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REVIEW

Understanding Depression in People Living with Multiple Sclerosis: A Narrative Review of Recent Literature

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ABSTRACT

Multiple sclerosis (MS) is a chronic neurodegenerative and autoimmune disease that affects approximately 1 million adults in the US. Psychologic disorders are typical comorbidities in people with MS (pwMS), with depression being the most common. Clinical depression in pwMS can substantially impact quality of life and factor heavily in treatment adherence. Depression can surface early in MS, becoming more prevalent as the disease progresses and the severity of clinical disability increases. The etiology of comorbid depression in pwMS is not completely understood, but recent research has indicated that structural and functional brain abnormalities, along with genetic and immunologic factors, may contribute to the pathogenesis of depression in pwMS. Although depression has a significant impact on pwMS, it is often underdiagnosed and undertreated. Furthermore, the efficacy of pharmacologic and non-pharmacologic approaches for treating depression in pwMS has not been thoroughly investigated, with most studies showing minimal or no beneficial effect. Improved evaluation and diagnosis of depression and a better understanding of its pathophysiology may provide a stronger foundation for treatment and management of pwMS suffering from depression. This review discusses recent research on the potential causes of depression, the risk factors associated with developing depression, and the overall impact of depression in pwMS. It also reviews patient-reported outcomes utilized to assess depression in pwMS and the impact of disease-modifying therapies on depression in pwMS. Consideration is also given to management of depression in pwMS (both pharmacologic and non-pharmacologic) to better facilitate the patient journey.

Keywords: Depression; Disease-modifying therapy; Health care professionals; Mental health; Multiple sclerosis; Quality of life

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Key Summary Points
Lifetime prevalence of depression in people with multiple sclerosis (pwMS) may be more than twice that of the general population, but depression is frequently underdiagnosed and undertreated in this population
While the etiology of comorbid depression in multiple sclerosis (MS) is not fully understood, genetic and immunologic factors, in addition to structural and functional brain damage, may contribute to the pathogenesis of depression in MS
Depression negatively impacts pwMS, leading to reduced treatment adherence, increased MS symptom severity, poorer quality of life, and worse disability and functional outcomes
Potential strategies to manage depression in patients with MS include pharmacologic and non-pharmacologic interventions (such as cognitive behavioral therapy), education for medical providers who treat MS, and establishing multidisciplinary care teams
Further studies are necessary to clarify the complex relationship between MS and neuropsychiatric disorders such as depression

INTRODUCTION

Multiple sclerosis (MS) is a chronic neurodegenerative and autoimmune disease that affects nearly 1 million adults in the US [1]. Psychologic disorders are common comorbidities in people with MS (pwMS), with depression (including symptoms of and diagnosable clinical depression) among the most common [2]. Clinically significant depressive symptoms are common in people with newly diagnosed MS (47.4% for depression) [3] and lifetime prevalence of depression in pwMS, which is estimated at 50% [4, 5], may be more than twice that of the general population, which is estimated at 16–20% [6, 7]. Furthermore, pwMS have a higher risk of developing common psychologic comorbidities and mood disorders compared with those without MS [8].

Despite being common, depression is frequently underdiagnosed and undertreated in pwMS [9–11]. Recent data from the UK-wide Trajectories of Outcome in Neurological Conditions-MS (TONiC-MS) study, involving 5633 pwMS, found nearly 30% of pwMS with depression were untreated (with either pharmacologic or non-pharmacologic therapies) according to their medication list or patient reporting of treatment for depression, even though 26.1% of participants had a symptom level consistent with a probable case of depression [11]. Another study involving 742 participants with MS found that, in the 87 patients with diagnosed depression and high depressive symptoms, only 19.5% reported that they were prescribed antidepressants and only 25.3% reported utilizing any psychologic services [10]. Depression in pwMS, particularly if undiagnosed and therefore untreated, can adversely impact quality of life (QOL) [10] and lead to decreased treatment adherence [12–14], increased symptom severity [15], and worse disability/functional outcomes [16, 17] and may impact suicide risk [18]. These studies suggest an unmet medical need exists for further guidance on the management of depression in pwMS. Indeed, there is no gold standard, single treatment for the management of depression in MS [19]. Current clinical practice guidelines are considered inconsistent and contain recommendations that are generally based on low-quality evidence [20].

In this review article, we discuss recent research on the potential causes of depression, the risk factors associated with developing depression, and the overall impact of depression in pwMS. We also discuss patient-reported outcomes (PROs) utilized to assess depression in pwMS and the impact of disease-modifying therapies (DMT) on depression in pwMS. Finally, we review recent findings on the treatment and management of depression in pwMS (both pharmacologic and non-pharmacologic) and provide resources on depression in pwMS for health care providers who treat MS as a means of improving the patient journey.

METHODS

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. PubMed searches were used to find applicable articles for inclusion in the review manuscript. Searches were initially limited to article title only, written in the English language, and published within the last 5 years; case-study type articles, letters, commentaries, and editorials were excluded. The following search terms (and limit terms [i.e., "Title" or "Title/Abstract"]) were used: (Prevalence[Title]) AND (depression[Title]) AND (multiple sclerosis[Title]). This search term was also modified to (depression[Title/Abstract]). Additional search terms included: (Multiple Sclerosis[Title]) AND (mental health[Title]); (multiple sclerosis[Title]) AND (suicide[Title]); (disease-modifying therapy name[title]) AND (multiple sclerosis[Title]); (multiple sclerosis[Title]) AND (depression[Title]) AND (assessment); (multiple sclerosis[Title]) AND (Hospital Anxiety and Depression Scale; Beck Depression Inventory or BDI, Patient Health Questionnaire or PHQ-9, Center for Epidemiological Studies Depression Scale; SymptoMScreen[Title]; (multiple sclerosis[Title]) AND (cognitive behavioral therapy OR cognitive behavioural therapy [Title/Abstract]); (multiple sclerosis[Title]) AND (care unit[Title]).

Additional references not included in the original PubMed searches were also included if recommended by the authors or were manually accessed if considered relevant to a statement in the review.

POTENTIAL CAUSES OF DEPRESSION AMONG PATIENTS WITH MS

The etiology of comorbid depression in MS is not fully understood although the causes are believed to be multifaceted because of the complex nature of the disease. Additionally, depression can be considered both a symptom of and a reaction to MS. Recent research has shown that genetic and immunologic factors, in addition to structural and functional brain damage, may contribute to the pathogenesis of depression in MS.

STRUCTURAL AND FUNCTIONAL BRAIN DAMAGE

White Matter Lesions/Disruption

MS is characterized by demyelinating white matter lesions present in the central nervous system [21]. Recent studies have suggested that the burden and location of these white matter lesions may be associated with onset of depression in MS [22, 23]. For example, people with MS with a depression diagnosis have greater burden of white matter lesions across the brain than those without depression [22]. Compared with pwMS without depression, those patients diagnosed with depression and MS had greater lesion burden in the white matter within a specific brain network associated with depression in pwMS (known as a "depression network") and within the fascicles inside the white matter depression network [22]. Another study found functional connectivity between MS white matter lesion locations and an a priori brain depression circuit correlated with depression severity in MS [23]. Although there are inconsistencies as to specific brain regions, lesion burden can have a strong effect on worsening depression symptoms in MS.

White matter tract disruption and white matter integrity may also be risk factors for depression in pwMS [24, 25]. Specific areas of white matter tract disruption in the conscientiousness-associated frontal-parietal network were associated with progression to clinical depression over 5 years in pwMS, independent of age, sex, lateral ventricular volume, disease-modifying treatment, and lesion volume [24], suggesting that new white matter development in this network may be a risk factor for developing depression in MS. In older adults with MS, lower white matter

integrity from the dorsolateral prefrontal cortex to the putamen nucleus was associated with higher symptoms of depression compared with older adults without MS, suggesting a possible role of frontal-striatal white matter tract integrity in developing depression in MS [25].

