COMORBIDITIES in MULTIPLE SCLEROSIS: A Clinical Resource Guide

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# COMORBIDITIES in MULTIPLE SCLEROSIS: A Clinical Resource Guide

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TARGET AUDIENCE
This activity is intended for neurologists, nursing professionals, PAs, rehabilitation professionals, mental health specialists, case workers, and other clinicians involved in the management of patients with MS.

LEARNING OBJECTIVES
Upon completing this activity, the participant should be better able to:
• List comorbidities commonly occurring in patients with MS
• Review the impact of comorbidities on initiating disease modifying therapy (DMT) for MS patients
• Identify symptoms of common comorbidities that may mimic symptoms of MS or MS relapse
• Apply strategies to diagnose comorbidities in MS patients
• Employ best practices for involving other members of the health care team or referrals if appropriate when managing comorbidities
• Review optimal treatment approaches to comorbidities in MS patients
• Employ best practices to engage patients in shared decision making regarding the management of their comorbidities and MS care

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INTRODUCTION

Multiple sclerosis (MS) is associated with significant neurological symptoms and accumulation of disability that can have an impact on a person’s quality of life, independence, and activity.\(^1\) Compared with persons who have other chronic diseases, persons with MS have lower scores on measures of health, physical function, and social interactions.\(^1\) Several conditions often co-occur with MS, with a variety of implications for the disease and the person’s well-being.

Comorbidity is defined as a co-occurring disease among individuals with an index disease, in this case MS.\(^2\) The aim of this resource guide is to help clinicians recognize and differentiate comorbidities from MS symptoms, understand the impact of comorbidities on individuals, make decisions about treatment in the setting of comorbidities, and manage comorbidities in collaboration with other health care professionals. The general prevalence and impact of comorbidities in MS will be reviewed, with the greatest focus on psychiatric, vascular/metabolic, and autoimmune comorbidities. Conditions defined as comorbidities in this document are those that are chronic in nature and that originate by a mechanism that is distinct from the underlying MS.\(^3\)
Among a group of 8,983 participants with MS who responded to a questionnaire, 77.1% indicated that they had at least 1 physical comorbidity: 30.4% had 1 comorbidity, 25.6% had 2 comorbidities, and 44.1% had 3 or more. Many of these comorbidities were severe enough to require treatment. Demographic characteristics that were associated with increased odds of having a physical comorbidity were male sex, African American race, lower socioeconomic status, and age over 60 years.

The presence of comorbid conditions with MS may partly explain the heterogeneity in outcomes of persons with MS.

A systematic review of 249 studies examined the incidence and prevalence of the comorbidities in MS. The resultant meta-analysis of population-based studies demonstrated that the comorbidities with the highest incidence (per 100 persons [95% confidence interval {CI}]) were cancer (4.3 [2.67, 6.1]), hypertension (3.73 [CI not available; 1 study]), and stroke (2.73 [2.51, 2.95]) (Figure 1). The most prevalent comorbidities (per 100 persons [95% CI]) in the meta-analysis were depression (23.7 [17.4, 30.0]), anxiety (21.9 [8.76, 35.0]), hypertension (18.6 [13.9, 23.2]), hyperlipidemia (10.9 [5.6, 16.1]), and chronic lung disease (10.0 [0, 20.9]) (Figure 2).

A health claims study of 23,382 incident cases of MS and 116,638 age-, sex-, and geographically-matched persons showed that persons with MS had a significantly higher prevalence of hypertension, diabetes, ischemic heart disease (IHD), inflammatory bowel disease (IBD), anxiety, bipolar disorder, chronic lung disease, depression, epilepsy, fibromyalgia, and schizophrenia at MS diagnosis compared with the matched population during the same period. The onset of MS symptoms may be related...
to the presence of comorbidities. In a registry-based study from the North American Research Committee on Multiple Sclerosis (NARCOMS) of 8,983 persons with MS, persons with physical comorbidities (e.g., vascular, autoimmune, gastrointestinal, or musculoskeletal) had an onset of MS symptoms at a later age compared with persons without comorbidities. In all categories except for gastrointestinal, an increase in the number of comorbidities correlated with an increase in the mean age of MS onset. The mean age of the onset of MS symptoms was not different between those with or without psychiatric comorbidities. The authors postulated several reasons for the relationship of age and comorbidity presence, including the increased prevalence of comorbidity with increasing age in the general population, or the possibility of comorbidity delaying the onset of MS or the recognition of MS, because symptoms are mistakenly attributed to another condition.

The presence of comorbidities may also be related to the clinical course of the disease. In the same registry study described above, persons had increased odds of relapsing MS at onset if they reported psychiatric comorbidities at disease onset (odds ratio [OR]: 1.48; 95% CI: 1.08, 2.01). Women also had increased odds of relapsing MS at onset if they had gastrointestinal comorbidities (OR: 1.78; 95% CI: 1.25, 2.52) or obesity (OR: 2.08; 95% CI: 1.53, 2.82).

Little is known about the cause of the increased prevalence of comorbid conditions in MS and further studies in this area are needed.
**Health-Related Quality of Life (HRQoL)**

Comorbidities in MS influence HRQoL. In the NARCOMS registry study of 8,983 persons with MS, the mean score for physical HRQoL as measured by the Short-Form 12 was 5 points lower in persons with a physical comorbidity than in those with no physical comorbidity, indicating a worse HRQoL (P<0.0001). Individual comorbidities that were independently associated with reduced physical HRQoL were hypertension, heart disease, lung disease, thyroid disease, peptic ulcer disease, arthritis, IBS, anemia, and fibromyalgia. There was an inverse relationship between the number of comorbidities reported and the physical HRQoL scores, which may suggest that clinicians should aggressively manage comorbidities as a means to improve HRQoL in MS. As one might expect, psychiatric comorbidities negatively affected mental HRQoL, as did IBS and fibromyalgia.

A group of 949 adults with MS self-reported their HRQoL; comorbidities; fatigue; diagnoses of depression, anxiety, and bipolar disorder; and symptoms of depression and anxiety (by the Hospital Anxiety and Depression Scale [HADS]) on a questionnaire. The most frequently reported comorbidities were depression (29.0%), hypertension (17.8%), migraine (17.3%), hypercholesterolemia (12.4%), and anxiety disorder (11.5%). In this study, 63% of the participants had HRQoL scores that indicated severe disability (i.e., Health Utilities Index Mark 3 global utility score <0.7). Physical comorbidity was associated with diminished HRQoL. However, the effects of physical comorbidity on HRQoL appeared to be mediated by the effects on mood and fatigue.

