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Psychiatric Issues in Multiple Sclerosis

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I. Overview

Multiple sclerosis (MS) is the most common chronic disabling central nervous system (CNS) disease in young adults, affecting 1 in 1,000 people in Western countries. [1] MS is a demyelinating disease of the CNS; a diagnosis of MS requires the occurrence of at least two neurological events consistent with demyelination in the CNS that are separated temporally and anatomically. Early onset (typically between 20 and 40 years of age) and long duration of disease result in tremendous individual, family, and societal costs as well as reductions in quality of life and work productivity. [2] MS has a variable and unpredictable course, with symptoms that can include weakness, visual loss, bowel and bladder incontinence, fatigue, cognitive impairment and mood symptoms. Persons with MS appear to have a higher prevalence of a number of psychiatric symptoms and disorders (Table 1). Depression and anxiety, in particular, have been associated with decreased adherence to treatment [3], functional status [4], and quality of life. [5] This review aims to summarize the existing literature on the epidemiology, impact, and treatment of psychiatric disorders among persons with MS, and to identify the areas in which further research is needed.

II. Impact of Psychiatric Disorders on MS

The most compelling reason to investigate psychiatric disorders among persons with MS is that reported rates of completed suicide in MS populations are high [6], and psychiatric disorders appear to be the major risk factor for suicidality [7]. Death certificate-based reviews indicate that suicide may be the cause of death for MS clinic patients in as many as 15% of all cases. [8] In retrospective analyses of completed suicides in MS populations, depression has been the most important risk factor for suicide. [9] Anxiety disorders also appear to be linked to suicidal intent and self-harm attempts. [10] Social isolation, a history of previous suicide attempts, and recent functional deterioration also appear to be important determinants of suicidal intent [11]; but level of neurological disability, per se, does not appear to be a risk factor for suicide. This epidemiological research led an expert consensus panel to conclude that the single most useful step that can be taken with regard to the primary prevention of suicide in MS is better identification and treatment of depressive disorders [12].

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Psychiatric disorders appear to have profound effects on wide-ranging aspects of the lives of persons with MS. Depression has been the most studied psychiatric disorder among persons with MS, with only a limited number of rigorous studies of the prevalence and impact of anxiety disorders, substance use disorders, or serious mental illness such as bipolar disorder or schizophrenia. MS patients with depression report subjective cognitive difficulties, including memory complaints [13], and in some studies, perform more poorly on objective neuropsychological measures relative to non-depressed MS patients. [14]. Quality of life is significantly lower among depressed MS patients than among non-depressed control patients with MS, even when controlling for factors such as level of neurologic disability and fatigue. [5] Depression adversely affects functional status among patients with MS, such as increased time lost from work. [15] MS patients with depression experience disruption of their social support and family systems beyond what can be attributed to neurologic disease factors alone. There is also evidence that depression decreases adherence to treatment regimens for MS, and that adherence improves with treatment of depression. [3] Lastly, a recent meta-analysis demonstrates a consistent association between stressful life events and subsequent MS exacerbation. [16] However, there is no definitive evidence that major depressive disorder or other psychiatric disorders affect the neurobiologic course of MS.

III. Psychiatric Effects of MS Treatment

Pharmacological treatments for MS include corticosteroids, beta interferon, glatiramer acetate, and immunosuppressants. Corticosteroids, which are used in high doses for short courses to treat acute exacerbations, have been associated with a variety of neuropsychiatric side effects, including increased energy, decreased sleep, and significant mood symptoms such as mood lability, euphoria, and depressed mood. [17–18] Epidemiologic studies suggest an incidence of neuropsychiatric side effects from corticosteroid treatment of 5–8%. [18–19] It is difficult to predict which patients are at highest risk for the emergence of neuropsychiatric symptoms during corticosteroid treatment. There is no clear evidence that a previous psychiatric history increases the risk of adverse neuropsychiatric events from steroid treatment [20], and overall there is little data to help identify individuals who are at increased risk. The potential risks of multiple courses of steroid treatment have not been explored.