Microstructural Changes and MS-Related Atrophy

Structural and functional brain damage that occurs in MS, such as microstructural changes and atrophy in specific brain regions, may be implicated in the development of depression in pwMS. Recent evidence suggests that brain microstructural changes in subcortical structures and the left mesocorticolimbic pathway may precede or contribute to the development of comorbid depression in MS [26, 27]. For example, a study involving 93 pwMS found that those with sustained fatigue and depression (as measured by a Center for Epidemiologic Studies Depression Scale [CES-D] score of ≥ 16) had significantly higher mean and radial diffusivity of the superolateral medial forebrain bundle (slMFB; also known as the mesocorticolimbic reward pathway) than non-depressed pwMS with sustained fatigue [26]. Depressed patients with sustained fatigue also showed higher left slMFB axial and mean diffusivity than healthy controls, suggesting that microstructural changes to the left slMFB may play a role in the development of depression in MS [26]. In another study involving 46 patients with relapsing-remitting MS, microstructural changes in subcortical structures were estimated using the free water fraction diffusion-based magnetic resonance imaging metric. Baseline free water fraction correlated with depression score (as measured by the Hospital Anxiety and Depression Scale [HADS]) in the thalamus, putamen, pallidum, hippocampus, amygdala, and accumbens at the 2-year follow-up [27]. This may suggest a relationship between higher levels of free water in the subcortical structures in early MS and the development of depression later in the disease.

MS-related atrophy may contribute to the development of depression in MS [28]. A study found that people with comorbid relapsing-remitting MS and depression had greater selective cerebellar atrophy (lower vermis crus I volume) than people with relapsing-remitting MS without depression [28].

PwMS with moderate-to-severe depression also have greater structural and functional changes in temporo-frontal regions, such as decreased white matter volume, decreased fractional anisotropy of the uncinate fasciculus, and decreased functional connectivity between the amygdala and frontal areas compared with non-depressed pwMS. This potentially suggests a fronto-limbic disconnection [29], which may explain the difference in depressive symptoms between the two groups. In summary, the white matter lesions and disruptions as well as other structural and functional changes in the brain that occur with MS, including microstructural changes and atrophy in specific brain regions, may contribute to the development and severity of depression in pwMS.

MONOAMINERGIC NETWORK DYSFUNCTION

Dysfunction within monoaminergic networks (particularly changes in resting-state functional connectivity) have been linked to depression/depressive symptoms in pwMS [30, 31]. The dopaminergic system has a broad spectrum of action and plays a role in functions such as motor control, reward processing, memory consolidation, and emotional regulation [32]. A study by Mistri et al. involving 49 pwMS found that those who developed depressive symptoms (as measured by a score > 9 on the Montgomery–Asberg Depression Rating Scale [MADRS] at follow-up [median follow-up of 1.6 years]) exhibited a widespread resting-state functional connectivity decrease within the dopamine network (mainly the orbitofrontal, occipital, anterior cingulate, and precuneal cortices) over time compared with patients who did not develop depressive symptoms [31]. Furthermore, decreased resting-state functional connectivity in dopamine and noradrenaline networks

correlated with concomitant increased depression scores [31].

GENETIC BASIS

Research suggests there may be a genetic link between MS and depression [33–35]. The rs16944TT genotype was recently identified as a susceptibility factor for the occurrence of depression and the development of persistent depression in pwMS [34]. The genetic variant rs1432639, which has been associated with depression in the general population, has also been associated with the development of depression in pwMS post-MS diagnosis [33]. Individuals with MS may also have higher susceptibility to developing depression due to having a higher depression genetic burden. One study found that individuals with MS and depression had a higher depression polygenic score compared with individuals with MS without depression as well as healthy controls [35]. However, another study found no causal association between major depressive disorder genetic liability and MS susceptibility, and vice versa [36].

IMMUNOLOGIC BASIS

The immune system plays a significant role in MS. Neuro-immunologic/inflammatory pathways may also be connected to depression in MS [37, 38]. One study revealed that CD4+T central memory (TCM) cells expressing low levels of CC chemokine receptor 7 (CCR7) cell frequency in the peripheral circulation were decreased in depressed pwMS compared to closely matched non-depressed pwMS and healthy controls [37]. Another study showed that the anti-inflammatory cytokine, interleukin 10, was significantly (and negatively) associated with depression in veterans with MS [38]. In addition, a separate study found that higher C-reactive protein (an inflammatory marker) levels positively correlated with severe depression in pwMS [39].

RISK FACTORS FOR DEVELOPING DEPRESSION IN MS

Several causes may increase the risk of developing depression, including biologic, psychologic, and social factors (Fig. 1). For example, the stage

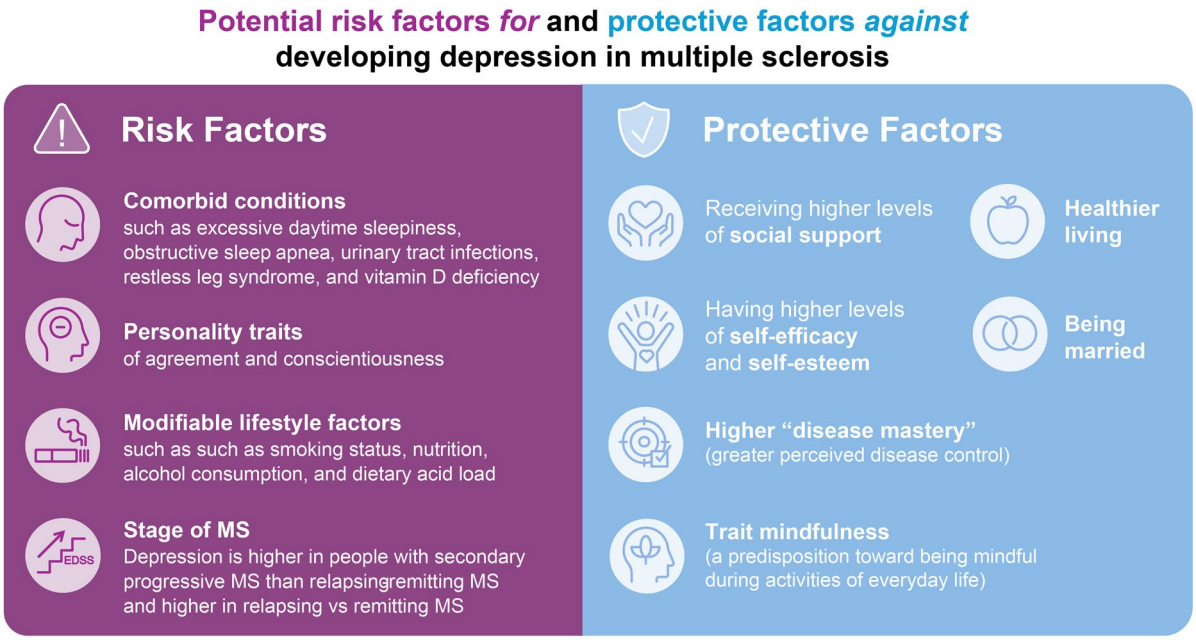

Fig. 1 Potential risk factors for and protective factors against developing depression in MS. *MS* multiple sclerosis

of MS may influence the prevalence of depression, with the highest prevalence of depression in secondary progressive MS (31.5%), followed by primary progressive (25.8%) and relapsing-remitting (23.2%) [11]. Similarly, a recent systematic review and meta-analysis found that the prevalence of depression was higher in people with progressive MS (19.13%) than in people with relapsing-remitting MS (15.78%) [40]. A study focusing on patients with relapsing-remitting MS found that depression scores (as measured by Beck Depression Inventory-II [BDI-II]) were greater in patients experiencing a relapsing phase than those who were remitting, possibly suggesting a role of inflammation in depression in MS [41].