Depression is one of the most significant predictors of low HRQoL in MS for several reasons. Individuals with depression have impaired motivation and interest, leading to decreased physical progress. Depression often occurs when an individual is not coping well and may indicate that the stressors are reaching a critical limit for the individual. The presence of depression may alter the individual’s perception of herself and her surroundings, such that her assessment is more negative than it would be otherwise. Other factors that affect HRQoL, such as pain, low self-esteem, or a lack of support, may also affect mood.

Anxiety is associated with reduced HRQoL in general, but there are few studies specifically in MS. A survey of 209 persons with MS in Spain showed that scores for HRQoL were correlated with scores on emotional tests (including anxiety), with decreased mental health functioning being associated with reduced quality of life. In a separate study, increased symptoms of anxiety were directly associated with reduced HRQoL, and this relationship became stronger when the indirect influence of anxiety through fatigue or depression were factored in. In this study, the effects of depression and anxiety on HRQoL were as large or larger than the effects of disability in MS. These findings indicate a substantial need to address and treat psychiatric comorbidities in persons with MS.

### Prevalent comorbid conditions in MS

- Depression
- Anxiety
- Hypertension
- Migraine
- Dyslipidemia
- Chronic Lung Disease
Relapses and Disability

Comorbidity in MS is associated with an increased risk of MS relapse. In a prospective study of 885 persons with MS, those with 3 or more comorbid conditions at baseline experienced more relapses over 2 years compared with persons who had no comorbid conditions at baseline (adjusted rate ratio: 1.45; 95% CI: 1.00, 2.08). Analysis of individual comorbid conditions revealed that migraine and dyslipidemia were independently associated with an increased risk of relapse.14

The presence of comorbidities in MS is also associated with disability. In a prospective, population-based register study of 4,519 persons with MS in Sweden, musculoskeletal and mental comorbidities were associated with a higher risk of having a disability pension, but cardiovascular comorbidities were not.15 In addition, psychiatric disorders and MS had a synergistic influence on the risk of a person with MS having a disability pension.15

Vascular and metabolic comorbidities have a substantial influence on the person with MS. Respondents in the NARCOMS registry with a vascular comorbidity at MS diagnosis had a decreased time to ambulatory disability compared with those without a comorbidity, as assessed by Kaplan-Meier analysis, and these individuals had a 1.5-fold increased risk of ambulatory disability.5 The presence of 1 vascular comorbidity at MS diagnosis was associated with a 51% increased risk of early gait disability (assessed by the Patient-Determined Disease Steps) and the presence of 2 comorbidities was associated with a 228% increased risk.5 Most of the prevalent comorbidities (dyslipidemia, hypertension, diabetes, and peripheral vascular disease) were independently associated with an increased risk of ambulatory disability across many endpoints that were examined.5

A cross-sectional, case-control study in an Italian hospital examined the Framingham General Cardiovascular Disease Risk Score (FR) in 265 persons with MS and 530 matched control persons.16 In this study, there was no difference between the two groups for predicted risk of cardiovascular events within 10 years, overall or by sex.16 However, cardiovascular risk factors, including modifiable ones, appeared to affect the MS-related disability (as measured by Multiple Sclerosis Severity Score), though it was the interaction of the cardiovascular factors (measured by FR), and not any one specific factor, that was associated with time to disability.16 General cardiovascular risk was also associated with a secondary progressive course of MS.16

A prospective study in Brazil of 110 persons with relapsing-remitting MS (RRMS) or secondary-progressive MS (SPMS) and 175 matched healthy volunteers examined the participants’ metabolic status and any interaction with disability status (individuals with a diagnosis of diabetes mellitus were excluded from the study).17 Body mass index (BMI) and waist circumference were not significantly different between the two groups.17 However, persons with MS had significantly higher plasma insulin, LDL cholesterol, and triglyceride levels than the control group.17 Additionally, the MS group had a significantly higher homeostasis model assessment – insulin resistance (HOMA-IR) score, a measure of insulin sensitivity – than the control group.17 The prevalence of insulin resistance was 40% in persons with...
MS and 21.1% in the control group (OR: 2.48; 95% CI: 1.47, 4.21). A multivariable analysis showed that plasma insulin and the HOMA-IR score were associated with Expanded Disability Status Scale (EDSS) score.

**MS Treatment**

Individuals with comorbidities may experience delays in treatment initiation. In a retrospective cohort study of claims data from 10,698 persons with incident MS, 29.6% initiated a disease modifying therapy (DMT) after the diagnosis (index date). One year after the diagnosis, a “dose-response” relationship was found such that each increase in number of comorbidities was associated with a 10% reduction in the likelihood that the person would initiate a DMT. Five years after the diagnosis, this figure was 42%. Individual comorbidities present at the index date that were significantly associated with a reduced likelihood of starting DMT were ischemic heart disease and anxiety. It should be noted that the primary DMTs available to treat MS at the time of this study were interferon beta (IFNβ) and glatiramer acetate (GA). The presence of comorbidities is also associated with lower medication persistence. A retrospective study of 20 Italian MS clinics representing 2,076 persons with MS found that comorbidities had a significant effect on the switch from the first DMT due to medication intolerance, specifically for IFNβ. There was no association between specific comorbidities and the probability of switching due to intolerance.

**Pain**

Pain that limits activity is common in persons with MS. A prospective study of 949 persons with MS recruited from 4 MS clinics in Canada used questionnaires to evaluate the relationship of MS and comorbid conditions with pain that interfered with activity. The incidence of new disruptive pain was reported by 31.1% of respondents. Of the participants who had a comorbidity, 54.5% reported experiencing disruptive pain compared with 30.7% of persons without a comorbidity (OR: 2.70; 95% CI: 2.07, 3.54). The presence of more comorbid conditions was associated with a greater frequency of disruptive pain. When the progression of pain was analyzed by comorbid condition, fibromyalgia, IBD, rheumatoid arthritis (RA), IBS, migraine, COPD, depression, and hypertension were associated with increased odds of pain, which persisted over time. Autoimmune thyroid disease was associated with the presence of worsening pain (adjusted OR: 1.49; 95% CI: 1.07, 2.08).

**Fatigue**

Fatigue is also a significant symptom of MS and interacts with comorbidity. An analysis of the same population revealed that some fatigue was reported by 78% of the cohort; 84.5% of those with comorbidities reported fatigue compared with 66.8% of those without a comorbidity (OR: 2.96; 95% CI: 2.16, 4.07). Individuals with glaucoma, fibromyalgia, cataracts, or anxiety reported the highest median fatigue scores. The presence of fatigue in MS was also related to autoimmune comorbidities. Persons with MS who had IBD at baseline were more likely to report fatigue.

