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Depression in People With Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) affecting an estimated 2.8 million people worldwide in 2020.[1,2] Living with a chronic disease like MS increases the risk of developing mood disorders, especially depression and anxiety. Multiple studies have reported significantly higher rates of depression and anxiety in people with MS than in the general population. The lifetime prevalence for depression in people living with MS ranges from 37% to 54%.[3] That translates to between 1,036,000 and 1,512,000 people experiencing depression as part of their MS journey. The graph below compares the estimated prevalence of depression among people with MS to those with other neurological conditions and the general population.[3-10]

It is also important to note that depression is more common in people with MS who are African American or Hispanic American.[11]

This special supplement focuses on persistent clinical depression, in which symptoms can last from 2 weeks to several months. Symptoms often reported by patients may include sadness, irritability, loss of interest in activities that once brought pleasure, loss or increase in appetite, sleep disturbances, fatigue, problems with concentration, feelings of worthlessness or guilt, and thoughts of death or suicide.[12] Depression is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the International Classification of Diseases (ICD-10) as a persistent depressed mood that causes significant distress and impairment in psychological and social functioning.[13]

Depression, in its various forms, is in fact one of the most common symptoms of MS.[12] However, the nature of depression in people with MS is not yet fully understood.[12] Research is uncovering increasingly complex etiology of depression in people with MS, which includes changes in the brain due to MS, genetic predispositions, early life experiences, and current circumstances. Despite these findings, a causal link between depression and an individual's degree of disability due to MS has not been established.[14] As demonstrated by Yuseuf et al, depression and anxiety can be present during the prodromal period of MS.[15]

Also, many studies have emerged linking inflammation to depression. Leighton et al cited that evidence for this link between inflammation and depression centers around these observations: Many patients experiencing depression present with elevated inflammatory cytokines even in the absence of medical illness, and inflammatory diseases are associated with higher rates of depression than noninflammatory illnesses.[16]

In addition, depression can be a side effect of some of the medications used to treat MS.[17] The National Multiple Sclerosis Society's brochure "Depression and Multiple Sclerosis" warns that some disease-modifying medications should be used with caution by individuals who have depressive symptoms or have experienced a depressive disorder in the past.[12]

The purpose of this supplement is to summarize some of the recent research on the subject of depression among people with MS in order to inform your clinical decision-making and patient care initiatives.

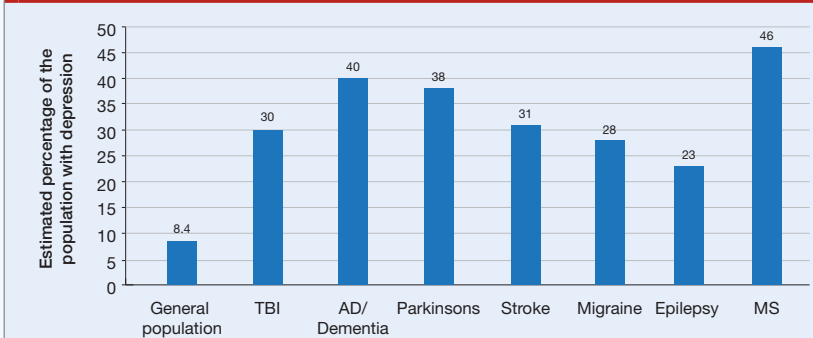
Symptom Interconnectivity

Chitnis et al, based on their review of 252 articles, believe that the co-occurrence of fatigue, cognitive impairment, depression, and pain in people with MS is associated with neuroanatomical changes, pro-inflammatory cytokines, dysregulation of monoaminergic pathways, and a hyperactive hypothalamic-pituitary adrenal (HPA) axis.[2] They further believe that finding a common pathway for these symptoms will impact both inflammation and neuroprotection.[2]

Interestingly, in their literature review, they found that depression is associated with the following manifestations of MS:[2]

- Global changes to the structure of the frontal, parietal, and/or temporal lobes of the brain and cortex
- Damage to subcortical structures, such as the caudate and nucleus accumbens, thalamus, and corpus callosum

Estimated Prevalence of Depression Across Other Neurologic Conditions [3-11]



Abbreviations: AD, Alzheimer disease; MS, multiple sclerosis; TBI, traumatic brain injury.