Other conditions such as excessive daytime sleepiness, obstructive sleep apnea, and symptoms of overactive bladder symptoms in female patients are all associated with an elevated risk of depression/depressive symptoms in pwMS [42, 43]. Additionally, positive correlations have been found between depression/depressive symptoms and lower urinary tract infections [44] as well as the presence of restless leg syndrome in pwMS [45]. Vitamin D deficiency is considered a possible contributor to depression in MS. A study involving 88 pwMS found that serum vitamin D levels were inversely correlated with depression risk score (Expanded Disability Status Scale [EDSS]), with more robust correlations in female than male patients [46]. Indeed, the TONiC-MS study involving 5633 participants with MS found that depression risk was increased with more comorbidities, which was the greatest risk factor for depression, followed by anxiety, fatigue, smoking, and disability [11].

Four modifiable lifestyle factors—smoking status, nutrition, alcohol consumption, and physical activity level—together constitute the "SNAP" risk factors, a construct designed for use in general practice to estimate prevalence of lifestyle risk factors, including in pwMS [47]. To examine the relationship between depression and modifiable lifestyle factors, a study by Gascoyne et al. utilized a "SNAP" score based on the above-mentioned factors plus body mass index [48]. This study found that healthier living (as defined by a higher SNAP score) revealed a significant and dose-dependent inverse relationship with depression prevalence and severity in pwMS [48]. Additionally, every unit increase in SNAP score was associated with a 17% reduction in prevalent depressive symptoms and a 0.44-unit lower actual HADS-depression score [48]. Higher dietary acid load (i.e., a dietary imbalance between acid-inducing foods such as meat, fish, grains, and cheese as opposed to alkali-inducing foods such as fruits, vegetables, milk, and yogurt), because of poor nutrition and alcohol use, may also contribute long term to the level of depression in pwMS [49]. At a 10-year review of the data, the level of depression was best determined by both the baseline dietary acid scores and baseline-5-year changes in dietary acid scores [49]. In addition to nutrition and alcohol consumption, smoking status is a contributor to depression in pwMS. One systematic review found strong evidence of increased prevalence of depression in pwMS who were either current or former smokers [50]. Often, poor nutrition, alcohol use, and smoking are associated with a sedentary lifestyle, although the impact of low physical activity on depression in pwMS is unclear [19, 51].

Recent research has shown that the personality traits of agreement (altruistic behavior, trust, warmth, and friendliness) and conscientiousness (ability to control impulses, focus on tasks, and follow rules) have been associated with higher levels of depression in MS [52]. On the other hand, trait mindfulness (which has been described as a predisposition of being mindful during activities of everyday life, as opposed to *state* mindfulness that is achieved during the practice of mindfulness meditation [53]) has been associated with lower depression/depressive symptoms in pwMS [54–56]. Trait mindfulness may mediate the relationship between illness intrusiveness and depression in pwMS [55]. Coping style may help moderate the effect of pain on depressive symptoms in MS. A study involving 54 pwMS found that in those patients who utilized more avoidant and less active coping strategies, pain was predictive of those more likely to have depressive symptoms [57].

Some social determinants of health, such as socioeconomic status, unemployment, and history of verbal or physical abuse, can impact depression in pwMS. One study found greater odds of moderate-to-severe depression in pwMS in the lowest socioeconomic status quartile, independent of race [58]. Another study found that, in a population of low-income minority patients with MS, the percentage of Latino patients reporting depression was twice as high as that of Black patients [59]. Unemployment has been identified as a risk factor for depressive symptoms [60]. History of verbal/physical abuse during childhood is also significantly associated with increased odds of depression in pwMS [61]. The impact of other factors, such as gender and sexuality/sexual orientation, on depression in pwMS warrants additional study, but it is important to note that, in the general population, LGBTQ+individuals experience higher rates of depression than heterosexual individuals [62]. To summarize, biologic factors including the stage of MS and the presence of other conditions, modifiable lifestyle factors, personality traits and coping mechanisms, socioeconomic status, unemployment, and/or history of physical or mental abuse can all impact the occurrence and severity of depression in pwMS.

IMPACT OF DEPRESSION ON PEOPLE LIVING WITH MS

Depression has a profound impact on pwMS (Fig. 2) as it can negatively affect areas such as treatment adherence, symptom severity, QOL, disability, and functional outcomes. Additionally, it can be a strong suicide risk factor.

Treatment adherence in MS is crucial, as poor treatment adherence can, in turn, lead to worse clinical outcomes. A systematic review of 24 studies found that adherence to DMT in pwMS ranged from 52 to 92.8% [14]. In five of these studies, a diagnosis of depression, depressive symptoms, or at least one psychiatric disorder was associated with poorer rates of adherence to therapy [14]. Additionally, a retrospective administrative claims analysis of a large commercial US database between 2011 and 2017 involving 10,248 pwMS found that 42% met non-adherence criteria [63]. Individuals with MS who adhered to treatment had significantly longer time to first relapse, a lower annualized relapse rate, and longer lag times to cane/walker and wheelchair use than individuals with MS who did not adhere to treatment [63]. Together, these findings may indicate that depression can negatively affect health outcomes in pwMS through reduced treatment adherence.

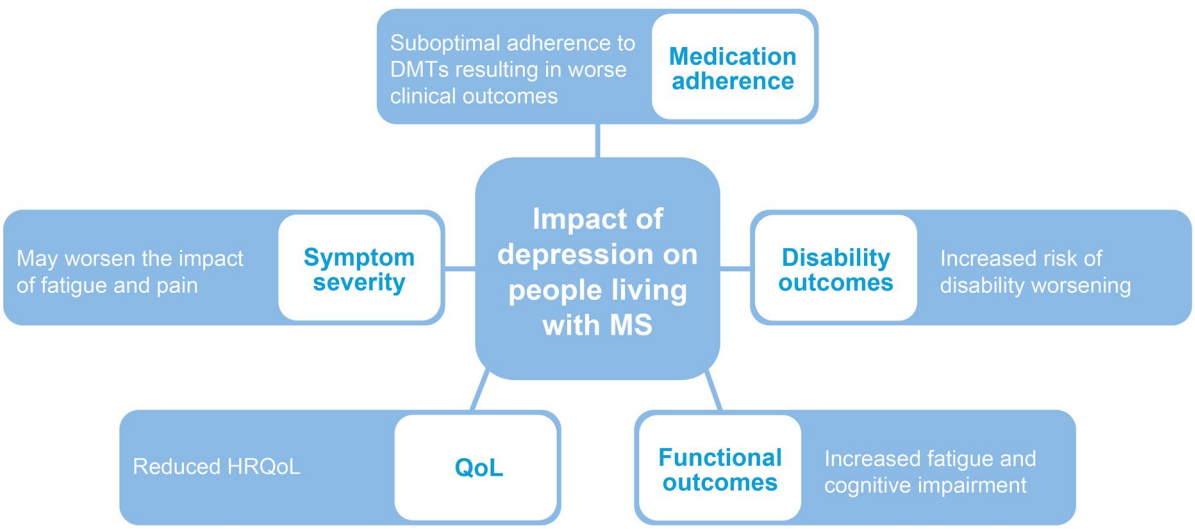

Fig. 2 Potential areas impacted by depression in pwMS. *DMT* disease-modifying therapies, *HRQoL* health-related quality of life, *MS* multiple sclerosis, *pwMS* people with multiple sclerosis

Furthermore, depression has been associated with reduced QOL in pwMS [10, 64, 65]. One study found that pwMS who reported having high depressive symptoms (based on self-reported depression diagnosis and scores on the HADS) also reported the poorest health-related QOL (HRQoL) [10]. In contrast, the group that reported receiving adequate treatment for depression was more likely to exercise, consume a healthy diet, and have high levels of participation in household, leisure, and out-of-home activities, thus reporting a higher HRQoL. The findings from this study suggest that treating depression can potentially improve HRQoL in pwMS. In a cross-sectional study involving 150 pwMS, depression scores (measured using the BDI-II) were significantly correlated with reduced mental and physical QOL, highlighting the impact of depression on mental and physical well-being in pwMS [64]. Finally, while anxiety and MS is beyond the scope of this article, comorbid anxiety in addition to depression may worsen the impact of depression on QOL in those with MS. A study involving 183 pwMS found that those with comorbid depression and anxiety reported worse QOL than those with MS and depression alone, possibly suggesting that anxiety may be an exacerbating factor [65].

