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Diagnosis and Treatment of Depression Comorbid with Neurologic Disorders

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ABSTRACT

Depression is common in patients with neurologic disorders such as Alzheimer disease, stroke, Parkinson disease, and multiple sclerosis. Diagnosing depression in the context of neurologic disease is challenging, given the overlap between many signs and symptoms of depression with those of the neurologic disorders. Cognitive impairment further complicates diagnostic evaluation. The etiology of depression in these patients is not well understood and variously has been attributed to emotional reaction to the diagnosis or disability associated with the neurologic condition, the anatomical and/or neurochemical outcomes of neurodegeneration, and the influence of other disease factors. Beyond the inherent burden depression places on patients and caregivers, it increases cognitive and functional disability and, depending on the neurologic disorder, poorer treatment adherence and recovery, earlier institutionalization, and increased suicide risk. Few controlled antidepressant trials are available to guide treatment. In the absence of validated diagnostic guidelines for depression in each neurologic condition, clinicians are urged to remain vigilant for this treatable comorbidity. Although more controlled trials clearly are needed, existing studies suggest that depression in patients with neurologic disorders responds to antidepressant medication and, in some disorders, to psychotherapeutic approaches. Investigating the neuroanatomical and neurochemical correlates of depression comorbid with neurologic conditions also may clarify depression etiology and treatment in the general population.

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Increasing evidence suggests that depression may be both a cause and consequence of some medical illnesses, with biological linkages that remain poorly understood.[1] Neurologic disorders are often accompanied by depression; the potential for determining neuroanatomical and/or biochemical disease correlates makes this a compelling target for depression research. Alzheimer disease (AD), stroke, Parkinson disease (PD), and multiple sclerosis (MS) are among the most common neurologic disorders that are associated with comorbid depression. The reported prevalence of depression comorbid with these conditions varies widely, reflecting differing study methodologies, inconsistent diagnostic criteria, overlapping symptoms of underlying disease and depression, and patient/caregiver factors that impede diagnosis. More certain is the understanding that adding depression to the existing burden of underlying conditions impairs rehabilitation, distresses patients and caregivers, increases treatment costs, and reduces quality of life.[2–4]

Some of the most significant challenges in diagnosing and treating depression comorbid with neurologic disorders include overlapping symptoms, reciprocal effects, and the potential for shared etiologies. Symptoms associated with neurodegeneration, such as aphasia, may mimic those of depression and can impair the ability of patients and clinicians to share information regarding emotional disposition. Varied presentations of depression can also interfere with diagnosis; in older adults, for example, symptoms including unexplained somatic complaints, a sense of hopelessness, and anxiety commonly displace reports or evidence of sadness.[5]

The goal of depression treatment in patients with neurologic disorders is relief of affective symptoms and improved

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functioning, with consequent decrease of patient and caregiver burden and maximization of resources available for coping with the neurologic condition. Few data are available to guide treatment efforts in these patients: controlled trials are rare, and heterogeneity in research methodology and diagnostic criteria confounds clinical findings. Beyond the presumption that further research would benefit patients who have depression comorbid with neurologic disorders, greater understanding of the relationships between these illnesses could help shed light on the neuroanatomy of depression in general and lead to better treatment outcomes for the broader population.[6,7]

ALZHEIMER DISEASE

The proportion of patients with AD in clinical settings who experience major or minor depression is estimated to be 30% to 50%, although prevalence rates ranging from 1% to 90% also have been cited.[3] Population studies, which are less susceptible to referral bias, suggest that the true incidence of AD and depression may be closer to 20%.[8,9] Factors thought to increase the risk that AD patients will experience depression include a prior depressive episode, history of mood disorder in a first-degree relative, female sex, and younger age of AD onset.[6,10] Although the etiology of depression in patients with AD is unknown, it is believed to be heterogeneous, as evidenced by 4 subtypes that have been identified: adjustment disorder, recurrence of earlier depressive episode, vascular depression, and depression associated with neurodegeneration.[3] The pathophysiology of the latter types may help account for the fact that depression is often one of the first symptoms of AD.[6]

Symptom overlap is a significant barrier to diagnosis of depression in patients with AD. Many of the symptoms that identify nondementia-related depression, such as difficulty thinking and concentrating, psychomotor retardation, insomnia, and emotional lability, are common symptoms in nondepressed patients with AD. Furthermore, depression symptoms such as diminished interest, fatigue, and hypersomnia are hallmarks of apathy, a common neuropsychiatric manifestation of dementia. Confounding efforts to understand the course of depression in patients with AD is the fact that symptoms appear to fluctuate over time.[3]