**Monitoring and treating comorbidities may help improve pain in MS, while also identifying potential (undiagnosed) comorbidities that may be present in persons with incident pain.**
IMPACT OF COMORBIDITIES IN MS (CONTINUED)

compared to those without IBD. Depression was associated with worsening fatigue over time (OR: 1.49; 95% CI: 1.08, 2.07).

In a study of a fatigue self-management intervention in 181 persons with MS, individuals with comorbid diabetes had a significantly slower rate of improvement on the Fatigue Impact Scale (FIS) than those without diabetes, and individuals with comorbid arthritis had a significantly worse ability to maintain improvements on the FIS over time. Therefore, protocols for fatigue management may need to be customized for persons who are managing MS while simultaneously managing diabetes or arthritis, and possibly other comorbid conditions, although further study is needed.

Hospitalization

Persons with MS who have comorbidities have an almost 3-fold increased rate of hospitalizations due to any cause, compared with those without a comorbidity (rate ratio [RR]: 2.88; 95% CI: 1.41, 3.43). Crude hospitalization rates increased with an increasing number of comorbidities. Comorbidities including hypertension, diabetes, ischemic heart disease, chronic lung disease, depression, and bipolar disorder were associated with higher rates of hospitalization in the MS population, which was also seen in the matched population. Comorbidity in MS was not associated with an increased risk of MS-related hospitalizations. Thus, prevention and management of comorbid conditions in MS may reduce hospitalizations that are not related to MS.

Vascular and metabolic comorbidities are linked to increased rates of hospitalization. A Canadian claims analysis of 4,875 persons with MS and 24,544 matched controls showed that hypertension was associated with an increased risk of non-MS-related hospitalizations (RR: 1.58; 95% CI: 1.36, 1.86), as was diabetes (RR: 1.49; 95% CI: 1.25, 1.77) and heart disease (RR: 2.01; 95% CI: 1.67, 2.41).

Mortality

A health claims study of 5,797 persons with MS and 28,807 matched persons showed that, within the MS population, comorbidity was associated with increased mortality. In this population, after MS, diseases of the circulatory system were the most common cause of death. However, depression in MS was associated with higher mortality in MS compared with the general population. Diabetes was associated with a 47% increase in the hazard of death (95% CI: 1.25, 1.73) and ischemic heart disease was associated with a 50% increase (95% CI: 1.28, 1.75) compared with persons with MS who did not have the comorbidity. However, the magnitude of this effect was less than in the matched population, possibly due to a ceiling effect. A separate claims analysis from the United States Department of Defense showed that persons with MS were twice as likely (RR: 2.1; 95% CI: 1.7, 2.7) to die from a disease of the circulatory system compared with individuals in a matched control group without MS.
Prevalence and incidence of psychiatric disorders in MS

The burden of psychiatric comorbidity in MS is substantial, although the estimated prevalence varies depending on the measurement approach used. Responses to a questionnaire from 8,983 persons with MS showed that nearly half reported a psychiatric comorbidity: 46.0% reported depression, 16.5% reported anxiety, 2.4% reported bipolar disorder, and 0.2% reported schizophrenia. Of these persons self-reporting a lifetime history of a psychiatric comorbidity, not all were currently being treated for the comorbidity: 74.6% of those with depression, 67.9% of those with anxiety, 65.0% of those with bipolar disorder, and 72.7% of those with schizophrenia were being treated for their condition.

From self-reports of 949 adults with MS, 39% reported clinically-meaningful symptoms of anxiety and 21% reported clinically-meaningful symptoms of depression. Another Canadian population-based study of health claims found that the age-standardized incidence of depression was 71% higher in persons with MS than in an age-, sex- and geographically-matched population, and the prevalence of depression was 79% higher. For anxiety, the age-standardized incidence was 42% higher and prevalence was 58% higher in persons with MS than in matched controls. The incidence and prevalence of bipolar disorder were 2-fold (approximately 200%) higher in persons with MS than in matched controls. The incidence of the psychiatric comorbidities, except schizophrenia, was stable over time (1990 through 2010), while prevalence increased slightly.

In another population-based analysis of health claims from Alberta, Canada, the prevalence of psychotic disorders in the general population was 1.3%, and around 2.5% in persons with MS, with the highest prevalence in the 15- to 24-year age group of just over 4%. Suicide may be twice as common in individuals with MS compared with the general population.

Most prevalent psychiatric conditions in MS

Depression

Anxiety

Demographic characteristics that were associated with an increased likelihood of self-reporting a psychiatric comorbidity were female sex, Caucasian race, and lower socioeconomic status. The prevalence of psychiatric comorbidities over time has been generally stable. A Canadian claims study showed that depression, anxiety, and bipolar disorder were more prevalent in women than in men, while schizophrenia was more common in men than in women. However, men have a disproportionately higher sex-specific prevalence of depression (82% higher) than women (59% higher) and anxiety (men: 78% higher; women: 57% higher) compared with a matched control population without MS.

Depression in MS can arise from different sources. In some cases, it is related to the challenge of coping with a difficult disease. In other cases, the cause of depression is similar to psychosocial stressors that affect the general population, including job stress, financial worries, or relationship issues with partners or family. Biologic factors in MS also play a role in developing depression. Structural brain changes in MS correlate with the presence of MS-related depression. Inflammation in MS may also be a contributing factor to developing depression, as the link between depression and inflammation has been noted in the general population.

Depression in MS is significantly related to disability scores on the EDSS, which appears to be an independent contributor.
Strategies for diagnosing psychiatric disorders in persons with MS

Psychiatric comorbidities are underdiagnosed in persons with MS. In a study of 8,983 persons with MS, 30% of participants who did not self-report a diagnosis of depression and 15% of those who did not report any psychiatric comorbidity had scores on the Center for Epidemiologic Studies Depression Scale (CESD) that were above the threshold for probable major depression. The rate of undiagnosed anxiety was not measured in this study. When diagnosed and undiagnosed neuropsychological comorbidities (depression, anxiety, bipolar disorder, schizophrenia) are considered, more than 60% of persons with MS may be affected.

In a prospective study of 152 persons seen at a Canadian MS clinic, 20 (13.2%) had scores on the Structured Clinical Interview for DSM-IV (SCID) that indicated they had depression at the time. Of this group, 16 (80%) were being treated for depression as follows: 13 (65%) were taking medication for depression, 3 (15%) were receiving nonpharmacological treatment for depression, and 6 (30%) were receiving both. The authors suggest that the under-treatment of depression may be diminishing as there is increased awareness of the extent of depression in MS and as the use of antidepressants in the general population increases as well. In addition, many of those individuals who were receiving treatment continued to be depressed, indicating that clinicians should focus on optimizing treatment for depression.