Depression may worsen the impact of MS symptoms, such as fatigue and pain [15], as well as disability/functional outcomes in pwMS [16, 17, 66, 67]. Early reduction in depressive symptoms has been associated with an overall reduction in pain interference and fatigue symptom impact in pwMS [15]. PwMS and comorbid depression have an increased risk for disability worsening compared with pwMS without depression [16]. Additionally, pwMS who report higher depressive symptoms have a higher risk of falls than pwMS who report lower depressive symptoms [66]. Depression may also negatively impact cognitive performance in pwMS, with one study finding that increased depression score (HADS-D) was positively associated with fatigue (Fatigue Severity Scale), disability (EDSS), and cognitive impairment (Symbol Digit Modalities Test [SDMT]) [17]. Management of depression may be beneficial in reducing the negative impact of depression on treatment adherence, symptom severity, QOL, and disability and functional outcomes in pwMS.

Lastly, some studies have suggested an increased risk of suicide and suicide attempt in pwMS. A meta-analysis of 16 studies found a positive association between MS and suicide risk and suggested that suicide risk was higher at MS diagnosis than MS symptom onset [18]. The risk of attempted and completed suicide has been found to be higher in pwMS compared with the general population (hazard ratios of 2.18 and 1.87, respectively) [68]. Women were found to be at higher risk of attempting suicide, although men were at higher risk for completing suicide [68]. The global prevalence of suicidal ideation in the MS population has been estimated at 13% [69], although research on suicidal ideation (thoughts of suicide) in people with MS, may not reflect the true risk/rate of suicide in the MS population. Taken together, depression can affect patient treatment adherence, symptom severity and QOL, as well as disability, fatigue, pain, and functional outcomes in pwMS.

ASSESSMENT OF DEPRESSION IN MS

Assessing depression in pwMS is challenging; MS and depression often have overlapping symptoms, such as fatigue and sleep difficulties [67], which makes measurement of depression difficult. Thus, it poses a diagnostic challenge for health care professionals [70]. In addition, many of the clinical practice guidelines for pwMS are older (e.g., the American Academy of Neurology [AAN] guidelines for the assessment and management of psychiatric disorders in individuals with MS [71] were published in 2014, and the Goldman Consensus group statement on depression in multiple sclerosis [72] was published in 2005) and may not reflect current clinical practice.

PROs can play an important role in assessing depression in pwMS. Multiple scales for assessing depression exist, with the most common PROs for assessing depression in pwMS including HADS [73], the BDI-I and BDI-II [74, 75], MS-specific BDI (MS-BDI) [76], the Patient Health

Questionnaire (PHQ-9) [77], the CES-D [78], the SymptoMScreen [79], and the Quality of Life in Neurological Disorders (Neuro-QoL) [80].

HADS is commonly used to measure depression and anxiety in pwMS. It includes 14 questions, 7 to measure anxiety (HADS-A) and 7 to measure depression (HADS-D). Items are rated on a 4-point severity scale [73]. The BDI-II is the most recently revised version of the BDI. It includes 21 statements that reflect symptoms and attitudes of clinically depressed people. Items are rated on a 4-point severity scale (0.3) [74, 75]. The BDI has since been modified to include only the items found to be most related to depression in MS, creating an MS-BDI measure [76]. A cutoff of 8 on the MS-BDI was found to have high specificity, suggesting it can be used to assess depression in pwMS [76]. Guidelines from the AAN for the assessment and management of psychiatric disorders in individuals with MS [71] recommends the BDI and a two-question tool to screen for depressive disorders in pwMS [81].

The PHQ-9 is a self-administered questionnaire consisting of nine questions to assess depression [77]. The PHQ-9 can be administered by any provider who knows how to interpret and score and can be administered as needed but not more frequently than every 2 weeks [82]. The PHQ-9 has been found to exhibit high internal reliability and test-retest agreement to demonstrate validity of measurement and to have high acceptability as a screening tool for depressive symptoms in pwMS [83]. In practice, many clinicians have moved to using the PHQ-9 to screen pwMS for depression because of its brevity and focus on depressive symptoms and suicidality.

A study evaluating the validity and reliability of six commonly used PROs for depression in MS found that the PHQ-9 had the highest sensitivity (84%), whereas HADS-D had the highest specificity (95%) [84]. Furthermore, a study evaluating the validity and reliability of six commonly used screening measures for anxiety and depression in pwMS (including HADS, PHQ-9, and Patient-Reported Outcomes Measurement Information System [PROMIS] Emotional Distress Depression Short-Form 8a) found that performance of the depression screening measures was similar, with reasonable psychometric properties for the MS population [84].

The CES-D is a measure assessing symptoms of depression including 20 statements phrased as self-statements (e.g., "I felt that I could not shake off the blues even with help from my family and friends") [85]. A study involving 493 participants with MS found that the CES-D demonstrated factorial validity in pwMS and therefore a coherent structure for examining depression in pwMS [78].

SymptoMScreen is a self-assessment tool for measuring symptom severity across 12 distinct domains commonly affected by MS, including depression. The SymptoMScreen consists of 12 items that are assessed on a 7-point Likert scale that ranges from 0 (not at all affected) to 6 (total limitation) [79]. A study involving 218 clinically stable patients with relapsing-remitting MS found that the SymptoMScreen exhibited high internal consistency and was a robust unidimensional scale. SymptoMScreen also showed appropriate convergent validity with the EDSS and total number of relapses [86]. SymptoMScreen is a valid tool for assessment of performance-based and clinician-assessed measures among pwMS [87].

The Neuro-QoL is a system of PRO measures that target neurologic disorders by using item banks across 13 domains and specific associated short forms of 6–10 items used for measuring HRQoL in specific neurologic disorders, including MS [80, 88]. Each short form has eight or nine items, and patients can complete the Neuro-QoL more quickly than many other QOL instruments [88]. In a study to examine discriminant validity (reliability, validity, and factor structure) of the Neuro-QoL in pwMS, records from 902 pwMS receiving any type of DMT who completed a core set of PROs, including the Neuro-QoL short-form scales, were analyzed [80]. Neuro-QoL demonstrated acceptable reliability and convergent validity compared with other measures of QOL, disease severity, and symptoms in pwMS, but a confirmatory factor analysis suggested most of the 12 domains tested had poor model fit, and additional research is needed to strengthen these measures for use in pwMS [80].

Emotional thermometers (a visual analog screening tool) may represent a new methodology for rapid screening of depression in pwMS. A study involving 190 participants with MS found that emotional thermometer performance was comparable to HADS-D without needing clinician scoring [89]. Furthermore, the brief version of the emotional thermometer (ET-4), performed as well as the full version (ET-7) [89].

An in-progress clinical study (NCT04979546) is currently examining the impact of more frequent PRO measures (every 6 months) on patient depression and anxiety outcomes in clinical practice; this study was completed in April 2024, although no results have been posted to date [90].