The impact of depressive symptoms comorbid with AD is not limited to effects on patients alone: caregivers experience greater levels of stress as a result of behavioral disturbances related to patient depression.[11] Depression symptoms are more strongly correlated to caregiver distress than disruptive behaviors or memory-related problems.[12] Additionally, patient depression is highly related to caregiver depression, which can hinder ability to provide patient care and objectively assess patient affect.[12] Behavioral interventions that target patient depression and include caregiver participation, however, have been shown to alleviate depression in both groups.[13]

The outcomes associated with comorbid depression and AD can be significant and severe. Patients may experience a decline in quality of life[14] and impairment in activities of daily living.[15] Physically aggressive behavior in patients with dementia has been linked to depressive symptoms,[16] and the presence of depression is positively correlated with institutionalizing patients with AD earlier.[17] Furthermore, depression and behavioral disturbances increase the likelihood that dementia patients will be moved from assisted living facilities to a higher level of care.[18] Furthermore, evidence suggests that depressive symptoms are predictive of future cognitive losses among elderly community dwellers with moderate cognitive impairment[19] and increased mortality risk in nursing home residents.[20]

Controlled pharmacotherapy studies of depression treatments in patients with AD have yielded conflicting results; however, a strong placebo response has been a fairly consistent finding in this population, as evidenced in trials involving the tricyclic antidepressants (TCA) imipramine[21] and clomipramine.[22] Selective serotonin reuptake inhibitors (SSRIs), which have a more benign safety and tolerability profile compared with the TCAs, have also been studied in depression in AD. In a citalopram trial[23] of 149 patients with depression, many of whom also had somatic disorders and/or senile dementia, significantly greater improvement in Hamilton Depression Rating Scale (HAM-D) ($P < 0.01$), Montgomery Asberg Depression Scale (MADRS) ($P < 0.05$), and Clinical Global Impression Scale ($P < 0.01$) scores occurred with active treatment than with placebo. Furthermore, the subgroup of patients with dementia experienced significant improvement in cognitive and emotional functioning with citalopram compared with placebo ($P < 0.05$), as measured by individual items on the Gottfries-Bråne-Steen Dementia Rating Scale.

Sertraline treatment was assessed in 31 female nursing home patients with late-stage AD using objective rating scales designed to detect depression and to evaluate facial behaviors in subjects with dementia.[24] Similar improvement was seen with sertraline and placebo in the 8-week trial; based on a trend favoring active treatment in the "knit brow" facial measure, the authors recommended further study in this population. A second, smaller (n = 22), 12-week sertraline study[25] used the Cornell Scale for Depression in Dementia as the primary measure of the effects of treatment in outpatients with major depression and AD; sertraline was associated with a significantly greater reduction in depressive symptoms ($P = 0.03$) and a greater response rate than placebo ($P < 0.05$). In addition, patients receiving placebo showed significant decline on the activities of daily living subscale of the Psychogeriatric Dependency Rating Scale at weeks 9 and 12, while sertraline-treated patients showed no significant change at any follow-up point. The dearth of randomized placebo-controlled trials and the high prevalence and morbidity of depression in this vulnerable elderly patient population provides strong rationale for further studies.

STROKE

Although clinicians have recognized a relation between stroke and depression since the early 1900s, systematic

studies of this association have been confined to the last 3 decades.[26] Estimates of poststroke depression prevalence range from 20% to 72%, depending on the diagnostic criteria used and patient population studied.[26,27] Incidence rates of major and minor poststroke depression in acute and rehabilitation hospitals are 19.3% and 18.5%, respectively; in community settings, the rates are 14.1% and 9.1%.[26] Because depression can develop long after stroke occurs, length of follow-up also accounts for differences in the reported rate of incidence; clinicians are urged to remain vigilant for symptoms that occur several years after the event.[27]

Poststroke depression is more likely to occur in women, for whom younger age, personal history of psychiatric disorder, and cognitive impairment are risk factors. Among men, risk factors include younger age and impairment in activities of daily living and social functioning.[28] One etiologic issue that has generated much debate is the influence of lesion location on the risk for developing subsequent depression. More than 20 years ago, Robinson and colleagues[29] reported elevated depression risk in patients affected by stroke in the left hemisphere of the brain, particularly the left anterior frontal pole. In 2000, Carson and coworkers[30] analyzed the numerous reports published on the topic and, with a focus on studies producing original data, found 2 reports that supported and 7 reports that failed to support the lesion-location hypothesis of depression risk. More recently, Bhogal and associates[31] reviewed the literature and called into question the ability to draw any robust conclusions from the data owing to wide variation of diagnostic methodologies and population samples.