Depression screening and diagnosis are improving in MS, but depression remains under-treated in MS. Primary care clinicians and MS specialists should conduct routine screening for psychiatric disorders in persons with MS, preferably at every clinic visit. Depression and anxiety are some of the most common preexisting conditions at MS diagnosis, particularly among individuals between the ages of 20 and 44 years old. Therefore, these comorbidities should be considered and persons with MS should be evaluated from MS diagnosis.

There is no standard tool that is consistently used to identify depression in MS. The American Academy of Neurology suggests that clinicians may use the Beck Depression Inventory and the General Health Questionnaire to screen for depressive symptoms. Many other psychiatric screening tools have been used in MS, but few have been fully evaluated so the nature of their use remains equivocal. A systematic review of psychometric studies found some evidence to support the use of the HADS and CESD instruments to screen for depression in MS. In addition, the use of the Beck Depression Inventory Fast Screen (BDI-FS) or the BDI-II was suggested to remove the influence of somatic symptoms or other MS-related factors from the measures. A recent study examining psychiatric screening tools in MS found that HADS-Depression and the HADS-Anxiety most closely estimated the prevalence of major depression and generalized anxiety, respectively, as diagnosed by the SCID, in a sample of persons with MS. The HADS also demonstrated good internal consistency, reliability, test-retest reliability, and evidence of construct validity. The same study also found that the Patient Health Questionnaire-9, and PROMIS Depression Short Form-8a performed similarly to the HADS.
In a prospective study of 25 persons who were admitted to the hospital for MS-related reasons, those who were diagnosed with depression (from the SCID, Axis I) showed elevated scores on the Hamilton Depression Rating Scale (HDRS), the In-person Multidimensional psychiatric scale, and the Montgomery-Åsberg Depression Rating Scale, providing some evidence for the clinical validity of these scales in MS. However, the authors point out that elevated depression scores, such as those on the HDRS, may be influenced by criterion contamination (ie, somatic symptoms of MS or side effects of MS therapy), and not completely reflective of depressive mood. The study used a small sample size and, therefore, the utility of the data in the general MS population is unknown.

The Patient Health Questionnaire-9 showed reasonable sensitivity and specificity to identify suicidal ideation in persons with MS. Additionally, asking persons about their hope for the future may help assess their risk for suicide. Persons with MS who have depression often show signs such as irritability, frustration, and discouragement, rather than guilt or low self-esteem. When possible, speak to family members, caregivers, or other healthcare professionals who know the person to discuss their observations of the person’s mood, behavior, and thought process. These discussions may help make a diagnosis and determine the severity of the symptoms, especially for manic symptoms, as persons may sometimes lack insight into their symptoms.

A systematic review in 2016 reported that three screening instruments for anxiety have been tested in MS: the HADS, the Beck Anxiety Inventory (BAI), and the 7-item Generalized Anxiety Disorder Scale (GAD-7). Of these tools, the HADS had the highest sensitivity and specificity and may be considered a potential screening tool for anxiety in persons with MS. A subsequent study found that the diagnostic performance of the HADS, PROMIS Anxiety Short-Form 8a, GAD-7, and Overall Anxiety and Severity Impairment Scale were adequate and similar.

Early data on IFNβ in RRMS showed a small number of study discontinuations due to psychiatric adverse events, such as a suicide, confusion, and emotional instability. Therefore, there were concerns about the effects of IFNβ on the risk of neuropsychiatric comorbidities. A secondary analysis of a later study on IFNβ showed no significant differences between the participants treated with IFNβ or placebo in 3 measures of depression during 36 months of follow-up. The results suggest that depression is not an adverse effect of treatment with IFNβ, though the authors point out that the data should not be interpreted as proof that IFNβ can never precipitate depression.

Differentiating psychiatric comorbidity symptoms from MS symptoms

Depression and MS independent of depression can each be characterized by symptoms such as insomnia, poor concentration, physical slowing, and fatigue. However, in a prospective study of 25 persons who were admitted to the hospital for MS-related reasons, persons who were diagnosed with major depression or dysthymia did not report more symptoms of fatigue than the persons who were not depressed. Asking persons about their hope...
for the future, if they’ve been sad/had low mood, or if they are interested in activities that they once found pleasurable may help detect true depression in persons with physical symptoms of MS.\textsuperscript{38}

Anxiety can present with physical symptoms, such as numbness or tingling, dizziness, and hand trembling, which can overlap with the symptoms of MS.\textsuperscript{41}

Figure 3 – Psychiatric comorbidities, such as depression and MS, can have overlapping symptoms.\textsuperscript{42}

**Figure 3 – Psychiatric comorbidities, such as depression and MS, can have overlapping symptoms.**

**Treatment considerations in the setting of psychiatric comorbidity**

Comorbid psychiatric conditions in MS are generally undertreated, especially depression and anxiety. In persons with MS who were diagnosed with depression or anxiety, in the year before MS diagnosis, only ~1.5% of this group were taking a tricyclic antidepressant and ~5.5% were taking a selective serotonin reuptake inhibitor (SSRI; as measured by the number of prescriptions filled in a registry study of 5,084 Danish persons with MS).\textsuperscript{44} After MS diagnosis, approximately 6% were taking a tricyclic antidepressant, and 12%–13% were taking an SSRI, indicating a limited awareness on the part of health care professionals to diagnose and treat the psychiatric disorders in persons with MS.\textsuperscript{44}

Prompt treatment for psychiatric comorbidities, where available, may greatly enhance the life of persons with MS.\textsuperscript{38} If possible, try to identify any modifiable contributing factors to the psychiatric condition (e.g., hypothyroidism or other contributing medical conditions, treatment side effects) and tailor the approach to treatment.\textsuperscript{38} With depression in MS, there may be multiple underlying causes, necessitating an individualized and flexible approach to treatment.\textsuperscript{38}

Clinicians should provide education for individuals affected by depression during difficult periods and ensure that these individuals have adequate social support. The American Academy of Neurology (AAN) guidelines for management of psychiatric disorders indicates that telephone-administered cognitive behavioral therapy (CBT) may be effective to treat depressive symptoms.\textsuperscript{29} CBT may help improve persons’ functional outcomes by coaching them to re-engage in daily activities despite fatigue, low energy, and a lack of motivation.\textsuperscript{38}