An important consideration for assessing depression in pwMS is the transition from in-person attendance to virtual care and how this may also influence depression outcomes in pwMS. Since the COVID-19 pandemic, many mental health providers, as well as MS providers, have transitioned their practice to telemedicine [91, 92]. Transition to telemedicine services may enhance accessibility to psychosocial support to pwMS by overcoming geographic and physical disability barriers, which are common in the MS population [93]. Furthermore, pwMS may prefer virtual care, as one study found that satisfaction scores provided by pwMS of telemedicine encounters remained stable compared to the results from traditional in-office evaluations [93]. However, one study reported that 84.6% of MS health care providers found it difficult to perform a full examination of a patient using telemedicine services [91]. Thus, while several PROs and screening tools for depression exist to assess depression in pwMS, many clinical practice guidelines may not reflect current clinical practice and use of screening tools.

IMPACT OF DMTS ON DEPRESSION IN MS

The impact of DMTs on depression in pwMS, whether positive or negative, is unclear (Table 1). While it is beyond the scope of this article, the efficacy of DMTs (lower, moderate, or high efficacy) may be correlated with depression in MS, although further clinical research and real-world experience are needed for further elucidation. Some studies suggest that choice of DMT may affect depression risk in MS [94, 95]. For example, one study found that pwMS treated with rituximab had a lower risk of being diagnosed with depression or initiating antidepressants compared with pwMS treated with interferons [94]. A systematic review of 78 studies found that no DMTs (natalizumab, fingolimod, dimethyl fumarate, teriflunomide, and alemtuzumab) were associated with an increased risk of adverse psychiatric effects; however, a beneficial effect on symptoms of depression by fingolimod was observed [96]. Similarly, a cohort study involving 440 participants with relapsing-remitting MS found that DMTs (including dimethyl fumarate, glatiramer acetate, interferons, alemtuzumab, natalizumab, cladribine, teriflunomide, and fingolimod) had no substantial impact on hidden disability, including depression based on the PHQ-9 [97].

Furthermore, it is difficult to characterize the impact of high-efficacy DMTs (referred to as high-efficacy treatment or HET) compared with moderate- or low-efficacy DMTs (referred to as low-efficacy treatment or LET) on depression in clinical practice. A cross-sectional study found that pwMS who were untreated had more fatigue and anxiety than pwMS treated with a DMT and greater depression than those treated with a DMT characterized as an LET (interferon beta-1a, interferon beta-1b, peginterferon beta-1a, and glatiramer acetate) [98]. Additionally, pwMS who were taking a DMT considered as an LET had lower fatigue and depression scores compared with those who were taking a DMT considered as an HET (alemtuzumab, ocrelizumab, rituximab, natalizumab, and cladribine) [98]. However, the greater depression seen in pwMS taking a DMT considered to be an HET should be interpreted with caution as these patients may have a greater number of white matter lesions or longer disease duration with disability accrual, hence the need for an HET. Conversely, pwMS on LET may experience less depression and fatigue because of having few white matter lesions as opposed to any treatment effects.

Table 1 DMTs and their impact on scales evaluating depression

DMT	Study reference	Overview of objective/participants	Assessment	Results
Interferons				
	Tardo et al. [95]	To determine if there is an association between DMT and depression rates based on PHQ-9 scores in multiple sclerosis. 2611 participants with MS at University of Texas Southwestern Multiple Sclerosis and Neuroimmunology Clinic 2017–2020	Retrospective chart review study. Patients' most recent PHQ-9 scores were used. Data extracted from patient charts: disease-modifying therapy, age, disease duration, gender, antidepressant use, and ambulatory status	The odds of a higher PHQ-9 total score were: 44.0% less for a subject treated with interferons (beta-1a/1b and peginterferon) relative to those not treated with a disease-modifying therapy 37.6% less for a subject treated with interferons relative to a subject treated with low-efficacy, cell depleters (teriflunomide and fumarates including dimethyl fumarate and diroximel fumarate) 45.4% less for a subject treated with interferons relative to a subject treated with high-efficacy, cell depleters (alemtuzumab, rituximab, ocrelizumab, cladribine) 42.5% less for a subject treated with interferons relative to a subject treated with high-efficacy, cell restrictors (natalizumab, fingolimod, siponimod) 25.9% less for a subject treated with high-efficacy, cell depleters (alemtuzumab, rituximab, ocrelizumab, cladribine) relative to a subject treated with low-efficacy, immunomodulatory treatments (glatiramer acetate), excluding interferons

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	Ouallet et al. [143]	To prospectively investigate emotional disorders at time of disease-modifying drug initiation and correlation between IFN-β and occurrence of emotional changes in patients with RRMS using recently validated EHD sensitive scale with categorical assessment that tests for specific sub-components of emotional factors. Of 79 recruited patients, 70 were analyzed	24-month, multicenter, single-arm, prospective study. Patients with RRMS started IFN-β treatment at baseline. Primary endpoint was lack of emotional control, measured using the "Echelle d'HumeurDépressive" (EHD) scale 3 times at baseline and at 10 post-treatment visits. Depression was a secondary endpoint and was measured using the Center for Epidemiologic Studies Depression Scale (CES-D)	Based on 24 months of prospective follow-up, the study highlights a broad spectrum of emotional disorders in the MS population at the time of disease-modifying drugs initiation, but no major IFN-β-related emotional disorders (mood dyscontrol, anxiety, depression) were observed
Teriflunomide				
	Nunes et al. [144]	To characterize adult patients with RRMS treated with teriflunomide in routine clinical practice in Portugal in terms of quality of life, comorbidities, treatment effectiveness, satisfaction, compliance, and safety. Of 99 participants, 25% were treatment-naïve	TeriLIVE-QoL was a multicenter, non-interventional, prospective cohort study that collected demographic and clinical characteristics, PROs, and adverse events from patients treated with teriflunomide of 14 mg over 2 years	Teriflunomide demonstrated improvements on mean anxiety scores but not depression after 24 months as assessed using the HADS: Annualized relapse rate and HADS score decreased after 1 ($p = 0.01$) and 2 years of treatment ($p < 0.001$), respectively Convenience ($p = 0.001$), effectiveness ($p = 0.002$), and global satisfaction scores ($p < 0.001$) presented high values ($p \leq 95.6$) and continued to improve during study Treatment persistence was 77%, and compliance reached 82% 2 years after initiation Three patients experienced SAEs

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	de Sèze et al. [145]	Real-world study involving 210 patients with RRMS treated with teriflunomide 14 mg for 2 years. Mean age was 45.4 years with mean ± SD EDSS score of 1.76 ± 1.43 at baseline. 52.4% of patients had no previous MS treatment	Teri-FAST was a 2-year, prospective, open-label observational study in France. Fatigue was assessed using French version of modified Fatigue Impact Scale (EMIF-SEP). Primary endpoint was change from baseline in EMIF-SEP score after 2 years of treatment. Secondary endpoints included evaluation of depression (BDI), HRQoL (Two-Life Scale TLS-QoL 10), self-reported physical activity, and AEs	In 163 patients who completed ≥ 1 follow-up visit, mean change in EMIF-SEP score at year 2 was − 1.54 (95% CI − 4.02, 0.94) indicating that fatigue remained stable No clinically significant changes in self-reported depression or quality of life: Mean ± BDI score at baseline was 5.9 ± 5.6, indicating slight depression that did not worsen after 2 years of treatment (5.0 ± 5.0); mean change from baseline (95% CI) at year 2 was − 0.6 (− 1.5, 0.3) HRQoL also remained stable over 2 years (mean ± TLS-QoL score was 2.6 ± 2.7 at baseline and 2.2 ± 2.6 at year 2; mean change from baseline [95% CI] at year 2 was − 0.3 [− 0.8, 0.1])
Alemtuzumab				
	Wilken et al. [146]	To assess effect of alemtuzumab on cognition across wider range of domains (e.g., memory, processing speed, and verbal fluency) using comprehensive cognitive battery. The study also sought to examine any effects on depression, fatigue, MRI, and safety associated with alemtuzumab. People with RRMS (aged 25–55 years) who were treated with alemtuzumab in clinical practice in the US and Canada	Longitudinal, single-arm, prospective study. Primary endpoint was change from baseline to post-baseline (month 12/24) in MS-COGnitive composite score. Secondary endpoints included depression using the HAM-D	Treatment with alemtuzumab was associated with improvement in HAM-D. At 12 months, mean change from baseline (95% CI) was − 2.19 (− 3.84; − 0.54), $p = 0.0054$; at 24 months the corresponding change from baseline was − 1.00 (− 4.02; − 2.02), $p = 0.6250$