The majority (75%) of cases of neuropsychiatric side effects from corticosteroids fit an affective profile, of mania and/or depression. Mania occurs more frequently than depression. Psychotic symptoms (in particular, hallucinations) are present in up to half of these cases. Fewer than 25% of cases of neuropsychiatric side effects have symptoms consistent with delirium. Psychotic symptoms typically last about a week, while affective symptoms often last for longer periods. While there have been no large studies of neuropsychiatric side effects of corticosteroids conducted specifically among MS patients, a study of a short course (14 days) of corticosteroid treatment in asthma patients demonstrated mild mood changes occurred early (3–7 days) into the treatment and returned to baseline 10 days after discontinuation prednisone. [21] Depressive symptoms can occur following the initial administration of corticosteroids, with long-term use, or with discontinuation of the steroid dosing. Cognitive deficits have been reported in association with even short-term steroid treatment. [22] Treatment of neuropsychiatric side effects involves tapering of the corticosteroid dose and administration of antidepressant or antipsychotic medications for symptom relief. Across studies, the outcome is complete recovery in over 90% of cases. [23]

Currently approved disease-modifying therapies for MS include glatiramer acetate and interferon (IFN) beta. [24] Glatiramer acetate has not been associated with neuropsychiatric side effects. [12] There are two types of IFN-beta approved for the treatment of MS. IFN-beta 1a (Avonex, Rebif) is administered through an intramuscular injection, given weekly or monthly. IFN-beta 1b (Betaseron) is administered by subcutaneous injection every other day.

The side effects of both IFN 1a and 1b include flu-like symptoms (fever and myalgias), elevations in liver function tests, and anemia. The data regarding the risk of mood symptoms related to IFN use is conflicting. Several clinical trials have reported an increase in depression in patients during the first two to six months of treatment with both interferon beta-1b [25] and interferon beta-1a [26], but it appears that these increases in depressive symptoms are more related to pretreatment levels of depression than to the administration of IFN. [27] However, two randomized controlled trials have found that depression is not an effect of treatment with IFN-beta 1a. In the SPECTRIMS trial of Rebif in secondary progressive MS, depression ratings were no different in the IFN group compared to the placebo group. [28] A second study found no change on Beck Depression Inventory scores in a cohort of MS patients before and twelve months after initiation of IFN beta 1a. [29] Based on the results of these, it appears there is no clear evidence that the administration of interferon to patients with MS increases the risk for depressive disorders. [30] Nonetheless, given the high prevalence of depression among persons with MS, expert panels have recommended that patients should be educated about depression and complete a measure of depression severity at regular intervals during the course of IFN treatment. [31]

There have been no reports to date of psychiatric side effects associated with two newer pharmacotherapies for MS. Mitoxantrone (Novantrone), an immunosuppressant, is approved for treatment of secondary progressive, progressive-relapsing, and worsening relapsing-remitting MS. Natalizumab (Tysabri) is a monoclonal antibody against integrin- α 4 that was approved by the FDA in 2006 for treatment of patients with relapsing forms of MS who have not responded to or are unable to tolerate the other treatments of MS. Because natalizumab increases the risk of progressive multifocal leukoencephalopathy, this medication is available only through a special restricted distribution program and not widely used.

IV. Major Depressive Disorder

Epidemiology and Clinical Correlates of Depression

Depression may be more common in MS than in other chronic neurological conditions. [32] The 12-month prevalence of major depressive disorder (MDD) among persons with MS is 15.7%, nearly double the prevalence of MDD in persons without MS (7.4%). [33] Reports of the lifetime risk for major depressive disorder (MDD) in MS populations have ranged from 27–54%. [32–34] The prevalence of clinically significant depressive symptoms is much higher [35] than the prevalence of major depressive disorder, but few studies have evaluated other depressive disorders such as dysthymia. [36]