Studies on pharmacological therapy and other forms of CBT (in person, group-based) have shown some positive results for treatment of depression in MS.\textsuperscript{29} A meta-analysis of 12 randomized, controlled trials of interventions for depression in MS showed that pharmacological and psychological interventions were generally effective in reducing depressive symptoms.\textsuperscript{45} The severity of depression scores improved in 8 of 11 trials (one trial was deemed an outlier) and showed significant difference to the control arm (standard mean difference: -0.34 [95% CI: -0.53, -0.16]).\textsuperscript{45} Pharmacological treatments for depression had robust effects on improving symptoms of fatigue.\textsuperscript{45} The same meta-analysis reported no change in anxiety severity in 3 psychological trials of depression treatment and a non-significant improvement in self-injection anxiety.\textsuperscript{45}

Though anxiety is one of the more common comorbidities experienced by persons with
MS, there are far fewer randomized, controlled trials that have been conducted on interventions for anxiety in MS. As data from randomized, controlled trials are lacking for treating depression and anxiety in MS, physicians should use data from general psychiatric populations as a starting point for treatment, with careful consideration of an individual’s neurocognitive and physical condition. For example, persons with prominent somatic symptoms of MS or neuropathic pain may benefit from treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine. More studies using antidepressants that may have improved tolerability are needed in the MS population, with particular consideration for the adverse effect profile and concomitant medications.

Treatment of manic episodes in MS is usually based on data from the general psychiatric population, and mood stabilizers (eg, lithium, valproic acid) are common treatments. Lithium and valproic acid are both associated with cognitive side effects, which may exacerbate any preexisting impairments in persons with MS. Atypical antipsychotics (eg, olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone) are another option to treat mania in MS, either as monotherapy or an adjunctive therapy. To offset the weight gain and metabolic effects of these agents, clinicians can counsel persons on healthy eating and incorporating physical activity into their routines.

Managing psychiatric comorbidity in collaboration with other health care professionals

A collaborative model of mental health care may be the most appropriate way to address comorbid conditions. Collaborative models occur along a spectrum that can include communication among the person-centered care team, physical proximity, and shared care between the mental health and medical care professionals. Core members of a collaborative care team include primary care professionals, behavioral health professionals, and psychiatric consultants (possibly a psychiatric nurse practitioner or physician assistant). All collaborative mental health care should be patient-centered, use screening tools initially and during treatment, and provide evidence-based care.

Embedding mental health care within an MS clinic may be a suitable strategy to manage psychiatric comorbidities, including depression and anxiety. With this approach, the care team should regularly evaluate the process for delivering shared care, the comorbidity outcomes, and MS-specific outcomes.

CLINICAL PEARLS

- Depression and anxiety are some of the most common preexisting conditions at MS diagnosis, particularly among persons between the ages of 20 and 44 years old.
- Persons who are treated with corticosteroids for acute exacerbations of MS may experience psychiatric consequences such as depression, mania, and psychosis.
- SSRIs and SNRIs side effect profiles include erectile dysfunction, which is also a common symptom among males with MS. Phosphodiesterase inhibitors can be helpful to treat erectile dysfunction associated with SSRI/SNRIs.
Prevalence and incidence of vascular and metabolic diseases in MS persons

A registry study of 8,983 persons in the United States with MS showed that 52.8% had a vascular comorbidity, including 37.0% with dyslipidemia, 30.1% with hypertension, 6.9% with heart disease, 6.1% with diabetes, and 2.4% with peripheral vascular disease. Over 15% of the respondents had 2 vascular comorbidities, 4.4% had 3 comorbidities, and 1.0% had 4 or more comorbidities.

The prevalence of vascular and metabolic comorbidities in persons with MS has increased over time. A population-based analysis of health claims in Canada showed that, from 1984 through 2006, there was a substantial increase in the prevalence of diabetes, dyslipidemia, and hypertension. The rate of increases generally reflected the increase in prevalence of these diseases in the matched general population.

In 2005, the age-adjusted prevalence in persons with MS was 7.6% for diabetes, 13% for dyslipidemia, and 20.8% for hypertension.

Most prevalent vascular/metabolic comorbidities in MS

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<tr>
<th>Comorbidity</th>
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<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Heart disease</td>
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<td>Diabetes</td>
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In a Canadian health claims study, the 2005 crude incidence of diabetes (per 100,000 persons) was 765 in the MS population and 740 in the matched population. The age-standardized incidence of diabetes was similar between MS and matched populations. The crude incidence of hypertension (per 100,000 persons) was 1,553 in the MS population and 1,796 in the matched population. The age-standardized incidence of hypertension was 13% lower in the MS population than in the matched population (incidence rate ratio: 0.87; 95% CI: 0.75, 0.99).

The age-standardized incidence rate of dyslipidemia was 36% lower, and the incidence of IHD did not differ between the MS and matched populations, though there was an increased risk among younger age groups. In addition, the incidence rates of diabetes in the MS population rose faster over a 10-year period than in the general population.

A population-based registry study found that individuals with type 1 diabetes mellitus have a 3-fold higher risk for developing MS than the general population. Additionally, the first-degree relatives of persons with MS had approximately 40% increased risk for type 1 diabetes.

The prevalence of diabetes, hypertension, dyslipidemia, and IHD in individuals with MS increases with age, at a time when individuals are developing progressive disability and cognitive impairment. Men with MS have a disproportionately higher prevalence of hypertension (48% higher) than women (16% higher) and of diabetes (men: 31% higher; women: 10% higher) compared with a matched control population.

Strategies for diagnosing vascular and metabolic comorbidity in MS persons

As hypertension and dyslipidemia are very common in MS, clinicians should be vigilant about screening persons for these conditions regularly. There are no specific guidelines to follow for diagnosing these comorbidities in persons with MS. Therefore, clinicians should follow general screening and diagnosis guidelines for vascular and metabolic comorbidities. It is advisable to check the blood pressure of individuals with MS at each clinic visit, especially because several DMTs increase the risk of hypertension (eg, fingolimod, teriflunomide).
organizations in the United States defines hypertension as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg. To ensure an accurate measurement, proper methods must be used in the clinic, in particular when using oscillometric devices.

Clinical practice guidelines from the American College of Cardiology and the American Heart Association provide several criteria meeting the definition of dyslipidemia. Hyperlipidemia requires pharmacotherapy if a person at any age has an LDL cholesterol level ≥190 mg/dL, or a person between the ages of 40 and 75 years has an LDL cholesterol level between 70 and 189 mg/dL.

The American Diabetes Association Standards of Care in Diabetes indicates that a diagnosis of diabetes is made when the fasting plasma glucose is ≥126 mg/dL (≥7.0 mmol/L) or when the 2-hour plasma glucose value is ≥200 mg/dL (≥11.1 mmol/L) after an oral glucose tolerance test or if the glycated hemoglobin (Hb) A1c value is ≥6.5% (≥48 mmol/mol). All of these tests are equally appropriate and valid for diagnostic testing. These tests can also be used to screen for diabetes and identify individuals with prediabetes.