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	Hvid et al. [147]	To assess effect of treatment with alemtuzumab for 2 years on physiologic, physical, and cognitive function and PROs in 17 patients with RRMS	Prospective, observational 2-year study. HADS scores were assessed prior to treatment initiation and again at months 3, 6, 12, and 24 after start of treatment	Patients with RRMS treated with alemtuzumab displayed stable depression outcomes at 24-month follow-up
	Bónitto [148]	To describe sustained changes in physical disability in an average 22-month follow-up after alemtuzumab infusion, and which demographic or clinical variables modulate change in EDSS, and AEs, changes in cognition, fatigue, and depressive symptoms after an average 15-month follow-up period. 23 Columbian patients with RRMS treated with alemtuzumab were identified from medical records; of these, 17 had a baseline neuropsychologic assessment and 12 had ≥ 1 follow-up neuropsychologic assessment	Retrospective cohort observational study. Depressive symptoms were measured with an Argentinian adaptation of the BDI-II	2 (16.6%) patients perceived improving depression symptoms, 4 patients reported no change and 6 (50%) reported worsening symptoms. Using paired *t*-tests to assess mean change between assessments, there were no changes in depression level at follow-up $t(11) = -0.7, p = 0.536, d = 23$
Natalizumab				

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	Hersh et al. [149]	To assess the impact of natalizumab on Neuro-QoL scores, including a depression domain. 164 natalizumab-treated patients met the selection criteria for the analysis	Annualized change in T-scores and likelihood of ≥ 5-point improvement over baseline were calculated for each Neuro-QoL domain after natalizumab initiation. Comparisons with ocrelizumab-treated patients were conducted after propensity score weighting and adjustment for relevant co-medications, year, and drug-year interaction	There were statistically significant improvements in depression in participants with MS treated with natalizumab and ocrelizumab, measured by adjusted annualized rate of T-score change In natalizumab patients, statistically significant improvement was observed in 9 of 12 Neuro-QoL domains, with greatest improvements seen in positive affect and well-being, sleep disturbance, and anxiety (rate [CI]: − 1.54 [− 2.99, − 0.10], $p = 0.04$) In ocrelizumab patients, statistically significant improvement was observed in 4 of 12 Neuro-QoL domains, with greatest improvements seen in positive affect and well-being, anxiety (rate [CI]: − 0.28 [− 1.02, 0.47], $p = 0.47$), and depression (rate [CI]: − 0.63 [− 1.13, − 0.13] $p = 0.02$)
	Edwards et al. [150]	To evaluate the effect of natalizumab treatment on neuropsychologic function in individuals with RRMS who had a measurable neuropsychologic deficit prior to natalizumab treatment. A total of 40 pwMS (mean age, 48.5 years; 77.5% female patients)	A single-center, open-label, retrospective study. Patients were evaluated on a neuropsychologic battery of 9 tests designed for pwMS before and after 6 or more months of treatment with natalizumab. Post-treatment results were compared with baseline. Changes in BDI-II score were assessed	BDI-II score improved by 2.45 points ($p = 0.001$) from a mean score of 13.30 at baseline to 10.85 at follow-up
Ocrelizumab				

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	Smoot et al. [151]	To evaluate safety and treatment outcomes of ocrelizumab in a community-based MS population, in the POR study. Of 355 patients enrolled, 71.9% were female; mean (SD) age was 51.8 (12.5) years; 78.3% had RRMS	A prospective cohort study that used data collected from patients who participated in the POR, and prescribed ocrelizumab between 28 March 2017 and 29 February 2020. Analyses included change from baseline to 12 months in the BDI-II	There were no significant differences in BDI-II from baseline to 12 months ($n = 88$; mean [SD] difference – 0.61 [± 7.6], $p = 0.4$)
	Manchon et al. [152]	PRO-MSACTIVE, a phase IV study, was designed to provide additional data on ocrelizumab efficacy, safety and PRO measures in patients with RMS in a pragmatic setting. 422 participants with active RRMS or SPMS who completed PRO questionnaires assessing different aspects of patients' quality of life (SymptoMScreen, MFIS, EQ-5D-5L, MusiQoL, and WPAI:SHP)	A national, multicenter, open-label, single-arm phase 4 French study	SymptoMScreen, MFIS, EQ-5D-5L, MusiQoL, and WPAI:SHP all showed a similar trend with the total score and per dimension of each scale remained broadly stable from baseline to week 48, regardless of the type of MS Mean change (SD) in scores between baseline and W48 for total population were as follows: SymptoMScreen −0.94 (0.93), MFIS −3.2 (13.6), EQ-5D-5L health state score + 4.3 (17.2), MusiQoL + 1.76 (11.16), WPAI:SHP overall work impairment −0.78 (25.08)
	Glanz et al. [153]	To examine the impact of ocrelizumab on HRQoL in individuals with MS. 98 individuals with relapsing and 32 with progressive MS were enrolled	Participants were administered a battery of PRO measures at their first ocrelizumab infusion, and infusions at 6 and 12 months. PRO measures included the Medical Outcomes Study SF-36 and Neuro-QoL	There was no significant longitudinal change in depression scores (Neuro-QoL depression domain) from baseline in individuals with MS treated with ocrelizumab. The estimated change per year (95% CI) after initiation of ocrelizumab for anxiety was −1.4 (−2.5, −0.2; $p = 0.018$) and for depression was −0.1 (−1.0, −0.8; $p = 0.791$)

Table 1 continued

DMT	Study reference	Overview of objective/participants	Assessment	Results
	Kister et al. [154]	To assess changes in symptom burden across 2 consecutive ocrelizumab infusion cycles. Of 103 pwMS enrolled, 68% were female; 33% were non-White; 41% had an EDSS score > 3; mean (SD) age was 46.7 (12.2) years; mean disease duration was 15.5 years	A prospective, 2-center study of 103 neurologically stable pwMS OCR-treated patients who were initiated on ocrelizumab or were receiving ocrelizumab for > 12 months. PRO measures included Neuro-QoL short forms, SymptoMScreen, and Work Productivity and Activity Impairment Questionnaire. Symptoms were assessed at the start-cycle, mid-cycle, and end-cycle time points in each of the two infusion cycles	Neuro-QoL domain scores did not change significantly across either cycle 1 or cycle 2 except for the Sleep domain in cycle 1 ($p = 0.03$) SymptoMScreen scores did not change significantly across either cycle 1 or cycle 2 except for the sensory domain of cycle 1, dexterity domain of cycle 2, and depression score in cycle 2 (Friedman test: $p = 0.024$, $p = 0.048$, and $p = 0.007$, respectively) SymptoMScreen depression score in infusion cycle 2 improved from week 36 to week 46 (1.07 ± 1.23 vs 0.84 ± 1.10, $p = 0.005$)

AE adverse event, *BDI* Beck Depression Inventory, *CES-D* Center for Epidemiologic Studies Depression Rating Scale, *CI* confidence interval, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *EHD* Echelle d'Humeur Dépressive, *EMIF-SEP* French version of modified Fatigue Impact Scale, *EQ-5D-5L* EuroQoL EQ-5D-3L, *HADS* Hospital Anxiety and Depression Scale, *HAM-D* Hamilton Depression Rating Scale, *HRQoL* health-related quality of life, *IFN-β* interferon beta, *MFIS* Modified Fatigue Impact Scale, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *MusiQoL* Multiple Sclerosis International Quality of Life questionnaire, *NAWM* normal-appearing white matter, *Neuro-QoL* Quality of Life in Neurological Disorders, *OCR* ocrelizumab, *PET* positron emission tomography, *PHQ-9* Patient Health Questionnaire-9, *POR* Providence Ocrelizumab Registry, *pwMS* people with multiple sclerosis, *QoL* quality of life, *RMS* relapsing multiple sclerosis, *RRMS* relapsing-remitting multiple sclerosis, *SD* standard deviation, *SAE* serious adverse event, *SPMS* secondary progressive multiple sclerosis, *TLS* Two-Life Scale, *W48* week 48, *WPAI:SHP* Work Productivity and Activity Impairment scale: Specific Health Problem