The diagnosis of poststroke depression is complicated by the number of symptoms that can be attributed to either stroke or depression; delineating the etiology of symptoms such as fatigue, psychomotor retardation, reduced concentration, and decreased appetite is difficult because of symptom overlap in the 2 conditions. Among the symptoms that are considered more sensitive for the diagnosis of poststroke depression are depressed mood, reduced appetite, and crying; apathy, feelings of guilt, and lack of insight in stroke patients are less reliable indicators of a mood disorder.[32–34]

Correct identification and treatment of poststroke depression is important in light of how the mood disorder can affect stroke morbidity and recovery. Although impairments in cognitive, physical, and social functioning have been identified as risk factors for depression in stroke patients, the relationship is also understood to be bidirectional. Poststroke depression has a negative influence on motor, cognitive, and social disability and recovery, with patients less likely to regain levels of _restrike functioning.[35–39] Furthermore, 2 large epidemiologic studies have linked psychological distress with increased risk for stroke. An analysis by Larson and associates[40] of 13-year follow-up data from the Baltimore Epidemiologic Catchment Area Study found a positive association between depressive disorder and stroke. In addition, May and colleagues[41] analyzed data from the Caerphilly Study that demonstrated greater risk for fatal ischemic stroke in subjects with greater degrees of psychological distress as measured by the General Health Questionnaire (GHQ).

Few controlled studies of the pharmacologic treatment of poststroke depression are available to guide treatment. An early trial[42] evaluated nortriptyline in 34 subjects using the HAM-D, Zung Depression Score (ZDS), Present State Exam (PSE), and an overall depression score (ODS) that comprised the 3 ratings. Nortriptyline was superior to placebo at end point (week 4 or 6) for the HAM-D ($P = 0.006$), ZDS ($P = 0.027$), and ODS ($P = 0.006$) assessments; difference in PSE change between nortriptyline and placebo was not significant. Tolerability was poor, with 3 of 14 patients on active medication experiencing delirium with confusion, drowsiness, and occasional agitation. Anticholinergic effects of TCAs often limit their treatment utility, particularly in the elderly.

Another small study,[43] conducted before the introduction of SSRIs, tested the serotonin modulator trazodone in patients with or without evidence of depression, as indicated by a clinical diagnosis of depression, ZDS score, or dexamethasone- suppression test (DST) results. Trazodone-treated patients with abnormal DST tests did significantly better according to the Barthel Activities of Daily Living Index than did patients receiving placebo ($P < 0.05$); patients who were classified as depressed by clinical diagnosis or ZDS score showed only a trend toward improvement. The DST results may indicate a subpopulation of stroke patients with depression who are more likely to respond to antidepressant therapy.

Andersen and associates[44] used the HAM-D to assess 6 weeks of citalopram treatment in 66 patients who became depressed 2 to 52 weeks after stroke. Of the 28 patients who entered the trial 2 to 6 weeks after stroke, half experienced remission (≥50% reduction in HAM-D) of depressive symptoms within 1 month regardless of treatment, suggesting a high rate of spontaneous remission. Among patients who became depressed ≥7 weeks after stroke, significantly greater improvement was demonstrated by patients treated with citalopram (67%) compared with patients given placebo (15%) ($P < 0.005$). In a 6-week placebo-controlled trial of fluoxetine (20 mg/day),[45] positive results were observed in 31 subjects who had experienced stroke ≤3 months previously. Fluoxetine compared with placebo was associated with significantly greater reduction in mean MADRS scores (16.6 and 8.4, respectively; $P = 0.02$). However, in a larger ($N = 104$), 12-week placebo-controlled study of fluoxetine (10 to 40 mg/day) or nortriptyline (25 to 100 mg/day)[46] in depressed and nondepressed patients with stroke, a significantly higher response rate (>50% reduction in HAM-D) was observed in patients with depression who were treated with nortriptyline (77%), compared with fluoxetine (14%; $P = 0.002$) or placebo (31%; $P = 0.05$). Although response in the fluoxetine group was not statistically different from that seen in the placebo group, fluoxetine treatment led to an 8% average

reduction in body weight over the course of the study, an effect not seen with nortriptyline or placebo.

