

Depression Comorbid With Stroke, Traumatic Brain Injury, Parkinson’s Disease, and Multiple Sclerosis: Diagnosis and Treatment

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Depression is common among patients with neurologic disorders, and it has long been considered more difficult to treat than depression in the general population. In this review, the authors consider challenges in the diagnosis and treatment of depression among patients with stroke, traumatic brain injury, Parkinson’s disease, and multiple sclerosis. For each disorder, the authors discuss the epidemiology and time course of depression as well as review the physiologic and psychological etiologies of depression. In addition, for each disorder, they review

screening tools and diagnostic considerations, including differential diagnosis; discuss etiological factors, both neurobiological and psychological; and assess evidence for various depression treatments, including pharmacologic, psychosocial, and neuromodulatory therapies. The evidence suggests that depression is common among patients with neurologic disorders and that it is crucial for general psychiatrists to provide treatment for this population.

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Depression is common among patients with neurologic disorders, and it has long been considered more difficult to treat than depression in the general population. In this review, we consider challenges in the diagnosis and treatment of depression among patients with stroke, traumatic brain injury (TBI), Parkinson’s disease, and multiple sclerosis (MS). These are common disorders, and it is crucial for the general psychiatrist to treat patients with comorbid neurologic disorder and depression. Patients with neurologic disease who develop depression may have *DSM-5* diagnoses of major depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, or persistent depressive disorder (1). The studies cited in this review use varying methods, including structured clinical interviews and rating scales, to classify patients as depressed, and treatment considerations are similar regardless of the specific *DSM-5* diagnosis.

STROKE

Stroke, or acute loss of blood supply to an area of the brain, affects nearly 800,000 people in the United States each year, and it is estimated that approximately 2.7% of the U.S. population has a history of stroke (2). Risk factors for stroke include age, hypertension, diabetes mellitus, atrial fibrillation, smoking, and family history. Physical and cognitive

disabilities are common sequelae. Stroke can affect various brain regions, to varying degrees. It is also mechanistically heterogeneous, with both ischemic (87%) and, less commonly, hemorrhagic (13%) etiologies (2). Despite this heterogeneity, poststroke depression has generally been studied as a single entity. The American Heart Association (AHA) and the American Stroke Association (ASA) have published a comprehensive report of recent findings in poststroke depression (3).

Poststroke depression has long been recognized as a common sequela of stroke. The most recent meta-analyses, including more than 20,000 patients, indicate a prevalence of depression of approximately 30% in the year following stroke (4, 5). Poststroke depression is associated with worse stroke outcomes over time, including poorer functional outcomes, disability, poorer quality of life, and increased mortality (3, 5, 6).

Factors associated with development of poststroke depression include more severe neurological deficits, physical disability, anxiety, and prestroke depression. Demographic factors such as age and sex do not appear to predict poststroke depression (5, 7); in contrast, idiopathic depression is more common in women and most commonly onsets in early to midadulthood (8). Stroke patients with a history of depression have a threefold increased risk of poststroke depression compared with stroke patients without a

depression history (9). Interestingly, depression itself is a risk factor for stroke, with meta-analyses indicating that depression is associated with a 34%–45% increase in stroke risk compared with the general population (10, 11).

The time course of poststroke depression varies greatly among patients, and of course individual patients can have multiple episodes of poststroke depression. Initial onset can be within several days of, or up to years after, the stroke. In general, poststroke depression appears to be a chronic and relapsing disorder (12). In meta-analyses, the proportion of patients affected at any time poststroke is generally stable at around 30%. It appears to peak at 2–5 months poststroke at 36% (4), and then it drops to between 20% and 30% at 2–5 years poststroke, remaining stable to the 10-year mark. Cumulative incidence of poststroke depression within 5 years of stroke is 39%–52% of total patients affected (4, 5).

Lesion location has historically been considered important in the development of poststroke depression, particularly within the first several months poststroke. Left-sided lesions in the frontal lobe and basal ganglia have been implicated most (13). More recent meta-analyses have yielded less consistent results. For example, Wei et al. (14) found no effect of lesion location, whereas Zhang et al. (15) found left hemisphere lesions associated with increased risk of poststroke depression. Such analyses are complicated by inconsistencies in definition of lesion location, neuroimaging techniques, and timing of imaging and symptom measurement poststroke (13). Certainly, on the level of the individual patient, lesion location currently has little predictive value for development of poststroke depression.

