraline over a 12-week period. This study highlighted the interrelationships between white matter disease and

depression outcome by demonstrating that both pre-treatment neuropsychological function and white matter hyperintensity severity independently predicted treatment response over the trial. Despite the poor response in this trial, there is still value in implementing antidepressant therapy, as even a small reduction in symptoms may enhance quality of life. Further, there is intriguing evidence that SSRI use may be associated with improved neural resilience in relevant areas such as the hippocampus (30,31) as well as novel evidence of a potential reduction in amyloid production associated with SSRI exposure which may have relevance in reducing cognitive decline (32).

The poor response to antidepressants in vascular depression has been well documented (9). Yet there may be potential insights from studies that suggest cognition may be targeted by antidepressants independently of mood symptoms in the context of major depression, although vascular depression has not specifically been studied (33). Among these, vortioxetine, a multimodal serotonergic compound has been associated with improvement in executive function and other cognitive domains (34–36). However, while some of these studies included older adults, the safety profile for elderly adults with vascular depression has not yet been clarified. Thus, while new pharmacologic strategies offer hope for the future, an approach that incorporates wellness and general health maintenance will likely remain essential to achieving optimal outcomes. These health issues include attending to regular sleep, exercise, healthy diet and medication compliance to minimize the impact of hypercholesterolemia, hypertension and glucose intolerance to the extent possible.

Addressing sleep may offer an important window of opportunity to provide some relief for older adults with depression early in the course of treatment while waiting for an eventual response to therapy or antidepressant treatment. Kay et al. (37) observed that impaired sleep may increase risk for suicidal behavior in middle aged and older adults even after adjusting for other risk factors. Further, the Established Populations for Epidemiologic Studies of the Elderly (EPSE) study demonstrated among 14,456 older adults in the community that poor subjective sleep quality was associated with an increase in risk of death by suicide over a 10-year period. Due to concerns regarding hypnotics in the elderly as well as a potential for an independent suicide risk (38), management should focus on lifestyle and general health issues while attending to risk of sleep disorders common in later life, such as sleep apnea. Sleep impairment may relate to reduced endogenous melatonin production with increasing age. Further, there is emerging evidence that melatonin may be advantageous for age-related brain changes, hence melatonin supplementation may be a useful strategy to reduce symptom burden in the context of vascular depression (39). A systematic review of the literature that synthesized sixteen studies of the use of melatonin in older adults noted that low doses are recommended, no more than 1 – 2 mg of immediate-release melatonin is optimal and should be administered approximately one hour prior to bedtime for disturbed sleep in this population (40).

Given high rates of polypharmacy and limited efficacy of psychotropic treatments for lowering depression burden in vascular depression, psychotherapeutic approaches to treatment have also been explored. To address sleep disturbance, Cognitive Behavioral Therapy for Insomnia (CBT-I) may be a useful tool. While CBT-I was initially demonstrated as efficacious for primary insomnia (41), it is also effective when the insomnia is comorbid

with a medical or psychiatric condition (42). Current psychotherapies often used in conjunction with other treatments to manage vascular depression have been developed to address symptoms that are more often associated with late life onset and cognitive deficits. For example, executive dysfunction, which includes impairment in task completion and difficulty with decision-making, may be addressed with skills developed through PST or a variant of problem focused psychotherapy, Problem Adaptation Therapy (PATH) (43). PATH is consistent with the process model of emotion regulation (13,44) however it uses an adapted approach to these emotion and behavioral psychotherapies through distinct features including home delivery, addressing compensatory strategies, environmental adaptations, and caregiver participation. Other related strategies may in part circumvent cognitive skills and rely on behavioral strategies and interpersonal therapy to help boost mood through caregiver engagement. Evidence-based psychotherapies have been shown to be superior to other strategies that have been used with older adults in the past, such as supportive therapy, which solely relies on empathic support in the absence of development of strategies that can actively adapt to the needs of adults with late onset depression, such as vascular depression. Psychotherapies such as PATH or PST as well as other behavioral or interpersonal psychotherapeutic strategies aimed at improving sleep hygiene or behavioral activation can be a flexible component to long term treatment plans.

One additional treatment option that may bear further exploration for refractory patients is repetitive transcranial magnetic stimulation (rTMS). One study by Jorge and colleagues studied rTMS for patients with vascular depression who had been unresponsive to at least one course of treatment with antidepressant medication. Participants received active or sham rTMS to the left dorsolateral prefrontal cortex. While there was a significant improvement in symptoms in the active group compared to the sham group, remission of depression remained very modest at 27% in the active group (45). However, it is notable that remission was achieved in patients previously unresponsive to antidepressant medication. The study also observed that improvement in depression was negatively correlated with age, which is consistent with other treatment studies of vascular depression. Additionally, for treatment-resistant or severe cases, the use of electroconvulsive therapy (ECT) is an important means of achieving remission (46). A recent study examined vascular risk factors in elderly inpatients receiving antidepressant management compared to ECT. The study noted that ECT was significantly more effective than medications among the elderly inpatients with depression in achieving remission. Further, remission from depression was not influenced by the vascular risk factor burden (47).

## Case Follow-up

In the case reported above, a comprehensive interview was conducted to understand not only his current symptoms but also factors contributing to his social isolation. During this interview, he identified some activities that he may take up, including a return to his local gym. He noted that early in life, he was quite conscientious about attending a gym, but this activity was sidelined during his executive years. He was receptive to restarting a regular workout program and had a senior discount for a gym membership in his neighborhood. A comprehensive review of his sleep-wake cycle suggested that he tended to spend a lot of time at the computer in the evening out of boredom. He was advised to reduce exposure to



light in the evening and begin melatonin at bedtime to help stabilize his day night cycle and increase the restfulness of his sleep. Additional management included the initiation of low-dose sertraline 25 mg by mouth every morning initially, increasing to 50 mg with a plan to further titrate the dose if well tolerated and needed. He was instructed to focus on positive health behaviors including resuming regular physical activity, engaging more proactively with his wife's community activities, and maintaining a healthy diet. He was advised to focus on finding meaningful activities with only a modest reliance on expectations for medications alone to remedy his symptoms. His wife actively supported the treatment plan, offering to provide assistance in observing his irritability, sleep, and daily activity. Over the following months he was able to see improvement in his motivation and was able to resume some remodeling projects and ultimately was able to regain a regular gym schedule which together with melatonin resulted in improved sleep and well-being.

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**Clinical Pearls in Summary:**

- Presenting features of vascular depression may involve poor motivation and slowed information processing as opposed to traditional mood complaints
- Although there is not currently an indication to obtain neuroimaging, when records are available the assessment includes reviewing MRIs for findings of deep white matter and periventricular hyperintensities as well as subcortical gray matter lesions
- Treatment planning should recognize there may be a modest response to antidepressants and that other treatments such as Problem Solving Therapy may offer additional benefit.
- Sleep hygiene may be important and the patient may benefit from treatment with low dose melatonin if indicated.
- Management should include active support for the patient to reduce obesity, hypertension, hyperlipidemia, glucose intolerance and engage in appropriate dietary and exercise strategies to reduce vascular risk