Exploration of prophylactic antidepressant treatment for patients with stroke has yielded promising results.[47] A recent study[48] randomized 176 nondepressed patients who had an acute stroke within the previous 3 months to a double-blind comparison of escitalopram or placebo, or a nonblinded problem-solving therapy (PST) group for 12 months. Placebo-treated patients were significantly more likely to develop depression than were those receiving escitalopram or PST (22.4% vs. 8.5% and 11.9%, respectively; $P < 0.001$). Escitalopram, but not PST, maintained superiority to placebo in the more rigorous intent-to-treat analysis ($P = 0.007$).

The literature relevant to depression and stroke reflects the lack of randomized placebo-controlled trials that have been conducted in this population. Understanding the etiology of the bidirectional nature of the occurrence of stroke and depression may help to inform the field regarding prevention of stroke, treatment of depression, and recognition of risk factors for both disorders.

Overall, the available data support antidepressant treatment for patients who experience depression following stroke. Further studies are needed to refine treatment guidelines for this population.

PARKINSON DISEASE

Depression is believed to affect 40% to 50% of patients with PD,[49] although prevalence rates ranging from 4% to 70% have been reported.[50] As with AD and stroke, the variance in prevalence rates may be attributed to significant symptom overlap between depression and PD; sleep disturbance, fatigue, psychomotor slowing, and difficulty concentrating are associated with both disorders. Furthermore, symptomatic consequences of neurodegeneration such as apathy and problems with concentration, attention, and memory may be misattributed to depression.[51] Elderly patients with PD and depression show less reported sadness, less anhedonia, and less feeling of guilt compared with patients with depression who do not have PD but present with greater concentration difficulties.[52] The overlap of signs and symptoms between depression and PD also has raised questions about the validity of commonly used depression rating scales (such as the HAM-D, MADRS, and Beck Depression Inventory [BDI]) in this patient population.[53–55] It has been suggested that use of the self-rated BDI may more reliably distinguish symptoms related to mood disorder from those attributable to neurodegeneration.[51]

The etiology of depression in PD is unclear.[51,56] That depression is at least in part a psychological reaction to PD-associated disability may be relevant in some cases, but it is likely not operative for those whose depression predates motor signs of PD.[57] Depression in patients with PD could be caused by their antiparkinsonian medications, but evidence in support of this position is weak.[56] An interesting biological hypothesis suggests that mood disorder arises from PD neurodegeneration in regions believed associated with the etiology of depression, including the ventral tegmental area, hypothalamus, dorsal raphe, and locus caeruleus.[51,56] A neurobiologic contribution is supported by higher depression rates in patients with akinetic rigid PD versus classic PD[58] and in patients with right-sided motor symptoms,[57,59] and first-degree relatives of patients with are significantly more likely to experience from depression and anxiety disorders than are first-degree relatives of controls.[60]

Comorbid depression in PD is associated with increased disease severity, poorer motor function, greater activities of daily living impairment, greater bradykinesia and axial rigidity,[61] and greater impairments in fine motor skills[62] and cognitive function.[63,64] Patients with dysthymic disorder or major depression showed general deficits in visuospatial and executive function compared with nondepressed patients with PD, while major depression was associated with additional impairment in working memory and language skills.[65] An international study[66] found that depression has a greater adverse effect on quality of life measures among patients with PD than both disease severity and use of medication.

Placebo-controlled studies of antidepressant treatment in patients with PD are rare. More than 25 years ago, Andersen and associates[67] evaluated nortriptyline, a TCA that inhibits reuptake of both norepinephrine and serotonin, in a small (N = 19), 16-week crossover trial in patients with PD and depression who were receiving levodopa. Using a self-made 31-item scoring system to assess depression, the authors reported that nortriptyline treatment led to a significantly reduced median depression score ($P < 0.001$).