The etiology of poststroke depression is multifactorial, and available evidence strongly suggests contributions from both neurologic factors related to brain damage and psychological responses to stroke-related deficits. Evidence for neurologic factors includes data on lesion location (as discussed earlier); observation of depression seen among patients with stroke-like pathophysiology but without disabling sequelae, for example, diffuse white matter damage (“vascular depression”) and depression after “silent infarcts” or transient ischemic attacks; poststroke depression observed among patients with anosognosia; and animal models of stroke in which depressive-like poststroke behaviors are observed (3, 13). The fact that larger neurologic deficits poststroke are associated with the development of poststroke depression likely reflects a bidirectional relationship between brain damage and reactive psychological response to functional deficits caused by that damage (13).

Diagnosis of poststroke depression can be challenging. In addition to poststroke depression, anxiety, fatigue, apathy, and “emotionalism” (increased lability) are all common poststroke neuropsychiatric syndromes (12) and have potential overlapping symptoms with poststroke depression. Neurovegetative changes, such as psychomotor retardation or agitation, insomnia or hypersomnia, fatigue, and changes in appetite or food consumption, could all be symptoms of poststroke depression or related to other, non-poststroke

depression effects of stroke. Neurologic deficits related to stroke, including aphasia or changes in ability to produce facial expressions, can make assessment of particular depression symptoms difficult or even impossible.

Thorough clinical evaluation, including obtaining collateral from caregivers, remains the optimal and preferred method for diagnosis of poststroke depression. However, multiple instruments have been evaluated in their ability to accurately screen for poststroke depression. The nine-item Patient Health Questionnaire (PHQ-9) has been found to be among the most effective screening tools for poststroke depression in a meta-analysis (16), and it is the recommended screening tool by the AHA and ASA (3). The PHQ-2 (a brief two-item form of the PHQ-9) does not appear to have adequate sensitivity as a screening tool for poststroke depression (16). Multiple stroke-specific screening and assessment instruments exist to more precisely diagnose poststroke depression accounting for various neurologic deficits (17, 18) but are not currently in widespread clinical use.

Inflammatory, genetic, neuroimaging, and neurophysiologic biomarkers are the subject of study in poststroke depression but are not currently predictive at the level of individual patients (19, 20).

Suicide rate among patients who have had a stroke is increased compared with the general population; a recent large study found the rate to be approximately double. Poststroke depression is the strongest predictor of suicidal ideation and behavior among patients who have had a stroke, and large lesions located in the brainstem have also been associated with increased risk (21). Screening for suicide risk is recommended for at least 5 years poststroke (21–23).

Antidepressant medication, psychosocial interventions, and neuromodulation have all been studied in the treatment of poststroke depression (24). Overall, as more data accrue over time, recommendations appear to be moving closer to recommending routine treatment of poststroke depression with antidepressant medication. A 2008 Cochrane review did not recommend routine use of antidepressants for poststroke depression (25). However, by 2017, the AHA and ASA stated that 12 trials suggest that antidepressant medications may be effective in treating poststroke depression, but timing, symptom threshold, and particular medications require more study (3). Antidepressant medications do appear to be associated with decreased mortality among patients with poststroke depression in several studies (13).

In one remarkable study, 9 years after the initial 12-week antidepressant randomized controlled trial (RCT), 68% of the treatment group but only 35% of the placebo group had survived, regardless of initial depression and whether depressive symptoms improved (26). The AHA and ASA also found that psychosocial interventions may be helpful in poststroke depression (3). Case studies and series of electroconvulsive therapy (ECT) have been reported for cases of severe, refractory poststroke depression with some benefit, although complications have occurred (27). Critical safety

considerations for ECT in poststroke depression include blood pressure control and anticoagulation, depending on original stroke etiology (28, 29). Studies of transcranial magnetic stimulation (TMS) and other neuromodulatory techniques are in early stages, and such treatments are not yet recommended in clinical practice (3, 24).

In addition to treatment of poststroke depression, antidepressant medications have also been studied for prevention of poststroke depression and overall enhancement of poststroke recovery. A *Cochrane Review* showed that among patients who had experienced a stroke, selective serotonin reuptake inhibitor (SSRI) treatment during the recovery period improved outcomes of dependency and disability, even among patients without depression (30). These analyses were not aimed at preventing or treating depression, but anxiety, depression, and neurologic symptoms all improved with SSRI treatment. Side effects, including seizures, gastrointestinal upset, and bleeding, increased but were not statistically significantly.