• Cortical reorganization that attempts to mitigate the effects of damage and the breakdown of neural networks

• Dysregulation of the HPA axis, which controls stress hormones

• Inflammation from cytokines and T cells

• Monoamine disruption, especially serotonin, dopamine, noradrenaline, and the kynurenine pathway that regulate mood.

The authors concluded that addressing the common pathways of these MS symptoms (fatigue, cognitive impairment, depression, and pain) is crucial and symptomatic therapy may be an unmet need among people with MS. They noted that, in a sample of 35,755 patients involved in the studies reviewed, only 74.5% of patients received either pharmacologic or non-pharmacologic therapy.[2]

Additionally, Feinstein et al studied the connection between MS and depression by analyzing a series of brain imaging studies. While the authors maintained that even with technological advances in brain imaging, such images only provide part of the etiology picture, the research is interesting. Table 1 provides details on the various studies they analyzed.[18]

While more imaging studies are needed within larger populations, these findings suggest that subtle brain changes may also underpin clinically significant depression.[10]

In addition, Feinstein et al theorized that inflammation may be the key to understanding psychiatric conditions. Several studies on schizophrenia, bipolar disorder, and major depression report that patients have increased circulating levels of molecules associated with inflammation. This situation might reflect the fact that proinflammatory cytokines are potent activators of the HPA axis, and the release of these cytokines leads to hyper-secretion of adrenal glucocorticoids, which have been linked to major depression.[18]

To support the idea that both structural changes in the central nervous system (CNS), such as demyelination and neurodegeneration, as well as inflammation in the CNS caused by cells of the immune system, Lazo-Gomez et al examined both processes and concluded that neuroinflammation and neurodegeneration are not isolated phenomena and should be the focus of developing therapies.[19]

Does Depression Hasten Progression of MS?

In a Swedish study, Binzer et al found a significant relationship between depression and disability progression among both men and women with MS. Their results suggest that the disease course of people with MS with medically recognized depression (ie, depression that is diagnosed and treated by a specialist with antidepressant medication) progress significantly faster than people with MS without indications of depression. However, the authors theorize that the association between depression and worsening MS may have other causes:

• Mood may be impacted by the course of the disease

• People with MS and depression are more likely to smoke, which can accelerate progression

• People with MS and depression are less likely to adhere to their DMT, which increases the risk for disability progression

• People with MS and depression are less likely to exercise, but exercise seems to be important for quality of life (QoL) and brain volume[20]

TABLE 1. Multiple Sclerosis and Depression: Brain-Imaging Studies[18]

Study	Number of participants	Assessment tools	Imaging modality	Imaging findings associated with depression	Laterality of findings
Sabatini et al.[21]	20 (10 depressed, 10 nondepressed)	DSM-III *	Single-photon emission CT	Increased perfusion in limbic areas	Left
Pujol et al.[22,23]	45	BDI-II#	T2-weighted MRI	Increased lesion load in the arcuate fasciculus associated with somatic and affective symptoms	Left
Fassbender et al.[24]	73 (23 with RRMS, 50 healthy controls)	DSM-III-R,* HRSD, ZSRDS	Gadolinium-enhanced MRI	Increased lesion load linked to increased cortisol and a positive dexamathasone supression test	None reported
Bakshi et al.[25]	48 (19 depressed, 29 nondepressed)	DSM-IV,* HRSD, BDI	T1-weighted MRI	Superior frontal, superior parietal and temporal lesions; enlargement of lateral and third ventricles; frontal atrophy	Left
Berg et al.[26]	78	DSM-IV *	T2-weighted MRI	Increased lesion load in temporal lobe	Right
Zorzon et al.[27]	90	DSM-IV,* HRSD	MRI	Atrophy in the left frontal lobe; severity of depressive symptoms associated with reduced right temporal lobe volume	Bilateral
Feinstein et al.[28]	40 (21 depressed, 19 nondepressed)	DSM-IV *	T1-weighted and T2-weighted MRI	Increased lesion volume in medial inferior prefrontal cortex; anterior temporal atrophy	Left
Passamonti et al.[29]	24 (12 with MS, 12 healthy controls)	CMDI, HAM-A#	Functional MRI	Reduced functional connectivity between ventrolateral prefrontal cortex and amygdala	Bilateral
Gold et al.[30]	49 (20 with RRMS, 29 healthy controls)	BDI-II#	MRI	Hippocampal atrophy, particularly in CA2, CA3, and dentate gyrus, linked to increased cortisol	Bilateral
Feinstein et al.[31]	62 (30 depressed, 32 nondepressed)	BDI-II#	T1-weighted MRI plus diffusion tensor imaging	Increased lesion volume in right medial inferior frontal region; atrophy of left superior frontal region; reduced fractional anisotrophy; higher mean diffusivity in left anterior temporal normal-appearing white and grey matter; higher mean diffusivity in right inferior frontal hyperintense lesions	Bilateral
Kly et al.[32]	88 (72 with MS, 16 healthy controls)	BDI-II#	MRI	Increased temporal horn volume correlated with mood-related aspects of the BDI-II, but not with somatic items	Left
Gold et al.[33]	109 women with MS	CES-D#	MRI	Reduced hippocampal thickness	Right