Wermuth and coworkers[68] conducted a 52-week, parallel-group study in 37 subjects comparing the SSRI citalopram (10 mg/day for patients ≥65 years and 20 mg/day for patients <65 years) with placebo. Both active treatment and placebo produced significant reductions in HAM-D scores during the 6-week acute phase of the trial. Of placebo- and of citalopram-treated patients, only 21% and 33%, respectively, completed the continuation phase; citalopram compared with placebo did not result in significantly greater HAM-D score reduction. A randomized study of the SSRI sertraline 50 mg/day or the TCA amitriptyline 25 mg/day demonstrated that both treatments significantly reducing HAM-D scores ($P < 0.001$ and $P < 0.01$, respectively).[69] Sertraline also significantly improved Parkinson's Disease Questionnaire (PDQ-39) mobility ($P < 0.001$), activities of daily living ($P < 0.03$), emotional ($P < 0.001$), and stigma ($P < 0.01$) subscores; the amitriptyline group did not show significant change from baseline in any PDQ-39 subscores. These results are in contrast to the belief of some clinicians that SSRI treatment can worsen motor function in patients with PD.[51,56]

In a small (N = 16), open-label, 4-week trial, reboxetine, a selective norepinephrine reuptake inhibitor, was associated with improvement of depression in patients with PD

Table 1 Antidepressant efficacy in neurological disease

Neurological Disease and Antidepressant Class	Clinical Trial Summary
AD	
TCA	• Mixed efficacy results for imipramine and clomipramine versus placebo[21,22]
	• Worsening cognitive impairment with TCAs noted[21,22]
SSRI	• Mixed efficacy results for sertraline and fluoxetine[24,25]
	• Evidence of efficacy for citalopram; improved cognitive function in subgroup with dementia[23]
Mixed class meta-analysis[104]	• Antidepressants are efficacious for treating depression in AD
	• Tolerability is similar to placebo
	• TCAs may be associated with a decline in cognition
Stroke	
TCA	• Nortriptyline has demonstrated efficacy in treating poststroke depression[42,46]
SSRI	• Citalopram and fluoxetine have demonstrated efficacy in small clinical trials[44,45]
	• Escitalopram demonstrated preventive efficacy in poststroke depression[48]
PD	
TCA	• Improvement in depression was reported for nortriptyline and desipramine in 2 older studies; well-validated measures of depression were not used[67,103]
	• Low-dose amitriptyline significantly reduced HAM-D scores[69]
SSRI	• Citalopram, fluoxetine, fluvoxamine, and sertraline improved depressive symptoms and did not worsen motor symptoms in an open-label trial[102]
	• Sertraline significantly reduced HAM-D scores and improved quality of life[69]
	• Similar efficacy for citalopram and placebo[105]
MS	
TCA	• Desipramine plus psychotherapy demonstrated modest beneficial effect; tolerability issues limited use in patients with MS[94]
SSRI	• Paroxetine was not significantly better than placebo; both groups showed improvement in depression symptoms[95]
	• Sertraline significantly reduced depression scores[98]

AD = Alzheimer disease; HAM-D = Hamilton Depression Rating Scale; MS = multiple sclerosis; PD = Parkinson disease; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

who had discontinued previous antidepressant treatment owing to insufficient clinical improvement or intolerable side effects.[70] Mean HAM-D scores at end point were decreased by 32% ($P < 0.008$); reboxetine was well tolerated in these patients.

Treatment with the dopamine agonist pramipexole significantly reduces the severity and frequency of depression and anhedonia in addition to improving motor deficits.[71] A comparison of pramipexole and sertraline in patients with PD but without motor complications who were treated with levodopa showed that both interventions significantly decreased HAM-D scores ($P < 0.001$ for both treatments) with no significant difference in treatments.[72]

Taken together, these studies of multiple antidepressants with differing effects on serotonergic, noradrenergic and dopaminergic neurotransmitter systems suggest that antidepressant therapy is likely effective in patients with PD, they also suggest that multiple neurotransmitter systems impaired in PD may contribute to the pathophysiology of comorbid depression.