Regarding prevention, a recent large multicenter RCT showed that escitalopram started within 21 days poststroke did not prevent poststroke depression; 13% of patients in both the treatment and placebo groups developed depression. However, the medication was very well tolerated (31). The AHA and ASA have stated that further study is needed to determine the timing and duration of potential antidepressant medication and psychosocial interventions to prevent poststroke depression (3). Of note, physical disability predicts poststroke depression, so rehabilitation measures may also help depression (7).

TBI

The National Institute of Neurological Disorders and Stroke has defined TBI as “a form of acquired brain injury, occur[ing] when a sudden trauma causes damage to the brain” (32). In 2014, there were approximately 2.87 million TBI-related emergency department visits, hospitalizations, and deaths in the United States (33). Worldwide, 50–60 million TBIs occur annually (34). TBI severity is often clinically classified by the Glasgow Coma Scale (GCS) score after injury, with patients with mild TBI (mTBI) scoring 13–15 on the GCS, patients with moderate TBI scoring 9–12, and patients with severe TBI scoring 3–8. Other TBI severity classification schemes include loss or alteration of consciousness subsequent to injury, presence of imaging abnormalities, and presence of posttraumatic amnesia. The majority (80%) of TBIs are mTBI in both overall worldwide (34) and U.S. military veteran (35) populations.

Risk factors for TBI have previously included male sex and younger age; however, in developed countries, as the population ages, the epidemiology is shifting to encompass more older adults affected by falls. Populations particularly affected by TBI include patients with alcohol use disorders or attention-deficit hyperactivity disorder, those in the military, and athletes (34). Of note, although a TBI may be

classified as “mild” or “moderate” on the basis of postinjury GCS, life-long disabling sequelae can still result. Damage can be physical, cognitive, or emotional (36). Damage resulting from TBI can be differentiated into primary damage, caused at the time of the trauma, and secondary damage, occurring in days to years after injury and driven in part by the brain’s response to the primary injury (34).

TBI is commonly followed by a host of neurobehavioral and neurocognitive symptoms. Neurobehavioral symptoms can include depression, mania, anxiety, agitation, irritability, psychosis, pseudobulbar affect, and apathy (37). TBI is associated with subsequent diagnoses of both unipolar depression and bipolar disorder (38). TBI is unique among the neuropsychiatric disorders in this review because post-traumatic stress disorder (PTSD) can often result from the same traumatic etiology as the brain injury (39). In U.S. veterans, TBI is associated with development of depression, substance use disorders, and suicide attempts compared with veterans without TBI (40). Neurocognitive sequelae can include deficits in processing speed, attention, memory, and executive dysfunction (37). Other symptoms, such as headaches and insomnia, can be troublesome for years post-TBI (41).

Prevalence of post-TBI depression varies by severity of injury and population studied as well as by definition of depression. In 11 studies before 2016, major depression as measured by clinical interview ranged from 7% to 63% in the first year after mild to severe TBI (42). Pooled odds ratio in a meta-analysis of 10 studies showed a 2.14-fold risk of developing depression compared with non-TBI control groups (38). In a 2017 meta-analysis, risk factors for development of post-TBI depression were female gender, preinjury depression, and unemployment after injury. Higher admission GCS, but not 24-hour postinjury GCS, was also associated with risk of developing depression (39). Depression after TBI is associated with worse functional outcomes (43).

We highlight several recent large studies of post-TBI depression. A recent large longitudinal cohort study, Transforming Research and Clinical Knowledge in TBI (TRACK-TBI), followed 1,155 patients with mTBI seen in the emergency department and a comparison group of 230 patients without head orthopedic trauma (44). Moderate to severe depression as measured by the PHQ-9 was found in 8.8% of patients with mTBI compared with 3.0% of patients without head trauma at 3 months postinjury (a statistically significant difference); similar rates were found at 6 months postinjury. Risk factors for development of major depressive disorder were having a psychiatric disorder before the injury, having less education, and being black. Of note, PTSD rates among patients with mTBI were 18.7% at 3 months and 19.2% at 6 months postinjury (compared with 7.6% and 9.8% among control patients without head trauma). Assault or violence as a cause of mTBI was related to a diagnosis of PTSD but not major depressive disorder.