*Participants were diagnosed with major depressive disorder by means of a structured clinical interview. #Depression was measured using rating scales, but no formal diagnosis was made. Abbreviations: BDI, Beck Depression Inventory; CES-D, Centre for Epidemiologic Studies–Depression Scale; CMDI, Chicago Multiscale Depression Inventory; DSM, *Diagnostic Statistical Manual for Mental Disorders*; HAM-A, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; MS, multiple sclerosis; RRMS, relapsing-remitting MS; ZSRDS, Zung Self-Report Depression Scale.

However, a 10-year study conducted by Koch et al suggest that depression in MS is unrelated to disease progression and that depression tends to persist at roughly the same level over time. (Note: authors also studied fatigue in the same study.) In their assessment of progression, the authors showed that people who were depressed at baseline were no more likely to have MS progression than people who were not depressed at baseline. They concluded that because of the length of follow-up and the frequency of monitoring from their study, the data are stronger and more reliable than data solely from imaging studies. Therefore, they believe that mechanisms other than progressive axonal degeneration underlie depression in MS. Koch et al do not, however, implicate or study the role of inflammation.[34]

Does the Progression of MS Increase Depression?

Feinstein et al, found that depression is less common early in MS than in its later stages. As MS progresses, rates of depression increase, although the findings are inconsistent when rates of depression are compared in people with relapsing MS and progressive MS. Higher rates of depression in relapsing MS over progressive MS suggest a possible role for inflammatory processes in the pathogenesis of depression.[18]

Depression Has Other, Invisible Symptoms

The authors of the many articles reviewed for this supplement recognize that the interconnection between MS, and depression often coincides with other comorbid features of MS, namely pain, fatigue, mood, sexual dysfunction, and cognitive impairment.[35-37]

Salora et al, in their analysis of depression in MS, found that pain, fatigue, and depression have a complex connection in people with MS. They proposed that these symptoms should be considered as a cluster that, when viewed as a whole, contribute to a poor QoL. The authors also included cognitive dysfunction as a major cause of disability in people with MS. Cognitive dysfunction manifests itself in losses in memory, learning, attention, and information processing speeds. Additionally, they recognized that depression and cognition are linked in some. They noted that people with depression and MS experience lower performance in working memory and information processing speeds, perhaps because, in part, cognitive impairment and mood disorders have the same underlying brain pathology.[35]

A study by Domingo et al sought to explore the prevalence of sexual dysfunction in an MS clinic population and identify the variables associated with sexual dysfunction in MS. The authors found that 46.9% of the study population experienced primary sexual dysfunction, 45.1% experienced secondary sexual dysfunction, and 29.6% experienced tertiary sexual dysfunction. Importantly, the authors observed that sexual dysfunction is a prevalent symptom in people with MS that goes unreported by patients. They also noted that assessment and treatment of depression can be a starting point for addressing sexual dysfunction in these people.[36,37]

Several authors, including McKay et al studied patients in MS clinics in Canada over a 2-year period, and found that alcohol dependence and smoking were associated with depression in this cohort. Their findings strongly support that having healthcare providers monitor and promote cessation of smoking and alcohol use will contribute to the improvement of mental health in people with MS.[38]

In addition, a study conducted by Bruce et al that examined the association between long-term adherence to disease- modifying therapies and neuropsychiatric symptoms of MS found that almost 63% of people with MS and a current mood or anxiety disorder showed varied or poor adherence during the study period.[39] Therefore, an effect of depression may be that MS progression is accelerated due to patients not taking their MS medications as prescribed.