MULTIPLE SCLEROSIS

Estimates of lifetime prevalence of depression in patients with MS range from 19% to 54%, depending on the population sampled (e.g., community versus clinical setting) and the diagnostic criteria used.[73–75] Risk factors for development of major depression in patients with MS include female sex, age <35 years, family history of major depression, and a high level of stress.[75] Research on several variables associated with the development of depression in patients with MS has yielded conflicting results. Although identified as a risk factor by some research, the influence of sex on comorbid MS and depression has also been questioned.[73] A positive association between degree of disability and depression risk has been reported,[73,76,77] but other studies suggest that these variables are independent.[74,78,79] Shorter duration of illness has been linked to increased depression risk,[73,80] suggesting that adjustment to MS may be a factor associated with comorbid depression. Although little is understood regarding the pathogenic factors contributing to depression in MS, proinflammatory cytokines have been suggested as playing a role.[81]

Diagnosis of depression in patients with MS may be complicated by overlapping symptoms such as fatigue, diminished ability to think or concentrate, and sleep disturbance.[82] Comorbid depression in MS increases risk for suicide.[83,84] Reports on the effects of depression on

Table 2 Treatment recommendations for comorbid depression and neurological diseases

Disease	Treatment Recommendations
General neurological disease	• Patients with neurological disease should be periodically screened for depression • Use evidence-based treatment guidelines to facilitate identification of depression comorbid to neurological disease • Educate patients and caretakers about depression symptoms and interventions • Discuss treatment options with patients and caretakers • SSRIs are relatively safe and effective for depression in patients with comorbid depression and neurological disease • When antidepressant medication is initiated, treat and assess for an adequate duration (e.g., 4–6 wk) • Assess treatment response with an evidence-based measure • Schedule regular patient follow-up
AD	• "Start low and go slow" when prescribing any antidepressant • Use caution when prescribing TCAs • Be vigilant for treatment-emergent AEs • Pharmacotherapy may be first-line treatment if patient is harmful to self or others because of severe comorbid depressive symptoms
Stroke	• Use standard measures (e.g., BDI, HAM-D) for depression screening; differentiation of stroke and depression symptoms may be difficult • Anticholinergic AEs may occur with the use of TCAs • Consider using escitalopram to prevent depression in poststroke patients without depression
PD	• Monitor for motor skill worsening and extrapyramidal symptoms when prescribing TCAs or SSRIs • SSRIs are a preferred treatment owing to their low AE profile • TCAs are contraindicated if the patient is already taking an anticholinergic medication • Beneficial anticholinergic effects may occur with TCA use in some patients; caution is still advised • Avoid the TCAs amitriptyline, amoxepine, and doxepine
MS	• SSRIs are considered a well-tolerated first-line agent • Include pharmacotherapy, psychotherapy/cognitive behavioral therapy, or combination therapy in treatment plans • Anticholinergic and cardiac AEs limit utility of TCAs • Screen patients with MS for suicidal ideation due to high cumulative lifetime risk for suicide

AD = Alzheimer disease; AEs = adverse events; BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; MS = multiple sclerosis; PD = Parkinson disease; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

functional impairment in patients with MS vary. Some studies[73,85] have attributed decreased cognitive function to depression, whereas others[80,86,87] have found no connection. Arnett and associates[88] assessed a range of cognitive abilities and reported that depression impaired skills that require greater attention, such as verbal recall, but not others that are more automatic, such as visual recognition.

In a study that measured subjective and objective assessment of functional abilities, Gottberg and colleagues[74] noted impaired memory function in patients with comorbid depression and MS. Although patients with depression and MS scored as well as nondepressed patients with MS on objective tests of walking and manual dexterity, those with depression subjectively reported deficits in areas that included ambulation and mobility. Maor and coworkers[89] correlated depression associated with MS with perceived cognitive impairment but not with objective measures of impairment. An additional study[90] demonstrated that patients with depression and MS were 3 times more likely than their physicians to perceive a higher level of disability. In patients with MS, depression has been shown to exert a greater negative effect than physical disability on self-reported physical health– and mental health–related quality of life.[91]

Treating depression in patients with MS improves adherence to therapy with interferon β-1b.[92] A 6-month follow-up in 85 patients found that those with self-reported depression were more likely to discontinue treatment with interferon; significantly more subjects who were treated with psychotherapy or antidepressants continued interferon therapy compared with patients who received no depression treatment (86% vs. 38%, respectively; $P = 0.003$). Treating depression associated with MS also may yield benefits beyond improved therapeutic compliance. In a 16-week trial,[93] 14 patients with depression and MS were randomized to individual cognitive behavioral therapy, group psychotherapy, or sertraline therapy to examine the relation between depression, depression treatment, and production of interferon-γ, a proinflammatory cytokine that has been linked to both MS pathology and depression. The study results suggested that depression treatment decreases pro-

duction of the cytokine, which potentially could alter the progression of MS.