**Treatment considerations in the setting of vascular and metabolic comorbidity**

Clinicians treating persons with MS should address factors that are known to impact vascular and metabolic diseases. For instance, smoking, physical inactivity, and being overweight or obese are linked to increased risks of developing some of the MS comorbidities that are strongly associated with adverse outcomes, such as diabetes, hypertension, dyslipidemia, and IHD. Generally speaking, clinicians should follow the guidelines that exist to treat or prevent the progression of these comorbidities. Little evidence exists to support different treatment targets for these diseases in persons with MS.

A prospective cohort study of 50 persons with RRMS who were obese and who had metabolic syndrome (defined as hyperinsulinemia or hyperglycemia plus at least 2 of the following: waist circumference ≥94 cm, dyslipidemia, or blood pressure ≥140/90 mmHg or requiring antihypertensive medication) examined administration of either metformin (n=20), pioglitazone (n=10), or no treatment (n=20).

After 24 months of therapy, there were improvements in many vascular/metabolic outcomes in both treatment groups compared with the untreated group. Individuals with MS who were treated with metformin or pioglitazone had significant reductions in fasting glucose levels; fasting insulin levels; HbA1c levels; total and LDL cholesterol; triglycerides; and systolic blood pressure (p≤0.03). After 24 months of metformin or pioglitazone, individuals had a significantly fewer new or enlarging T2 lesions on brain MRI, compared with the group that received no treatment and compared with pretreatment measures. There were no significant differences in the number of new or enlarging lesions between the two medication groups. Treatment with IFNβ results in a delay of approximately 1 year in the progression of disability, compared to an untreated/placebo group. Contrast that with the fact that the risks associated with vascular comorbidities mean that persons with these comorbidities

**Aggressive treatment of vascular comorbidities may improve MS outcomes.**

While we have evidence of the adverse effects of vascular comorbidities on MS outcomes, we currently lack evidence that treating them improves outcomes.
need to use a unilateral assistive device for ambulation 6 years earlier than persons with MS who do not have a vascular comorbidity.\textsuperscript{5} Vascular comorbidities have a substantial effect on MS outcomes, which appear to be of a greater magnitude than common DMTs for MS.\textsuperscript{5} This suggests that aggressive treatment of the modifiable comorbidities may improve outcomes for persons with MS.\textsuperscript{5}

A retrospective study examined the relationship between DMTs and cardiovascular risk factors in 188 persons with MS who were treated at a MS clinic in New York, compared with 110 persons in the same clinic who were DMT-naïve.\textsuperscript{57} Of the persons receiving a DMT, 106 (56.4\%) were taking IFNβ, 40 (21.2\%) were taking GA, and 37 (19.6\%) were taking natalizumab.\textsuperscript{57} A greater proportion of persons who were receiving a DMT were also taking other medications to treat cardiovascular or neurocognitive conditions compared with the DMT-naïve group, though only antidepressants/stimulants (50\% vs 16.3\%, respectively) and antispasmodics/anticonvulsants/anxiolytics (43.2\% vs 15.4\%, respectively) were significantly different.\textsuperscript{57} Persons using DMTs had significantly higher diastolic blood pressure readings, HDL cholesterol levels, and glucose levels than persons who were not using DMTs.\textsuperscript{57} There were no significant differences between the groups in BMI or smoking (current or prior).\textsuperscript{57} The differences in cardiovascular risk factors between persons using DMTs and those not using DMTs were more significant in persons with chronic progressive MS than those with RRMS, suggesting a time-dependent effect of DMTs on cardiovascular risk factors.\textsuperscript{57} Among the different DMTs, natalizumab was more closely associated with an anti-atherogenic lipid profile than the other agents.\textsuperscript{57} Treatment with fingolimod is associated with bradycardia and/or atrioventricular conduction after the first dose, and with hypertension.\textsuperscript{58} After the first dose of fingolimod, persons should be monitored for bradycardia, and blood pressure should be monitored while treatment is ongoing.\textsuperscript{58} Treatment with mitoxantrone is associated with cardiotoxicity and, therefore, left ventricular ejection fraction should be measured at baseline and before each dose. Long-term monitoring of cardiac function after completion of treatment is also recommended.\textsuperscript{58}

Managing vascular and metabolic comorbidity in collaboration with other health care professionals

Collaborative care involving nurse-led consultations may affect the care of vascular and metabolic comorbid conditions in persons with MS. A recent randomized, controlled study examined the effect of nurse-led consultations for comorbidity management in RA.\textsuperscript{59} Participants in the consultation group had significantly more measures against comorbid conditions taken during the study than participants in the self-assessment (control) group overall, and specifically for cardiovascular diseases.\textsuperscript{59} In the 6-month follow-up period when therapy intensification was proposed by the treating rheumatologist, 17.2\% of participants in the consultation group accepted the intensification versus 10.9\% in the self-assessment group (P<0.001).\textsuperscript{59} These results were obtained following a single visit between the nurse and the person with RA.\textsuperscript{59}

CLINICAL PEARLS

- The Dietary Approach to Stop Hypertension (DASH) diet can lead to significant improvements on systolic and diastolic BP, as well as significant reductions in total cholesterol and LDL concentration in the general population, which may be applicable to address hypertension and dyslipidemia in persons with MS.\textsuperscript{60}
- Flaxseed consumed as a whole seed may reduce blood pressure slightly and can also help manage constipation in MS.\textsuperscript{61}
Prevalence and incidence of autoimmune comorbidity in MS persons

A recent meta-analysis of 170 studies of comorbidities in MS showed that the most prevalent autoimmune diseases (per 100 persons [95% CI]) were thyroid disease (6.44 [0.19, 12.7]) and psoriasis (7.74 [n/a; 1 study]). A Canadian health claims study of 4,911 persons with MS and 23,274 age-, sex-, and geographically-matched persons measured the prevalence of psoriasis in MS at 4.7 (4.0, 5.3) per 100 persons.

A family-based study of 176 families explored the co-occurrence of MS and other autoimmune disorders in both index cases and first-degree relatives. The prevalence of at least one coexisting autoimmune disorder in index cases was 26%. The most prevalent autoimmune diseases in index cases were: Hashimoto thyroiditis (10%), psoriasis (6%), IBD (3%), and RA (2%). Of the 176 families surveyed, 112 (64%) reported an autoimmune disorder (excluding MS) in a first-degree relative. In both index cases and first-degree family members, Hashimoto thyroiditis was the most prevalent autoimmune disorder. When individuals reported both MS and Hashimoto thyroiditis, families were 4.8 times more likely to report an additional case of Hashimoto thyroiditis (OR: 4.8, 95% CI: 1.7, 13.5; P=0.005). Similarly, index cases reporting both MS and psoriasis were 4.4 times more likely to have a relative who also suffered from psoriasis (OR: 4.4, 95% CI: 1.1, 16.7; P=0.04).