Recognizing, Diagnosing, and Treating Depression in People With MS

From a healthcare standpoint, the National Multiple Sclerosis Society recognizes that depression, when it occurs, deserves the same careful assessment and treatment as other symptoms of MS. Furthermore, if left untreated, depression reduces QoL and may exacerbate other symptoms, such as fatigue, pain, and cognitive impairment. Additionally, increased depression may lead to suicidal thoughts or actions.[12]

There is a strong recommendation from the AAN Evidence Based Guidelines for healthcare providers to screen all people with MS for depression, as it is often an important part of a person's MS journey.[39]

The National Multiple Sclerosis Society encourages people living with MS to ask themselves the following questions regularly:[12]

- During the past 2 weeks, have I felt down, depressed, or hopeless?
- During the past 2 weeks, have I had less interest in or pleasure from doing things I normally like?

For healthcare professionals, the National Multiple Sclerosis Society encourages asking their patients these questions at every patient visit. In addition, healthcare professionals should attempt to determine if their patient is looking positively toward the future.

However, to truly evaluate patients, healthcare professionals should consider using one of the recognized tools for assessing depression in people with MS. These scales include

- Beck Depression Inventory
- Beck Fast Screen
- Center for Epidemiologic Studies Depression rating scale (CES-D)
- Hospital Anxiety and Depression Scale (HADS-D)
- Patient Health Questionnaire (PHQ-9 or PHQ-2)
- Structured Clinical Interview for DSM (SCID)[27]

In a study comparing SCID (considered the gold standard for assessment tools) to the four scales listed above it, considered the gold standard of assessment tools), Patten et al found that, while all scales performed well (in terms of sensitivity and specificity), they preferred the PHQ-9 because it is brief and available in the public domain.[40] Also, Kroenke et al found that PHQ-9 is a reliable and valid measure of the severity of depression and that its brevity enhances its use as a clinical tool.[41]

It is important to note that the American Academy of Neurology, in its bulletin, *Assessment and Management of Psychiatric Disorders in Individuals With Multiple Sclerosis*, reports that the evidence to support the use of the Beck Depression Inventory is weak.[39]

There are options for treating depression in people with MS. The first avenue to explore is cognitive-behavioral therapy (CBT), commonly referred to as talk therapy. Feinstein et al reported sufficient evidence supporting the use of CBT in people with MS. Further, a trial comparing the use of sertraline in daily doses from 50 to 200 mg found that this medication and CBT were equally effective.[39]

Exercise is also recommended in many published articles.[35,39]

Obviously, as when treating any patient with depression, there is no one best treatment option for addressing depression in patients with MS, and treatment needs to be individualized. While antidepressant medications can be prescribed for patients, their MS symptoms should be monitored more regularly to ensure that the medication is not counteracting the effects of MS therapies.[42]

Risk of Suicide in People With MS

According to the National Multiple Sclerosis Society, the potential for suicide is real and needs to be monitored in patients with MS who exhibit signs of or have been diagnosed with depression.[12] According to Kalb et al an alarming 77% of people who die by suicide had contact with a physician within a year before their death, and 40% had been seen by a doctor within the last week before

their death.[43] The authors cited, whether the patient is in a comprehensive care setting or living independently, the following potential red flags:[43]

- Positive depression screening
- Abrupt changes in health and/or behavior
- Intense/ongoing sense of bereavement
- Statements of hopelessness ("I hate my life; my life is terrible")
- Social isolation
- Substance or alcohol abuse
- Worry about being a burden
- Inadequate support system
- Concern about family members[43]

If you believe that a patient is seriously considering suicide, call 911 or, if in a hospital setting, have the patient escorted to the emergency department.

Healthcare providers should also be attuned to signals from the patient's care providers that may warn that the patient's depression is deepening: for example, saying they are tired of living like this can certainly be an indication that the patient is considering suicide.

Some helpful suggestions for reacting to your patients' expressions of their thoughts/fears, can be found in Table 2.[43]

For clinicians dealing with patients at risk for suicide, there are multiple resources available, some of which are listed in Table 3.

Concluding Thoughts

While the connection between MS and depression is clear, the exact mechanism of the interplay between the two requires more study. However, clinicians, in dealing with people who have MS, regardless of the setting, or the stage of the patient's disease, should actively and regularly look for signs of depression and develop management techniques that are comfortable for both the patient and the clinician.