Few antidepressant treatment trials in patients with MS have been published, and fewer still have been placebo controlled. Schiffer and Wineman[94] randomized 28 patients with MS and major depression to treatment with the TCA desipramine (target serum level 125 to 200 ng/mL) plus individual psychotherapy or placebo plus psychotherapy for 5 weeks. HAM-D change from baseline was significantly greater for patients who received desipramine ($P = 0.02$); a significant difference in favor of desipramine was not observed on the BDI. Tolerability was considered a potential obstacle to treatment in this population. A more recent study[95] compared a flexible-dose of the SSRI paroxetine (10 to 40 mg/day) with placebo in 42 patients with MS and major depression for 12 weeks. Both groups showed improvement in HAM-D scores from pretreatment to posttreatment, with no significant differences between groups. A 16-week psychotherapy trial in patients with MS and depression compared telephone-administered cognitive behavior therapy (CBT) with telephone-administered supportive emotion-focused therapy (SEFT); the results showed significant improvements from baseline in depression and concomitant decrease in disability and fatigue for both interventions.[96] Compared with SEFT, CBT was associated with significantly greater reductions in disability and fatigue even after controlling for reduction in depression, suggesting additional benefits of CBT for patients with MS independent of its effects on depression.

Studies[97–99] in which subjects were randomized to CBT, supportive group therapy, or sertraline found that depression treatment reduced fatigue and improved depression and quality of life; limited evidence suggested that both sertraline and CBT were more effective than group therapy.[98,99] Furthermore, a meta-analysis[82] of depression therapy associated with MS concluded that all treatments are significantly more effective than no treatment, with no significant difference observed between pharmacotherapy and psychotherapy.

Treating depression in patients with MS is critical to the management of this neurologic disorder and is associated with enhanced quality of life, improved treatment adherence, and reduction in fatigue and disability. Nevertheless depression is undertreated in this population, with <50% of patients with depression receiving antidepressant medication.[100,101] Novel approaches to case-management programs may be required to ensure that adequate depression screening and therapy is provided to all patients with MS.

SUMMARY

Depression is significantly more common in people with neurologic disorders than in the general population, and its presence is associated with increased symptom burden, morbidity, and treatment costs. Depression in this patient population is often unrecognized owing to a high level of symptom overlap between mood and neurologic disorders. The development of diagnostic criteria that are specific for depression in the context of neurologic disease is warranted. Until better diagnostic guidance is available, signs and symptoms consistent with the presence of depression in patients with neurologic disorders should prompt the clinician to consider prescribing a carefully monitored trial of antidepressant treatment. In the patient with MS, psychotherapy also should be considered.

The etiology of depression comorbid with neurologic disorders deserves greater research attention. Understanding the neuroanatomical and neurochemical correlates of depression in the context of neurologic disorder may help elucidate depression pathogenesis in general. Neurodegenerative aspects of neurologic disease, such as subcortical white matter hyperintensities and neuronal loss in the ventral tegmental area, hypothalamus, dorsal raphe, and locus caeruleus affect neural networks implicated in the pathobiology of depression, provide important new insights into the neurobiology of depression, and may have implications for depression in patients who are not neurologically compromised. In view of the overall modest remission rates seen in depression treatment trials, new therapeutic strategies are highly desired.

Additional research into the effects of existing antidepressant treatments for depression comorbid with neurologic disorders is clearly needed. The scarcity of controlled trials and the variability of study methodologies reported in the literature complicate interpretation and generalization of results; a summary of pharmacotherapy trials reviewed here (Table 1)[21–25,42,44–46,48,61–69,94,95,98,102–104] underscores this conclusion. The most useful recommendation may be that all treatments appear more effective than no treatment at all, and that therapeutic nihilism is unwarranted. It also should be kept in mind that neurologically impaired patients may be at risk for lower seizure thresholds with bupropion[105] or delirium caused by the anticholinergic effects of TCAs. Clearer guidance for managing comorbid depression and neurologic disorders becomes increasingly important as the population ages (Table 2). New approaches to mental health management within the primary care setting have demonstrated significant improvement in depression outcome at relatively low cost.[106,107] Diagnosis and treatment of patients with depression occurs most commonly in the primary care setting, and the extent to which treatment is optimally managed has a significant bearing on overall health, functioning, morbidity, and treatment costs.

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