The depressive syndromes associated with MS occur throughout the natural history of the disease, including in patients with very mild forms of MS. [37] Some studies have found associations between depression and severity of MS as reflected by degree of disability [38], but other studies have not replicated these findings. [33,39] The association of depression with the duration of MS illness is also unclear, with most studies finding no correlation [38–39], but others reporting a greater risk of depression in the first year after diagnosis [35] and in patients younger than 35. [40] Most studies have not found a correlation between depression and female gender among persons with MS. [35,38–39]

Neurobiology of Depression in MS

Several lines of evidence suggest that neurobiological risk factors specifically associated with MS contribute to the increased incidence of depressive disorders among MS patients. There is, however, no clear consensus about what the neurobiological differences between depressed MS patients and non-depressed MS patients might be. While some comparative studies using MRI have found no differences in lesion distribution between depressed and non-depressed

MS patients [38], other studies have suggested an increase in lesions in specific brain areas among depressed MS patients, including the right temporal lobe [41], the left hemisphere suprasylvian region [42], and the superior frontal or parietal regions. [43]

Similarly, little is known about the specific nature of the interactions between the neuroimmunology of MS and depressive disorders. Hypothalamic feedback regulation is abnormal in many MS patients with 50% of MS patients demonstrating a failure of suppression on the dexamethasone suppression test. This is similar to the pattern seen in many patients with major depressive episodes. [44] Failure to respond to dexamethasone challenge has also been associated with the presence of gadolinium enhancing lesions on MRI in MS patients, suggesting that some of the depressive symptomatology in MS could be related to disease activity. [45]

Treatment of Depression in MS

Depression in MS patients appears to be under-detected and under-treated by neurologists, consistent with studies of primary care samples. [46] In a study of 260 outpatients with MS treated by 35 neurologists in a large health maintenance organization, 26% of patients met criteria for major depressive disorder (MDD). Among these patients with MDD, 66% received no antidepressant medication and 4.7% received subthreshold doses from their neurologist. [47] Despite the development of reliable, user-friendly screening tools to detect depression in MS patients, [48] and the recommendation by expert consensus panels for routine screening for MDD in MS clinics, screening has not been widely adopted.

Treatment for depression in persons with MS should be individualized and involve psychotherapy, psychopharmacology, or a combination. [12] A meta-analysis published in 1999 found that both psychotherapy and pharmacotherapy are effective for decreasing depressive symptoms in persons with MS; but only five studies were of sufficient methodological rigor (randomized clinical trial, objective measure of depressive symptoms) to be included in the meta-analysis. [49]

Pharmacotherapy

Although antidepressant use is common among persons with MS [50], the literature on the effectiveness of antidepressants in MS is small and largely anecdotal. Only two randomized trials of pharmacotherapy for depression have been published to date, neither of which utilized a placebo control. A small (N = 28) trial found desipramine to be effective relative to a case management control. [51] The second trial evaluated the efficacy of sertraline (n = 21) relative to two psychological treatments: individual cognitive behavior therapy (CBT; n = 20) and supportive-expressive group therapy (SET; n = 22). In this study, 24% of those in the sertraline group had a treatment response as compared to 50% in the CBT group and 14% in the SET group. Attrition was greatest for the sertraline group, with 29% dropping out prior to completing the study. [52]

Several conclusions can be drawn from the available literature on pharmacotherapy for depression in MS. First, antidepressants reduce depressive symptom severity in persons with MS and should be considered for treating MDD in this patient population. However, although depressive symptoms may be responsive to pharmacotherapy, they do not necessarily result in full remission of symptoms for all individuals with MS who use them. Research on methods for identifying MS patients or symptoms that are particularly responsive to antidepressant medications would improve the treatment of MDD among MS patients. Given the clinical characteristics of MS, side effects of antidepressants may be particularly bothersome in this population, and lead to higher rates of non-adherence and premature treatment termination in clinical practice than in clinical trials. The small sample sizes in the existing studies suggest

that it is difficult to enroll large numbers of participants into pharmacotherapy clinical trials in this disease group; future research evaluating antidepressants should consider multi-center trials.