TABLE 2. Recommendations for In-the-Moment Conversations

Do say	Avoid saying
I am glad you feel comfortable sharing with me Depression is a very common symptom of MS I am concerned for you and care about you. May I connect you with someone who can help? For your safety, I need to contact…	Nothing This is going to be OK I get depressed sometimes, too Do not worry about it, this feeling will pass Let us take your mind off it with some good stretching/exercises

TABLE 3. Suicide Prevention Resources[43]

Resource	Contact
National Suicide Prevention Lifeline	Dial or text 988
Zero Suicide Toolkit	https://zerosuicide.edc.org/toolkit
Mental Health America	https://www.mhanational.org/
Means Matter from the Harvard T.H. Chan School of Public Health	https://www.hsph.harvard.edu/means-matter/
SAFE-T Pocket Card for Clinicians	https://www.samhsa.gov/resource/dbhis/safe-t-pocket-card-suicide-assessment-five-step-evaluation-triage-safe-t-clinicians
Suicide Prevention Resource Center	https://www.sprc.org/
Suicide Prevention and the Clinical Workforce	https://theactionalliance.org/resource/suicide-prevention-and-clinical-workforce-guidelines-training
TALK Line	1-800-273-TALK or 988

REFERENCES

1. Ferreira AM, Leal B, Ferreira I, et al. Depression and anxiety in multiple sclerosis patients: the role of genetic variability of interleukin 1β. *Mult Scler Relat Disord.* 2021;52:102982.
2. Chitnis T, Vandercappellen J, King M, Brichetto G. Symptom interconnectivity in multiple sclerosis: a narrative review of potential underlying biological disease processes. *Neurol Ther.* 2022;11(3):1043-1070.
3. Hoang H, Laursen B, Stenager EN, Stenager E. Psychiatric co-morbidity in multiple sclerosis: the risk of depression and anxiety before and after MS diagnosis. *Mult Scler.* 2016;22(3):347-353.
4. Fiest KM, Dykeman J, Patten SB, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology.* 2013;80(6):590-599.
5. Antonaci F, Nappi G, Galli F, et al. Migraine and psychiatric comorbidity: a review of clinical findings. *J Headache Pain.* 2011;12(2):115-125.
6. Hackett ML, Pickles K. Part I: Frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9(8):1017-1025.
7. Cong S, Xiang C, Zhang S, et al. Prevalence and clinical aspects of depression in Parkinson's disease: a systematic review and meta-analysis of 129 studies. *Neurosci Biobehav Rev.* 2022;141:104749.
8. Alzheimer's Association Depression. Accessed April 6, 2023 https://www.alz.org/help-support/caregiving/stages-behaviors/depression.
9. Guillamondegui OD, Montgomery SA, Phibbs FT, et al. *Traumatic Brain Injury and Depression*. Agency for Healthcare Research and Quality; 2011; AHRQ publication. 11-EHC017-EF.
10. National Institutes of Health. Major Depression. Published January 2022. Accessed April 6, 2023. https://www.nimh.nih.gov/health/statistics/major-depression
11. Kister I, Bacon T, Cutter GR. How multiple sclerosis symptoms vary by age, sex, and race/ethnicity. *Neurol Clinl Pract.* 2021;11(4):335-341.
12. National Multiple Society. Symptoms and signs of MS/symptoms & diagnosis/MS symptoms/depression. Accessed July 22, 2022. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Depression#section-4.
13. Jones CD, Motl R, Sandroff BM. Depression in multiple sclerosis: is one approach for its management enough? *Mult Scler Relat Disord.* 2021;51:102904.
14. Minden S. *Depression & Multiple Sclerosis*. National Multiple Sclerosis Society; 2019.
15. Yusuf FLA, Ng BC, Wijnands JMA, et al. A systematic review of morbidities suggestive of the multiple sclerosis prodrome. *Expert Rev Neurother.* 2020;20(8):799-819.
16. Leighton SP, Nerurkar L, Krishnadas R, et al. Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Mol Psychiatry.* 2018;23(1):48-58.
17. Gasim M, Bernstein CN, Graff LA, et al. Adverse psychiatric effects of disease-modifying therapies in multiple sclerosis: a systematic review. *Mult Scler Relat Disord.* 2018;26:124-156.
18. Feinstein A, Magalhaes S, Richard JF, et al. The link between multiple sclerosis and depression. *Nat Rev Neurol.* 2014;10(9):507-517.