The separation of treatment efficacy and induction of depression/fatigue in pwMS is further supported by a retrospective chart review involving 2611 pwMS taking interferons (beta-1a/1b and peginterferon), low-efficacy immunomodulators (glatiramer acetate), low-efficacy cell depleters (teriflunomide, dimethyl fumarate, and diroximel fumarate), high-efficacy cell depleters (alemtuzumab, rituximab, ocrelizumab, and cladribine), or high-efficacy, cell restrictors (natalizumab, fingolimod, and siponimod). In this study, no significant differences in the odds of being diagnosed with depression were found between treatments [95]. Another study determined that there was no association between treatment with moderate-efficacy (interferons, glatiramer acetate, dimethyl fumarate, and teriflunomide) or high-efficacy DMTs (fingolimod, natalizumab, ocrelizumab, rituximab, alemtuzumab, daclizumab, and autologous hematopoietic stem cell transplantation) and fatigue in people with relapsing MS [99]. It is important to note that classification of DMTs as low-, moderate-, or high-efficacy treatments may be subjective, and classifications can differ depending on the study and the practitioner's real-world experience in clinical practice.

Depression is listed as a side effect in the prescribing information for several DMTs approved for MS (Table 1). Depression is listed as an adverse reaction for natalizumab [100] and as a warning/precaution for Avonex (interferon beta-1a) [101]. The prescribing information for Avonex states to consider discontinuation in depression occurs (Avonex, US Food and Drug Administration, 1996). Depression is not listed as a side effect, adverse reaction, or warning in US prescribing information for teriflunomide [102], alemtuzumab [103], ocrelizumab [104], ofatumumab [105], ublituximab [106], fingolimod [107], siponimod [108], ozanimod [109], ponesimod [110], cladribine [111], diroximel fumarate [112], dimethyl fumarate [113], or glatiramer acetate [114]. Nevertheless, these data should be cautiously interpreted since most randomized controlled trials in MS have not included depression as a primary, secondary, or tertiary endpoint. The impact of DMTs on depression in pwMS, whether positive or negative, is unclear and beyond the scope of this article; further clinical research and real-world experience are needed.

MANAGEMENT OF DEPRESSION IN MS IN CLINICAL PRACTICE

Early screening for depression and intervention is important, as depression can become persistent in pwMS [115]. PwMS experience barriers to identifying and managing symptoms of depression in clinical practice. For example, MS providers have reported not regularly screening for depression [116], and standardized tools are not frequently used to screen for depression in clinical practice [117]. In one study involving 260 participants with MS, only 24% were screened with a depression tool, with MS providers preferring to rely on subjective assessment [117]. MS providers reported that lack of screening was, in part, due to lack of support staff and a perception of limited treatment options [117]. MS providers have reported lacking the time and expertise to manage depression once identified and often opt to leave mental health management to the patient's primary care provider [116]. As mentioned earlier, if depression is not addressed in pwMS it is likely disease will worsen because of adverse effects on QOL [10], decreased treatment adherence [14–16], increased symptom severity [17], and worse disability/functional outcomes [18, 19] and may impact suicide risk [20]. For treating depression in pwMS, the AAN guidelines suggest clinicians consider using a telephone-administered cognitive behavioral therapy (CBT) program as evidence supporting or refuting use of antidepressants and individual and group therapies was lacking at the time the guidelines were developed [71].

STRATEGIES TO MANAGE DEPRESSION IN PATIENTS WITH MS

Pharmacologic and non-pharmacologic therapies are widely used to treat depression in pwMS. However, further research is needed to support or refute the effectiveness of many treatments in the MS population [81]. Currently, there is no gold standard, single treatment for the management of depression in MS [19]. Combination therapy may be beneficial; however, further research is needed to determine efficacy, safety, and feasibility [19].

Potential strategies to manage depression in patients with MS include pharmacologic and non-pharmacologic interventions, education for medical providers who treat MS, and establishing multidisciplinary care teams. These multifaceted approaches are discussed in more detail below.

Non-pharmacologic Interventions

Several non-pharmacologic interventions for depression in pwMS have been studied (Table 2), with generally mixed findings. CBT is commonly used and may be an effective strategy to treat depressive symptoms in the MS population. CBT is usually delivered by a mental health specialist as part of the MS care team, such as a psychologist or psychiatrist (either virtually or in person), and can take place in either an individual or group setting [118]. CBT interventions reduce symptoms of depression, anxiety, pain, and fatigue in pwMS [119–125]. The AAN Evidence-Based Guidelines for the Assessment and Management of Psychiatric Disorders in Individuals for MS states a 16-week program of individual CBT administered on the telephone is possibly effective and may be considered in treating depressive symptoms in pwMS [71]. Notably, the AAN guidelines were published in 2014; thus, more up-to-date guidelines for the management of depression in pwMS are needed.

Recently, an MS-specific internet-based CBT (iCBT) tool has demonstrated efficacy in reducing depressive symptoms in pwMS [119]. A phase III, randomized, controlled trial involving 279 pwMS and depressive symptoms evaluated the safety and efficacy of an MS-specific, iCBT program for the treatment of depressive symptoms associated with MS. The study revealed that the iCBT program (on top of usual treatment) significantly reduced depressive symptoms compared with the control group who received the usual treatment [119]. In addition, the ongoing ACTION-MS study, a phase II randomized controlled trial, is currently assessing the effectiveness of a tailored CBT intervention for newly diagnosed MS compared to a supportive listening intervention in pwMS and depression (ISRCTN trials registry, ISRCTN63987586) [126]. In contrast, another study indicated that CBT was ineffective in reducing depressive symptoms in pwMS experiencing pain [120], which may suggest that efficacy of CBT therapy to treat depression in MS may depend upon the individual's MS symptoms.

Emerging evidence suggests that mobile/digital apps may be beneficial tools in managing depression in pwMS. A systematic review of 13 randomized controlled trials that studied mobile health interventions for pwMS suggest that mobile self-guided digital health applications may have utility in improving depression in pwMS [127]. The MS CATCH (Care technology to Ascertain, Treat and engage the Community to Heal depression in patients with MS) is a single-site, randomized, phase II study examining the clinical impact of a novel smartphone-based depression management tool on depressive symptoms in pwMS [128]. The tool aims to help bridge the communication gap between patients and their clinician by having patients complete monthly questionnaires, the results of which are made available to the clinician via their electronic medical record.

Newer, efficacious cognitive behavioral therapies, including acceptance and commitment therapy (ACT), dialectical behavior therapy, mindfulness-based stress reduction, and

mindfulness-based cognitive therapy, may be effective to treat depression in pwMS, but currently available evidence of their benefit is mixed [129]. ACT has demonstrated promising effects in long-term conditions including chronic pain and chronic disease [130, 131], which may translate to MS. We believe that the type of language used in ACT (such as allowing, flexibility, etc.) may be better suited to pwMS and generalizable across chronic health conditions compared with the type of language used in CBT (such as challenge and rationalize).