C.2. Psychotherapy

Several randomized controlled trials have demonstrated the effectiveness of CBT for treatment of major depressive disorder among persons with MS. [52–53] In these studies, response rates to CBT have been equal to or higher than response rates to antidepressant medications or to other psychotherapy modalities, with response rates approaching 50% of patients. [52] Moreover, attrition is typically very low for the CBT intervention in these trials (5%). Recent studies have also shown that CBT delivered by telephone is an effective form of psychotherapy for depression in MS relative to usual care [53] and relative to a telephone delivered supportive emotion-focused therapy. [54] Attrition was also low for the telephone delivered interventions, and in one study, adherence to MS disease-modifying medications was significantly better at follow-up among those who participated in the telephone CBT. [54] Telephone delivered CBT shows considerable promise as a viable and potentially cost-effective treatment for MDD that may overcome many of the common barriers to face-to-face treatment such as fatigue, stigma, and logistical issues (lack of access to treatment, transportation, child care, or financial limitations). Unfortunately, at this time, psychotherapy delivered by telephone is not typically covered by most health insurance carriers. Interpersonal therapy or behavioral activation have not been empirically evaluated as depression treatments in the MS literature. The Goldman Consensus group has recommended that psychotherapy, particularly cognitive behavior therapy (CBT), be offered as a treatment option for persons with MS and depression. [12] As skills learned through CBT produce improvements beyond the nonspecific effects of supportive treatment [52], standard CBT for depression may be considered as the treatment of choice.

Exercise

Although physical exercise has not been formally studied as a treatment for major depression in MS, it has widespread beneficial effects among persons with MS, including improvements in mood, pain, fatigue, quality of life, sexual functioning, recreation, and psychosocial functioning. [55] The effect of exercise on MDD has been studied in healthy adults, persons with psychiatric conditions, and older adults. [56] Across studies, exercise appears to be more beneficial than no treatment, and in some studies it has been as effective as antidepressant medication and psychotherapy for mild to moderate depression. [57] Exercise has also been associated with lower depression relapse rates compared to pharmacotherapy. [56,58] Moderate exercise (walking 20 minutes a day at 60% maximum heart rate) has been more effective than vigorous exercise and is associated with fewer drop outs. [59]

Anxiety Disorders in MS

In contrast to the extensive literature on depression in patients with MS, less attention has been paid to anxiety disorders. Several studies using self-report scales of anxiety symptoms have found a point prevalence of clinically significant anxiety ranging from 25–41%. [38,60–61] Only two studies have used structured clinical interviews to evaluate formal diagnoses of anxiety disorders, and both of these found lifetime prevalence rates of 36% [10,62], which is much higher than the 25% lifetime rate of anxiety disorders in the general population reported in the National Comorbidity Survey. [63] Generalized anxiety disorder appears to be the most common anxiety disorder among persons with MS, with 18.6% of patients meeting criteria for this disorder. [10,62] Panic disorder and obsessive compulsive disorder may also be much more common among MS patients than among the general population. MS patients with anxiety disorders were more likely to be female, and to have a lifetime diagnosis of major depressive disorder or alcohol abuse. They were also more likely to report greater social stress, less social

support and to have contemplated suicide. In one of the studies, only 34% of those with an anxiety disorder had previously been given a documented psychiatric diagnosis; and none were given a diagnosis of an anxiety disorder. More than half of the patients were not receiving any treatment. [10] There have been no studies specifically evaluating PTSD among persons with MS.