Another large longitudinal cohort study followed 559 patients with complicated mild, moderate, or severe TBI

(45). Mild to severe depression on the PHQ-9 was found in 31% of patients at 1 month and in 21% of patients at 6 months; overall, 53% screened positive for depression at some time during the year following injury. Factors related to major depressive disorder were younger age, female sex, substance use, and having a psychiatric diagnosis before the injury. A third study used the TBI Model Systems National Database. Among several thousands of patients with mild to severe TBI, mild to severe depression as measured by the PHQ-9 was found in 24.8%–28.1% of patients throughout 20 years of follow-up (46).

Finally, using insurance claims data, Albrecht et al. (47) compared a very large sample of patients with TBI (>200,000) with more than 400,000 control participants without TBI. Depression was defined by any in- or out-patient claims during the study period; patients with pre-TBI depression were excluded. Overall, the adjusted hazard ratio for developing depression after TBI, compared with without a TBI, was 1.83. Male sex, older age, and pre-TBI psychiatric diagnosis were the greatest predictors of a post-TBI depression diagnosis; this finding differs from idiopathic depression in which female sex is a risk factor.

As in poststroke depression, time course is variable in post-TBI depression; predictors of post-TBI depression seem to change with time since injury. To assess patterns of change over time, Bombadier et al. (48) used linear latent class growth mixture modeling of PHQ-9 scores, collected monthly over the first year postinjury, in a cohort of 559 patients with complicated mild to severe TBI. Their model was used to divide patients into four distinct trajectories: low depression (70% of patients); persistent depression (6%); recovery, or early depression that improves (10%); and delayed depression (13%). Interestingly, the recovery group was more likely to have cerebral contusions and was less likely to have severe nonhead injuries compared with the delayed depression group, suggesting possible differential etiology of the depression in these two groups. Singh et al. (49) assessed differential predictors of post-TBI depression at 10 weeks and 1 year postinjury among 690 patients; they found that 10-week postinjury depression was associated with TBI severity and computed tomography (CT) scan abnormalities, whereas 1-year postinjury depression was associated with abnormal CT scan, history of psychiatric diagnosis, alcohol use, and female gender. In a longer-term study that used the TBI Model Systems Database, depression and suicidal ideation at 1 year postinjury were associated with depression and suicidal ideation at 5 years postinjury (46).

The etiology of post-TBI depression may vary, depending on the amount of time that has elapsed since the injury. Early postinjury depression is more likely to be associated with direct injury to brain tissue in regions that regulate mood (50). Hypopituitarism due to direct injury to the pituitary by the trauma may also contribute (51). Later postinjury depression may be more related to the psychological response to other persistent symptoms, such as headache, motor

impairment, and cognitive dysfunction, as well as to resulting interpersonal and occupational difficulties (37). Brain changes seen on imaging scans, serum cytokines and growth factors, and genetic data are beginning to provide clues to the disease mechanisms in post-TBI depression (52–55).

Diagnosis of post-TBI depression is made with a full clinical evaluation, including collateral from caregivers, depending on the severity of postinjury deficits. The differential diagnosis is broad because multiple other postinjury phenomena have potentially overlapping symptoms with depression. During early postinjury phases, particularly in hospitalized patients, substance withdrawal should be considered. Apathy and pseudobulbar affect may mimic some aspects of depression. Other psychiatric diagnoses of increased likelihood after TBI include PTSD and bipolar disorder (38, 50).

Among the post-TBI population, neuroendocrine abnormalities secondary to hypopituitarism warrant special consideration. Thyroid hormone and growth hormone deficiencies can both occur and can be associated with depressive-like symptoms, so screening is indicated (50). Growth hormone replacement in deficient patients with TBI has been shown to alleviate depressive symptoms (51). Depression scales are appropriate for screening and following progress over time. The PHQ-9 has good evidence for sensitivity and specificity in post-TBI depression (56, 57). Scales designed particularly for the TBI population, such as the Traumatic Brain Injury–Quality of Life scale, have also been developed (58). As in poststroke depression, inflammatory, genetic, neuroimaging, and neurophysiologic biomarkers are actively being studied in post-TBI depression but do not yet offer clinically actionable information at the level of individual patients (37).