Most prevalent autoimmune comorbidities in MS

- Thyroid conditions
- Psoriasis
- Inflammatory bowel disease

A registry study of 1,792 persons with different forms of MS reported that 20.4% of treatment-naïve persons and 17.2% of persons using a DMT had a comorbid autoimmune disease. The most commonly reported autoimmune diseases were thyroid disease (33.3% vs 33.8%), RA (21.2% vs 10.0%), and psoriasis (15.2% vs 17.8%) in the treatment-naïve and DMT groups, respectively. Factors that were significantly correlated with the presence of an autoimmune disease were female sex and an older age at MS symptom onset.

The most prevalent specific autoimmune disease for both men and women were RA (hazard ratio [HR]: 1.39; 95% CI: 1.03, 1.87) and uveitis (HR: 1.38; 95% CI: 1.01, 1.89). The prevalence of IBD was 0.56% in individuals with MS and 0.30 in a matched general population, from a Canadian claims study.

IBD is one of the physical comorbidities of MS that has the highest relative prevalence to the general population (RR: 1.68; 95% CI: 1.38, 2.04). Females and males with MS have similar prevalence rates.

Smoking is a risk factor for MS and other autoimmune disorders, including RA and IBD. As evidenced by a 2010 registry study, smoking increases the risk of comorbid autoimmune disease in MS. A study by Marrie et al. (2010) used the NARCOMS registry to compare the risk of comorbid autoimmune diseases in MS persons who smoke with non-smoking MS persons. The study included 8,875 participants, of whom after adjustment for age, sex, and year of symptom onset, female smokers had a nearly 30% increased risk of developing a comorbid autoimmune disease (CAD) (HR: 1.29; 95% CI: 1.12, 1.5).
1,649 (18.5%) reported a CAD. Ever-smokers (current or past) had an increased odds ratio of reporting a CAD (OR: 1.22; 95% CI: 1.08, 1.38). Among the 7,830 participants without a CAD at MS onset who reported their smoking status, 3,035 (36.8%) currently smoked, while 3,805 (48.6%) never smoked. Further, smokers had an increased risk (HR: 1.23; 95% CI: 1.08, 1.41) of developing a CAD after MS onset.

**Strategies for diagnosing autoimmune comorbidity in MS persons**

Fatigue and depression are common and disabling symptoms of both MS and hypothyroidism. Clinicians should recognize that thyroid disease is a possible source of fatigue that should be evaluated when fatigue develops or worsens in someone with MS. Thyroid hormones are critical for CNS myelination and may be important for remyelination. In severe cases of hypothyroidism, individuals may also experience muscle weakness.

A 2009 study examined whether persons with MS were more likely to have other immune disorders compared with age and gender matched controls. The investigators were particularly interested in the incidence and prevalence of other autoimmune disorders before MS diagnosis. Electronic clinical records were used to identify 5,296 MS cases and 26,478 matched controls. Prior to MS diagnosis, persons were more likely than controls to have uveitis (OR: 3.2, 95% CI: 1.7, 5.7), IBD (OR: 1.7; 95% CI: 1.2, 2.5), Guillian-Barré syndrome (OR: 5.0; 95% CI: 1.6, 15.4) and bullous pemphigoid (OR: 6.7; 95% CI: 1.5, 29.9). The authors proposed that the elevated risk of IBD and uveitis prior to the diagnosis of MS could alter the immune system in such a way that predisposes a person to develop MS. Prior to MS diagnosis, however, cases were not more likely than controls to have or develop RA, lupus, or thyroiditis. This result provides additional evidence that certain MS treatments, not genetic predisposition, may be responsible for the development of thyroiditis and RA in some MS persons.

**Differentiating autoimmune comorbidity symptoms from MS symptoms**

Hyperthyroidism is almost always coincident with reductions in thyroid-stimulating hormone (TSH) secretion from the pituitary. TSH secretion is inhibited by several drugs, at least one of which, prednisone, is indicated for treatment of acute exacerbations of MS. Consequently, administration of prednisone could confound the interpretation of TSH concentrations and any subsequent diagnosis of hyperthyroidism. For instance, persons receiving prednisone are likely to exhibit TSH values in the range of 0.08 to 0.4 mU/L. To differentiate these persons from those whose TSH values have been suppressed by hyperthyroidism (values typically <0.01 mcU/mL), the TSH test should be performed before corticosteroid treatment is started or after it concludes. Additionally, more individuals are taking the supplement biotin, which can alter the results of thyroid laboratory tests, including T4, T3, and TSH, depending on how the tests are conducted.

**Treatment considerations in the setting of autoimmune comorbidity**

A randomized, controlled trial of 334 previously untreated individuals with early RRMS (CAMMS223) examined the safety and efficacy of alemtuzumab versus IFNβ over a...
36-month period. In this study, there were more reports of autoimmune diseases in participants receiving alemtuzumab (either 12 mg/day or 24 mg/day) than in participants receiving IFN. Thyroid-associated events were reported in 22.7% (49/216) of participants receiving alemtuzumab and 2.8% (1/107) of participants receiving IFNβ (P<0.001). The most commonly reported event in the alemtuzumab group was hyperthyroidism (14.8%). Idiopathic thrombocytopenic purpura was also reported more often in the alemtuzumab group (2.8% [6/216]) than in the IFNβ group (0.9% [1/107]).

A median follow-up of the CAMMS223 trial at 57.3 months revealed a greater prevalence of thyroid dysfunction in persons receiving alemtuzumab (34%), compared with 6.5% of persons who received IFNβ (P<0.001). Graves hyperthyroidism (22%) was the most observed thyroid dysfunction, followed by hypothyroidism (7%), and subacute thyroiditis (4%). Of the persons who developed Graves hyperthyroidism, 23% of cases spontaneously resolved, and 15% of cases spontaneously developed hypothyroidism. With no clear time-dependency of the onset of thyroid adverse events, thyroid function should be routinely monitored.

A cohort study of persons with MS confirmed earlier data showing that new autoimmunity (measured by antibodies) developed in 22.2% of those who were treated with alemtuzumab. The mean time to developing an autoimmune disease after alemtuzumab was 23.4 months, with the peak rate of autoimmune disease development occurring between 12 and 18 months after the first treatment. Risk factors for developing an autoimmune disease after alemtuzumab treatment were a family history of autoimmune disease and any current or prior cigarette smoking. Neither the total dose received nor the dosage interval increased the risk of developing an alemtuzumab-induced autoimmune disease.