Serious Mental Illness in MS

Numerous case reports have documented an association between bipolar disorder and MS. [64–67] Bipolar symptoms may precede other neurological signs of MS, and there have been reports of MS presenting as frank mania. [66–67] Affective lability, in particular, may occur in tandem with an MS exacerbation. Some researchers have hypothesized that the comorbidity of bipolar disorder may be related to the location of the MS lesions. [65] Several clinical studies have identified elevated rates of MS among patients with bipolar disorder. [68–69] Other small clinical studies have identified elevated rates of bipolar disorder among MS patients [36,70], with some reporting bipolar disorder in more than 10% of MS patients. [36] The few epidemiologic studies that have been conducted have documented the comorbidity of MS and bipolar disorder at more than twice the expected rate based on the prevalence of each disorder in the population. [70–71] In a recent study of more than 650 outpatients with MS, the prevalence of bipolar disorder was 0.3 %, significantly greater than the general population prevalence of 0.2 %. [72] These epidemiologic studies have been limited by either small sample sizes or the method of diagnosing bipolar disorder. To date, there have been no large, population-based epidemiologic studies of the prevalence of bipolar disorder among persons with MS. Lastly, there have been no epidemiologic studies of the relationship between multiple sclerosis and schizophrenia spectrum disorders.

Substance Use Disorders in MS

Alcohol and illicit drug use may be more problematic in people with MS than in the general population, potentially causing further neurologic damage to an already compromised central nervous system, or leading to dangerous interactions with prescription medications. Heavy alcohol use can magnify the subtle cognitive impairment associated with MS [73], and has been shown to cause persistent cognitive impairment, even in persons who do not meet the criteria for alcohol abuse or dependence. [74] Moreover, alcohol tolerance may diminish as MS progresses, resulting in more impaired balance and coordination. [73] Substance abuse is associated with a poorer psychological adjustment in people with disabilities [75], and with suicidal intent in persons with MS. [9] Substance abuse may exacerbate depression symptoms, and complicate treatment of co-morbid depression. [76]

Alcohol use disorders

Several studies have shown higher rates of “problem drinking” among MS patients (when compared to the general population). [40,77–78] In a detailed study of alcohol consumption patterns of 140 MS clinic patients, no subjects met criteria for alcohol dependence but 13.6% had a lifetime prevalence of alcohol abuse by structured psychiatric interview (SCID-IV). [79] An additional 5% of subjects met the national guidelines criteria for “problem drinking” [80] In a large community-based sample, 14% of subjects screened positive for possible alcohol abuse within the previous month, using the alcohol screen from the Patient Health Questionnaire. [81] In this study, alcohol misuse was significantly and independently correlated with depression symptom severity. [78] Since rates of alcohol problems are comparable to primary medical care settings, MS clinicians should consider routine screening for alcohol misuse as is recommended in primary care. [82] As with depression, brief screening measures, such as the CAGE [83] or the PHQ alcohol screen [81] are relatively easy to integrate into routine clinical practice. It is important to recognize that physician advice to stop or cut

down on alcohol use is an effective means of reducing problem drinking, particularly for those patients with less severe alcohol problems. [84]

Substance use disorders

The only published study reporting substance abuse rates among persons with MS was a community survey in which drug abuse was evaluated by a single question from the 1992 National Household Survey on Drug Abuse. [85] In this study, 18.7% of subjects reported either drug misuse or possible alcohol abuse within the past month. Significantly higher rates of alcohol and/or drug misuse were found among people with MS who were younger, still employed, and had less severe MS. [78] **Cannabis.** Cannabinoids have been purported to alleviate a variety of MS-related symptoms including spasticity, pain, tremor and bladder dysfunction [86], but clinical trials of cannabinoids in MS have not consistently demonstrated beneficial effects. A large randomized controlled trial (n=660) compared the effects of oral cannabis extracts with pure oral THC and placebo on spasticity. The study found no differences with respect to spasticity, but did note significant subjective improvements in pain and sleep. [87] Even though cannabis remains illegal and there is limited evidence for its clinical efficacy in relieving MS symptoms, almost a third of MS patients have used cannabis in an attempt to alleviate symptoms [88], with rates of current medicinal cannabis use of 14–18%. [88–89] In a large (n=337) survey of MS clinic patients at three hospital-based clinics, 43% reported using cannabis at least once in their lifetime, with first cannabis use being evenly split between before and after MS diagnosis. 90% of the subjects who started using cannabis after MS diagnosis reported that they started using it because of MS symptoms, most commonly for pain and spasms. The majority of patients using it for these symptoms reported benefit. Seventy-one percent of individuals who had never used cannabis stated that they would try the drug if it were legal or available by prescription. [88]