Patients with TBI are at increased risk of suicide, particularly when depressive symptoms are present. A Swedish population study found an adjusted odds ratio of 3.3 for death by suicide among people with TBI compared with those without (59). During the first year after injury, a quarter of patients with TBI experienced suicidal ideation, with depression scores being the strongest predictor (60). Over a 20-year follow-up period, between 7% and 10% of patients with TBI experienced suicidal ideation in a given year, with 0.8%–1.7% attempting suicide annually; more than 80% of patients with suicidal ideation met criteria for major depressive disorder (46).

Antidepressant medication, psychotherapy, and neuro-modulation have all been studied in the treatment of post-TBI depression. Three recent meta-analyses of medications for depression, including SSRIs, tricyclic antidepressants (TCAs), and methylphenidate, failed to demonstrate a significant effect of medication in RCTs but did show significant medication effects in single-group studies (61–63). This lack of evidence to date from RCTs does not necessarily argue against antidepressant medication treatment of post-TBI depression; it is noted that these patients have benefited from the placebo effect in RCTs and that patients with

depression following an mTBI in particular resemble patients with idiopathic major depressive disorder and thus may benefit (64). However, these medications are not without possible adverse effects; SSRIs generally have either absent or negative effects on cognitive and functional recovery in patients with TBI (65), although improvement in isolated cognitive measures even in the absence of significant antidepressant effect has also been demonstrated (66).

Of note, patients with TBI appear to be more sensitive to side effects, so the adage “start low, go slow” for medication dosing applies (41). It is also important to ensure that trials are of adequate dose and duration before abandoning a medication as ineffective (37). Comorbid post-TBI symptoms may guide medication choices; for example, methylphenidate has evidence for efficacy in both depression and cognitive dysfunction, and tricyclics may alleviate post-TBI headaches (41).

Cognitive therapies, including cognitive-behavioral therapy and mindfulness-informed cognitive therapy, delivered by various means (in person, phone, online) have shown promise in the treatment of post-TBI depression (67). Evidence for ECT in post-TBI depression exists only at the case-study level, and there is reluctance to use ECT in a population already at increased seizure risk (68); however, patients with refractory depression may benefit. Several initial studies have shown promise in the use of TMS for post-TBI depression (69, 70); however, risk of seizure with TMS will be an important consideration in any future clinical recommendations.

Several trials have examined pharmacologic prevention of depression after TBI (71), with mixed results. One RCT of 24 weeks of 100 mg of sertraline daily found decreased likelihood of post-TBI depression compared with placebo, with a number needed to treat of 5.9, with minimal adverse effects (72). Another RCT of 3 months of 50 mg sertraline daily found some effect at 3 months (10% depression rate in placebo group vs. 0% in the sertraline group); however, at 1 year postinjury, after the drug was stopped, there was no difference between groups, arguing against prophylactic early administration for longer term prevention (73). It is also important to note that there is evidence for antidepressant-related cognitive dysfunction in patients with TBI who do not have depression (74).

PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disease defined by progressive rigidity, bradykinesia, and tremor. The diagnostic criteria were recently revised in 2015 (75). The new criteria continue to emphasize bradykinesia either in combination with resting tremor, rigidity, or both. Supportive criteria may include both motor and nonmotor symptoms, such as response to dopaminergic therapy, asymmetric resting tremor, and olfactory loss.

Parkinson's disease is the second most common neurodegenerative disease both in the United States and

worldwide, second only to Alzheimer's disease (76). Overall prevalence ranges from 1–2 per 1,000 (77). Although it is rare before age 50, Parkinson's disease can reach a prevalence of up to 4% for those ages 85–94 (78, 79). Although some cases appear to be associated with a monogenetic mutation, about 90% of cases are sporadic (76). Several risk factors have been identified, including exposure to pesticides (80) and heavy metals (81). Cigarette smoking appears to have an inverse effect on development of Parkinson's disease (82–84). Research into other risk factors such as diet, alcohol exposure, or sex differences have been inconclusive (76).

Premotor symptoms of Parkinson's disease often predate the formal diagnosis by months or years. Rapid eye movement (REM) sleep behavior disorder is the most common prodromal finding in Parkinson's disease, with 38% of patients developing Parkinson's disease within 5 years of REM sleep behavior disorder diagnosis and 81% of patients with REM sleep behavior disorder eventually developing a neurodegenerative disease (85).