Behavioral factors that may have a protective effect against depression in MS have also been identified (Fig. 1). Disease "mastery" (greater perceived disease control) may reduce the risk of developing depression in pwMS [132, 133]. A longitudinal study analyzing data from the Health Outcomes and Lifestyle in a Sample of People With Multiple Sclerosis (HOLISM) study involving 839 participants found that those who reported the highest disease mastery (as measured by the Pearlin Mastery scale) had a > 60% reduced risk for developing depression (as measured by PHQ-9) [132]. Moreover, receiving higher levels of social support has been associated with lower depression (as assessed using CES-D) in pwMS [133]. Other factors including having higher levels of self-efficacy, self-esteem, and being married have been associated with a reduced risk of depression in pwMS, which may suggest that improving self-esteem and self-efficacy are possible targets for intervention to reduce depression in MS [11].

Providing mental health training and education to health care providers who treat MS may be an effective strategy to improve management of depression in MS. MS clinicians (including nurses and neurologists) have reported a need for evidence-based guidance and more education and training to improve practices, including screening for depression and collaborative management [116]. To improve collaborative management of patients, adopting a multidisciplinary care approach may be an effective strategy in managing depression in pwMS. A multidisciplinary MS Care Unit is comprised of different health care professionals, such as MS neurologists and nurses, neuropsychologists, clinical psychologists, physiotherapists, occupational therapists, speech therapists, social workers, and administrative personnel, who work together as well as work with the patient [134]. Cross-team collaboration/co-management of patients between neurologists and mental health professionals may help to overcome reported barriers to depression management (e.g., lack of time/lack of expertise in managing depression reported by neurologists/MS nurses) [116]. However, many countries do not provide pwMS adequate access to or coverage/reimbursement for a multidisciplinary care approach [135], suggesting the need for systemic change.

Adequate nutrition is another factor for consideration in treatment of pwMS and depression. This is highlighted by data indicating that serum vitamin D deficiency may be a risk factor for depression in pwMS [46]. Furthermore, vitamin D supplementation may be effective in reducing depressive symptoms in pwMS, though evidence is mixed [136, 137]. More evidence is needed to determine whether vitamin D supplementation is of actual benefit to pwMS and depression.

Pharmacologic Intervention: Antidepressants

Antidepressants are commonly prescribed to treat depression, including in pwMS [71]. However, few clinical studies have been conducted using antidepressants to treat depression in pwMS, making comparisons across agents difficult [138]. Recently, a small observational study found that 6 months of treatment with vortioxetine significantly reduced depression (as measured by BDI-II) in a population of 17 pwMS and depression [139].

When selecting an antidepressant for a person living with MS, it is important to consider the whole patient as an individual and consider which side effects they can tolerate [138]. The AAN Evidence-Based Practice Guideline for the Assessment and Management of Psychiatric Disorders in Individuals with Multiple Sclerosis states that "there is insufficient evidence to support or refute the efficacy and use of sertraline, desipramine, and paroxetine in the MS population" [71].

Table 2 Summary of non-pharmacologic interventions to treat symptoms of depression in pwMS

Intervention	Administration	Summary of evidence
CBT	Mental health specialist, e.g., psychologist or psychiatrist	A meta-analysis of 15 clinical trials found that CBT is effective in managing depression in pwMS [122] CBT administered on the telephone has led to improvements in depression [123] No significant difference between CBT + SOC vs MS-related education + SOC in reducing depressive symptoms in patients experiencing pain [120] CBT has demonstrated positive effects for other MS symptoms including pain and fatigue [120, 125]
Internet-based CBT	Internet-based, self-administered by the patient	Internet-based CBT + SOC significantly reduced depressive symptoms vs SOC alone in a phase 3 study [119] Significant effect in favor of internet-based CBT vs control group in a randomized controlled trial [155] Numerically favorable results for CBT + SOC vs SOC alone in a small pilot study [156]
Newer, efficacious CBT, e.g., Acceptance and commitment therapy (ACT) Dialectical behavior therapy Mindfulness-based stress reduction Mindfulness cognitive therapy	Usually via mental health specialist, e.g., psychotherapist	May be effective, although current evidence is mixed; more rigorous and conclusive evidence is needed [129] ACT has demonstrated promising effects in other chronic conditions [130, 131]
Vitamin D	Oral supplement	Evidence is mixed: a small study indicated that symptoms improved with vitamin D replacement (10,000 IU daily for 12 months) [136], while a randomized, placebo-controlled study found no significant difference (14,000 IU daily for 48 weeks) [137]

CBT cognitive behavioral therapy, *HADS-D* Hospital Anxiety Depression scale-Depression Subscale, *IU* international unit, *MS* multiple sclerosis, *SOC* standard of care, *pwMS* people with multiple sclerosis

Several clinical studies have been conducted to determine whether there are any beneficial effects of cannabinoids for relieving MS symptoms in pwMS, including QOL and depression [140]. Most of these studies demonstrated positive effects of cannabinoids in reducing many MS symptoms, including pain and spasticity, although the evidence for QOL, including depression, proved inconsistent [141, 142]. Since no single treatment exists for management of depression in pwMS, a combination of pharmacologic and non-pharmacologic interventions, education for medical providers, and multidisciplinary care teams may be beneficial.

RESOURCES FOR HEALTH CARE PROVIDERS TREATING PWMS

The following resources are available to health care providers who treat MS for further information on MS and the role that depression and other mental health factors play in this debilitating illness:

- UpToDate resource:
  - Symptom management of multiple sclerosis in adults. (Includes module on depression.) Link: https://www.uptodate.com/contents/symptom-management-of-multiple-sclerosis-in-adults?search=depression%20multiple%20sclerosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
- National MS Society resources:
  - Resources and tools for clinicians. Link: https://www.nationalmssociety.org/for-professionals/for-healthcare-professionals/clinical-practice-tools/resources-and-tools
  - Publications for clinicians on mental health: Link: https://www.nationalmssociety.org/For-Professionals/Clinical-Care/Resources-for-You-and-Your-Practice/Publications#section-2

CONCLUSIONS

Although it is frequently unrecognized, underdiagnosed, and undertreated, depression is a prevalent comorbidity in pwMS. Depression negatively impacts pwMS, leading to reduced treatment adherence, increased MS symptom severity, poorer QOL, and worse disability and functional outcomes. The pathogenesis of depression in pwMS is complex and may involve factors such as brain abnormalities, genetics, and immune pathways as well as personality traits, presence of comorbid conditions, and lifestyle factors.

Assessing depression in pwMS is challenging, as symptoms of MS and depression overlap. There are multiple PROs for evaluating depression and some have been specifically adapted for use in pwMS, such as the MS-BDI. However, much work is still needed in standardizing assessment methodologies for pwMS and depression across the clinical landscape.

In addition to evaluating depression in pwMS, the impact of DMTs on depression outcomes in this population has been examined in some clinical studies, although recent studies have been ambiguous at best, ranging from therapies having "no impact" to having "some improvement." Furthermore, strategies for depression management in pwMS, such as pharmacologic and non-pharmacologic interventions, have seen some advancements. CBT-based interventions appear effective for managing depression in pwMS. Providing mental health training and education to health care providers who treat pwMS and establishing multidisciplinary care teams have emerged as positive ways forward to improve management of depression in pwMS, although these approaches are still in development.

Despite positive developments in this disease area, further studies are necessary to clarify the complex relationship between MS and neuropsychiatric disorders such as depression. To improve the overall patient experience and QOL for pwMS, there is a clear and critical need for a greater understanding of and insight into the how factors such as functional and structural

brain abnormalities, genetics, immunology, and side effects related to DMTs ultimately may influence depression in MS. Standardized evaluation tools and consistent management strategies for MS providers are also an integral part of diagnosing and treating depression in MS. Many of these issues can potentially be explored as important endpoints within the framework of larger randomized controlled trials that assess the effectiveness of pharmacologic therapies and psychotherapy in pwMS and with depression. In addition, updated guidelines integrating up-to-date information about screening tools and recommendations for managing depression would greatly improve outcomes in pwMS.

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Declarations

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