VIII. Pseudobulbar affect

In addition to mood disorders, MS patients may also experience disorders of affect, typically an expression of affect that is not representative of the underlying emotion. [90] Some MS patients may laugh or cry out of proportion to or in the absence of the expected feeling, a phenomenon which has been referred to as “pathological laughing and crying”, or pseudobulbar affect (PBA). PBA has been recognized in association with MS for many years, but even today its etiology is not well understood. PBA has traditionally been considered to be a disconnection syndrome resulting in the loss of brainstem inhibition of a putative center for laughing and crying. PBA occurs in approximately 10% of MS patients. [90] In general, MS patients with PBA have greater physical disability and are more likely to be in the chronic progressive stage of the disease (compared to MS patients not exhibiting PBA). Evidence suggests that PBA can be modulated through pharmacological intervention. Most commonly, MS patients are treated with tricyclic antidepressants [91] or selective serotonin reuptake inhibitors. [92] There is evidence that other medications, such as levodopa or dextromethorphan/quinidine may also be beneficial [93–94], but these are not commonly used in practice for this indication.

Resilience and posttraumatic growth

Although psychiatric conditions are highly prevalent among individuals living with MS, many persons with MS do not exhibit clinically significant levels of depression, anxiety, or other serious mental illness. The ability to maintain psychological well being and functioning in the face of adversity, such as loss, trauma, and serious medical illness is often referred to as **resilience**. [95] Being “resilient” does not mean that the individual never experiences any negative emotions, thoughts, or actions in response to adversity or loss. Such experiences are common and may in fact be part of the resilience process, but in resilient individuals, they are

typically transient, occur with positive emotions, and do not significantly interfere with functioning. [95] **Posttraumatic growth** has been defined as positive psychological changes resulting from or in response to a challenging circumstance such as a traumatic event or loss. [96] It is thought to involve more than resilience, namely, growth and improved functioning beyond a return to a pre-event level of psychological functioning. Posttraumatic growth can be manifest in a variety of ways, including an increased appreciation for life, feeling increased personal strength, experiencing improved interpersonal relationships, changing life priorities, gaining positive spiritual changes, or finding new meaning and purpose in life. Future research should be conducted using theoretically driven models of psychosocial functioning that take into account not only what goes “wrong” after the onset of MS, but perhaps more importantly, on what goes “right”, and the risk and protective factors predicting both. Such research may lead to greater recognition of and interventions for promoting psychological well-being after the onset of MS.

X. Summary

Major depressive disorder and anxiety disorders are highly prevalent among persons with MS, and have been associated with decreased adherence to MS treatment, and poorer functional status and quality of life. Effective treatment is available for major depressive disorder, but this disorder continues to be under-detected and under-treated by MS providers. Treatment with pharmacotherapy is particularly challenging in this patient population, given the somatic symptom overlap between MS and depression, and the increased burden of side effects. Larger randomized controlled trials are needed to further elucidate the effectiveness of pharmacotherapy and identification of subgroups of patients who would benefit from this type of depression treatment. There have been few rigorous studies of the prevalence and impact of anxiety disorders, substance use disorders, or serious mental illness such as bipolar disorder or schizophrenia, in MS samples.

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Table 1

Increased prevalence of psychiatric disorders among persons with MS compared to the general population

Disorder	Prevalence in MS	Prevalence in general population
Major depressive disorder, 12-month	15.7% [33]	7.4% [33]
Major depressive disorder, lifetime	22.8% [40]	16.2% [97]
Any anxiety disorder, lifetime	36% [10,62]	25% [63]
Generalized anxiety disorder	18.6% [10,62]	3.0% [98]
Bipolar disorder, lifetime	0.3% [72]	0.2% [99]
Alcohol abuse, lifetime	13.6% [77]	7.4% [100]
Substance misuse, past month	18.7% [78]	11.1% [100]