Depression increases the risk of Parkinson's disease 2.4–3.24 times in some studies (86, 87). Patients who develop Parkinson's disease are highly likely to have been treated with an antidepressant up to 2 years before Parkinson's disease diagnosis, evidence that depression predates motor symptoms and may be a prodromal symptom (88). Current or, to a lesser extent, prior diagnosis of depression has been associated with development of Parkinson's disease. In a case-control study, current depression diagnosis was associated with an odds ratio of 4.7 of Parkinson's disease diagnosis, whereas depression diagnosed 15 years or more prior was associated with a 1.7 odds ratio of current Parkinson's disease diagnosis (89). Both increasing age and difficult-to-treat depression are independent risk factors for Parkinson's disease among patients with depression (87).

Depression has been a presenting symptom of Parkinson's disease in up to 2.5% of cases, and initial presentation with depression or any nonmotor symptoms has resulted in a median delay of diagnosis of 0.6 years versus patients presenting with motor symptoms (90). There are a variety of risk factors for patients with Parkinson's disease to develop depression. They include anxiety (91), premorbid history of depression (92), family history of depression (93), cognitive impairment (94), longer duration of illness (95), motor disability and gait as well as balance impairments (96), younger age (97), sleep disorders and restless leg syndrome (98), and female sex (99).

People with Parkinson's disease may develop multiple phenotypes of depression. There is a 2.7%–55.6% prevalence of major depressive disorder in Parkinson's disease. Additionally, there is a 13%–34.5% prevalence of minor depression and 2.2%–31.3% prevalence of dysthymia in Parkinson's disease (99–102). It is therefore not atypical for patients to lack the full *DSM* criteria for major depression but to continue to experience distress because of a spectrum of depressive symptoms. Meanwhile, the rigid-akinetic subtype of Parkinson's disease, rather than tremor-predominant,

has been found to have a higher association with major depressive disorder, although rates of dysthymia have been similar in both subtypes (101).

Patients with Parkinson's disease and depression experience a variety of symptoms. Chronic neurological illness and depressive illness often share symptoms, such as sleep disturbance and anergia. Patients experiencing depression and Parkinson's disease showed more anhedonia, rumination, suicidal thoughts, hopelessness, negative cognitions, appetite disturbance, and decreased libido when compared with patients with Parkinson's disease without depression (103). Attention to these, as well as specifically the nonsomatic, symptoms of depression assist in discriminating between neurological illness and depressive illness.

Risk of suicide among patients with Parkinson's disease has previously been downplayed in the literature, and at times, some have thought that a neurological diagnosis was protective against suicide. However, a recent systematic review found that a Parkinson's disease diagnosis was associated with increased suicidal ideation and suicide attempts, although rates varied by country (104). Lee et al. (105) found that the standardized mortality rate (SMR) for suicide was 1.99, or twice the rate expected in the general population. Suicide risk appears to be increased among patients with Parkinson's disease who are male; who are European American; who are diagnosed as having depressive disorder, bipolar disorder, psychosis, or addiction; and who have a history of suicide attempts (104).

Nazem et al. (106) studied current and past suicidal thoughts and behavior in 116 patients with Parkinson's disease. In this sample, 4.3% had a lifetime history of suicide attempts; regarding current thoughts of death or suicide, 28.4% had current death ideation, 11.2% had current suicide ideation, and 30.2% had both. They found that more severe depressive symptoms, diagnosis of major depression, psychosis, and history of impulse control disorders were significantly associated with passive or active suicidal ideation. In summary, recent evidence demonstrates increased suicide and high rates of suicidal ideation among patients with Parkinson's disease. As in the general population, increasing severity of depression and comorbid psychiatric illness increases the risk of suicide ideation and attempts.

Development of depression among patients with Parkinson's disease is thought to be related to dopaminergic and serotonergic dysfunction. Neuroimaging studies have shown varying results, but both nigrostriatal and extranigrostriatal pathways appear to be involved (107). Some studies have suggested an increase in frontal lobe atrophy among patients with depression and Parkinson's disease (108), with a decreased metabolism in frontotemporoparietal regions potentially serving as a marker for depression in Parkinson's disease (109). Inflammation may play a role in Parkinson's disease depression, with an elevated C-reactive protein demonstrating a correlation with Hamilton Depression Rating Scale (HAM-D) scores among patients with Parkinson's disease and depression (110). More research into the

neuroanatomical and functional correlates of depression and Parkinson's disease is necessary.