19. Lazo-Gomez R, Velázquez GLL, Mireles-Jacobo D, Sotomayor-Sobrino MA. Mechanisms of neurobehavioral abnormalities in multiple sclerosis: contributions from neural and immune components. *Clin Neurophysiol Pract.* 2019;4:39-46.
20. Binzer S, McKay KA, Brenner P, et al. Disability worsening among persons with multiple sclerosis and depression: a Swedish cohort study. *Neurology.* 2019;93(24):e2216-e2223.
21. Sabatini, U. et al. Involvement of the limbic system in multiple sclerosis patients with depressive disorders. *Biol. Psychiatry.* 1996;39:970–975.
22. Pujol, J, et al. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology.* 1997;49:1105–1110.
23. Pujol, J. et al. Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. *Psychiatry Res.* 2000;99:151–159.
24. Fassbender, K. et al. Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: association with cerebral inflammation. *Arch. Neurol.* 1998;55:66–72.
25. Bakshi, R. et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. *Neuroreport.* 2000;11:1153–1158.
26. Berg, D. et al. Lesion pattern in patients with multiple sclerosis and depression. *Mult. Scler.* 2000;6:156–162.
27. Zorzon, M. et al. Depressive symptoms and MRI changes in multiple sclerosis. *Eur. J. Neurol.* 2000:9:491–496.
28. Feinstein, A. et al. Structural brain abnormalities in multiple sclerosis patients with major depression. *Neurology.* 2004;62:586–590.
29. Passamonti, L. et al. Neurobiological mechanisms underlying emotional processing in relapsing–remitting multiple sclerosis. *Brain.* 2009;132:3380–3391.
30. Gold, S. M. et al. Smaller cornu ammonis 2–3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. *Biol. Psychiatry.* 2010;68:553–559.
31. Feinstein, A. et al. Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. *Mult. Scler.* 2010;16:189–196.
32. Kiy, G. et al. Decreased hippocampal volume, indirectly measured, is associated with depressive symptoms and consolidation deficits in multiple sclerosis. *Mult. Scler.* 2011;17:1088–1097.
33. Gold, S. M. et al. Detection of altered hippocampal morphology in multiple sclerosis-associated depression using automated surface mesh modeling. *Hum. Brain Mapp.* 2014;35:30–37.
34. Koch M, Uyttenboogaart M, van Harten A, et al. Fatigue, depression and progression in multiple sclerosis. *Mult Scler.* 2008;14(6):815-822.
35. Solaro C, Gamberini G, Masuccio FG. Depression in multiple sclerosis: epidemiology, aetiology, diagnosis and treatment. *CNS Drugs.* 2018;32(2):117-133.
36. Domingo S, Kinzy T, Thompson N, et al. Factors associated with sexual dysfunction in individuals with multiple sclerosis: implications for assessment and treatment. *Int J MS Care.* 2018;20(4):191-197.
37. Minden SL, Feinstein A, Kalb RC, et al; Guideline Development Subcommittee of the American Academy of Neurology. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2014;82(2):174-181.
38. McKay KA, Tremlett H, Fisk JD, et al; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS). adverse health behaviours are associated with depression and anxiety in multiple sclerosis: a prospective multisite study. *Mult Scler.* 2016;22(5):685-693.
39. Bruce JM, Hancock LM, Arnett P, Lynch S. Treatment adherence in multiple sclerosis: association with emotional status, personality, and cognition. *J Behav Med.* 2010;33(3):219-227.
40. Patten SB, Burton JM, Fiest KM, et al. Validity of four screening scales for major depression in MS. *Mult Scler.* 2015;21(8):1064-1071.
41. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606-613.
42. Assessment and management of psychiatric disorders in individuals with multiple sclerosis (summary of evidenced-based guidelines for clinicians). Accessed July 16, 2022. https://www.aan.com/Guidelines/home/GuidelineDetail/628.
43. Kalb R, Feinstein A, Rohrig A, et al. Depression and suicidality in multiple sclerosis: red flags, management strategies, and ethical considerations. *Curr Neurol Neurosci Rep*. 2019;19(10):77.

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