The presence of depression among patients with Parkinson's disease has a significant negative impact on quality of life; in fact, depression conveys a greater impact on quality of life than motor symptoms of Parkinson's disease (111). Depression with Parkinson's disease is associated with a higher rate of cognitive decline and worsening of activities of daily living (94). Depression among patients with Parkinson's disease is also associated with a higher frequency of hopelessness, suicidality, and social withdrawal. Patients with depression and Parkinson's disease are more likely to experience pain than patients with Parkinson's disease who are not depressed (112). Independent measures of health-related quality of life are also worsened among patients with Parkinson's disease and depression (111). A large multicenter study demonstrated a high frequency of all nonmotor symptoms of Parkinson's disease (98.6%), with the highest frequency being psychiatric nonmotor symptoms (67%). The psychiatric nonmotor symptoms had a significant impact on worsening of quality of life and worsened with disease progression and severity (113).

Detecting depression among patients with Parkinson's disease is essential for improving prognosis and quality of life. Screening tools are helpful to detect depression, but there have been concerns regarding overlap between neurological and psychiatric symptoms as noted earlier. A review of depressive rating scales by the Movement Disorder Society in 2007 showed efficacy and validity for common instruments, including the 17-item HAM-D, the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (114). The American Academy of Neurology found that the BDI, the 17-item HAM-D, and the MADRS were accurate and appropriate for depressive screening among patients with Parkinson's disease (115). A meta-analysis has shown that the 15-item Geriatric Depression Scale, in addition to other instruments mentioned earlier, has validity in Parkinson's disease (116). Consideration of depression in the differential diagnosis of a patient with Parkinson's disease is difficult for several reasons. Much of clinical practice is focused on the motor, rather than nonmotor, symptoms of Parkinson's disease. Additionally, some families, patients, and providers may struggle to recognize depressive symptoms. Expressions of sadness may be normalized as grief because of the difficulties of a progressive neurological illness.

Treatment of depression among patients with Parkinson's disease is often successful and leads to improvement in activities of daily living and quality of life over time. Research into Parkinson's disease-specific treatment modalities, however, is unclear. As with all patients, psychoeducation and psychotherapy, including cognitive-behavioral therapy (117), are essential components of successful treatment. Families and caregivers may also benefit from supportive therapies and treatments. Rehab services

including physical therapy, occupational therapy, and speech therapy are helpful components of an overall treatment plan (118). There is evidence for the utility of SSRIs in treatment of Parkinson's disease depression (117, 119).

Additionally, there is evidence demonstrating efficacy of TCAs in the treatment of Parkinson's disease depression (120, 121). There are also some data for dopamine agonists (122). Additionally, rivastigmine (123) and N-methyl-D-aspartate antagonists (124) have, in preliminary studies, shown modest effects in the treatment of Parkinson's disease depression. A 2016 review of ECT in Parkinson's disease depression reported a robust response to treatment, with more than 90% of patients responding; however, many patients developed confusion or delirium, in some cases requiring treatment discontinuation (125). Other non-pharmacological treatments such as repetitive TMS have inadequate efficacy evidence in the treatment of Parkinson's disease depression (122).

MS

MS is another common neurological disorder associated with depression, and its prevalence appears to be increasing. A recent study found a prevalence of MS in the United States of 309.2 per 100,000, the highest rate to date in the United States (126). Rates of depression in this population range from 23% to 54%. This prevalence of depression is higher than that seen in both the general population as well as other patients with chronic medical conditions (127). Similar to Parkinson's disease, earlier onset and greater severity of illness increase the likelihood of developing depression with MS (128). Depression may predate the neurological diagnosis and, in up to 75% of cases, is thought to delay the definitive MS diagnosis (129). Risk factors for MS depression include female sex, age older than 35, family history of depression, current anxiety (130), and high levels of psychosocial stress (131). Presence of psychiatric illness increases the severity of progressive neurological symptom burden (132).

Suicide and suicidal ideation significantly affect people with MS. In a study of Canadian patients with MS, 28.6% of deaths in the sample were by suicide (133). A Danish study found an SMR of 1.83, with the highest risk being in young men (134). A more recent study demonstrated an SMR of almost twice that expected, also with an increase in younger men within the first few years of diagnosis (135). Additionally, severity of depression, social isolation, and alcohol use disorder are associated with increased thoughts of suicide (135).

Although the pathophysiology linking MS to depression has not been fully elucidated, hypointense T1-weighted magnetic resonance imaging of brain lesions has been predictive of major depression, particularly in the frontal and temporal lobes and their associated connections (136). Disconnection of the hippocampus from several brain networks also may contribute to development of depression among

patients with MS (137). In addition, some studies have suggested that MS treatments, including interferon β , have been independently associated with major depression (138). However, further studies have cast doubt on that conclusion (139, 140). These data suggest that depression is likely a consequence of the neurological burden of disease rather than a psychosocial sequela.

Making the diagnosis of depression among patients with MS may be challenging. Symptoms of MS that overlap with symptoms of major depression include fatigue, sleep problems, and cognitive disturbance. Fatigue is the most common symptom of MS, with a prevalence of 80% (141). Therefore, screening tools are quite helpful to detect depression as early as possible. A variety of depression screening tools have been studied in MS, including the BDI, HADS, PHQ-9, MADRS, and HAM-D (142). The American Academy of Neurology recommends use of the BDI in screening for depression (143). Use of a semistructured interview is equally as effective in detecting depression among patients with MS (144).

As with the previous neurological disorders discussed, depression has a significant impact on quality of life among patients with MS (145). In some studies, in fact, it appears to be the primary determinant of quality of life (146). This area has been extensively studied in multiple populations with consistent results (147). The interaction between depression and fatigue also conveys a significant burden on health-related quality of life (148–150). Depression also negatively affects caregivers of people with MS, but attention to both members in the dyad may modulate this challenge (151).

Treatment of depressive symptoms in patients with MS is associated with improved adherence to MS treatments (152), quality of life (153, 154), cognitive function (155), reduced fatigue (156), and overall improved prognosis (157). Despite the clear benefits of treatment, there are limited data on specific pharmacological treatments of depression among patients with MS. A Cochrane meta-analysis included only two controlled double-blinded studies (158). Both studies demonstrated mild benefit from both TCA and SSRI treatment but no statistically significant separation from placebo. A variety of open-label studies demonstrated some efficacy with a range of SSRI and TCA medications (142). In another study by Mohr et al. (159), sertraline was found to be equally effective with cognitive-behavioral therapy, and both of them were more efficacious than supportive-expressive therapy. ECT has been studied in this population, but only to the level of case report, and concern has been raised for worsening of neurological function due to ECT by altering plaques or increasing edema (142). Although TMS has been studied in the treatment of cognition and fatigue among patients with MS, there are no articles demonstrating efficacy for the treatment of depression.

Several nonsomatic therapies have shown some benefit for symptoms of depression and psychological distress among people with MS. Mindfulness-based therapies have demonstrated some efficacy in the improvement of mental well-being (160). Patients with MS also have demonstrated

better outcomes with training and therapies focused on improving resilience (161). The benefits of exercise in reducing symptom severity among patients with MS and depression are also clear (148, 162). A meta-analysis of depressive treatments showed good response to either psychotherapy or medications for depression, and it found that therapies with a focus on coping skills were superior to insight-oriented therapies (163).

CONCLUSION

Depression and suicide are more common among patients with stroke, TBI, Parkinson's disease, and MS than in the general population. Depression in these disorders has both physiologic and psychological etiologies. In all these disorders, depression is currently diagnosed by clinical interview and history rather than biomarkers. Tools such as the PHQ-9 may be useful for screening and following treatment progress. Diagnosis can be challenging because of symptoms that could be due to either the neurologic disorder itself or depression, such as apathy and neurovegetative changes. Premorbid psychiatric conditions, particularly depression, predict depression after neurologic disorder onset. Recommended treatment is generally qualitatively the same as in idiopathic depression, although efficacy data in some neurologic disorders remain equivocal. Of note, many patients with neurologic disease are more sensitive to the side effects of antidepressant medications, so the adage "start low, go slow" applies. Treatment of depression among patients with neurologic disorders is important for prevention of suicide and improved quality of life.

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