Persons receiving alemtuzumab should have a complete blood count with differential, serum creatinine levels, and urinalysis with urine cell counts before treatment and monthly during and for 48 months after treatment to allow for early detection and treatment of autoimmune reactions. With increased awareness of the need for autoimmune disease monitoring during and after alemtuzumab treatment, there is some evidence that serious autoimmune diseases can be identified rapidly.

Psoriasis can be affected by treatments commonly used for MS. Case reports indicate the possibility of an onset, or worsening of psoriasis after the initiation of IFNβ treatment. Treatment with daclizumab may induce hepatic injury, including autoimmune hepatitis, or immune-mediated disorders, such as skin reactions and non-infectious colitis. Prior to beginning treatment and through at least 6 months after the last dose, clinicians should monitor the serum transaminase and total bilirubin levels in persons treated with daclizumab.

The mean time to development of an autoimmune disease after initiating biologic therapy is 40 weeks, and 68% of the cases appeared between 1 month and 1 year after initiation. Most cases of biologic-induced autoimmune disease have a favorable outcome. In most cases, the instigating biologic is discontinued, and corticosteroids, immunosuppressive agents, or intravenous immunoglobulins can be used to manage the autoimmune disease. As of 2010, there were a total of 175 reported cases of demyelinating CNS disorders, including MS, that occurred after initiating biologic therapy.
Managing autoimmune comorbidity in collaboration with other health care professionals

As MS is an autoimmune disease, there are opportunities to coordinate the management and treatment of both MS and the comorbid autoimmune condition. However, there are also scenarios in which MS and the comorbid autoimmune disease need to be carefully managed so as not to exacerbate either one. For instance, tumor necrosis factor (TNF)-α inhibitors, which are mainstays of therapy for RA, may precipitate flares in MS.\(^7\)

Dimethyl fumarate may improve psoriasis that is co-occurring with MS. In a randomized, controlled study of individuals with moderate-to-severe chronic plaque psoriasis, significantly more participants who were taking dimethyl fumarate achieved an improvement on a measure of psoriasis severity and area than those who were taking placebo, and very few participants taking dimethyl fumarate showed rebound symptoms 2 months after treatment ceased.\(^7\)

Natalizumab is a therapy that is approved to treat relapsing forms of multiple sclerosis and moderately-to-severely active Crohn’s disease and should be a treatment consideration for persons with these conditions.\(^7\)

Because alemtuzumab is associated with an increased risk of autoimmunity, treatment should be initiated and supervised by neurologists experienced in the treatment of persons with MS and who have fully familiarized themselves with the efficacy and safety profile of alemtuzumab.\(^7\)

In the United States, prescribers, healthcare facilities, and pharmacies must be enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program.\(^7\) In the United Kingdom, alemtuzumab is subject to additional monitoring through adverse event reporting by healthcare professionals.\(^7\)

CLINICAL PEARLS

- Clinicians should be aware of opportunities for coordinated care and optimization of treatment with other autoimmune comorbidities.
- Comorbid autoimmune disease may increase the risk of adverse effects from some DMTs.

Chronic lung disease

A recent population-based Canadian health claims analysis showed that chronic lung disease occurs in 12.1% of persons with MS and 9.14% of the (matched) general population without MS.\(^7\) The prevalence of chronic lung disease was 13.5% in women with MS and 9.90% in men with MS.\(^7\) Additionally, women with MS had a disproportionately higher prevalence of chronic lung disease (39% higher) than men with MS (21% higher) compared with the matched population.\(^7\)

In a Swedish registry study of hospital admissions, there was an increased risk of having MS in individuals who were hospitalized for chronic obstructive pulmonary disease (COPD).\(^83\) The authors indicated that the increased risk could not be fully be explained by current or prior smoking and that there may be some shared genetic component that increases the risk for both diseases.\(^83\) Mothers and siblings of individuals hospitalized for COPD also had an increased risk of having MS.\(^83\)

Cancer

A systematic review examined the literature on cancer in MS. In the 38 articles that met the criteria for review, the incidence of any cancer varied from 0.5% to 10.55%.\(^84\) If the studies examined the relative occurrence of cancer to the general population, the
cancer incidence in the MS population was usually lower. The cancers with the highest crude incidence in the MS population are cervical, breast, and digestive cancers. In the pooled analysis of the studies included, there was no significant difference in the incidence of brain cancer, breast cancer, lymphoma, melanoma, or bladder cancer in the MS population compared to a general population. However, the risk of meningiomas was slightly higher than expected, which may reflect ascertainment bias from more frequent use of brain MRI in MS.

Epilepsy and Migraine

Epilepsy is a common comorbid condition with MS, with a crude prevalence of 1.93% in persons with MS and 0.89% in a matched control population. Persons with MS have an almost 3-fold higher risk of having epilepsy compared with the general population (P<0.0001). The prevalence of epilepsy in MS increased with age. Men with MS have a disproportionately higher prevalence of epilepsy (284% higher) than women (225% higher) compared with a matched control population.

From an analysis of the Nurses’ Health Study II, migraine was more common in individuals with MS than in those without. Women who had an existing diagnosis of migraine at baseline in the study had a 39% greater risk of developing MS than those who had no existing migraine.

A prospective survey of 357 persons with RRMS who were being treated at an Italian MS clinic examined the relationship between headache and treatment with IFNβ. Most (219/357; 61.3%) of the cohort had preexisting headache. Of the 219 persons with preexisting headache, 55% (121/219) had a worsening of their headache during treatment with IFNβ. Of the 138 subjects who did not have preexisting headache, 68.8% (95/138) experienced new headache within 12 months of starting IFNβ treatment. Treatment with higher doses of subcutaneous IFNβ-1a or with intramuscular IFNβ-1a was more strongly linked to worsening of preexisting headache.

Fibromyalgia

A Canadian health claims study of 4,129 individuals with MS and 20,940 matched individuals in the general population showed that the age-adjusted prevalence of fibromyalgia in the general population was 3.04% (95% CI: 2.77, 3.32) and in MS was 6.82% (95% CI: 5.91, 7.72). The prevalence of fibromyalgia was 2-fold higher in women than in men in both groups. The mean age of fibromyalgia onset was 53.1 years in persons with MS, similar to the general population.

Sleep disorders

A survey of the Northern California Chapter of the National MS Society asked persons with MS about their sleep. From 2,375 respondents, 70% of the group showed signs of at least one sleep disorder, such as obstructive sleep apnea, insomnia, or restless legs syndrome. Half of the respondents indicated they had never discussed issues related to their sleep with their healthcare professional and most had never been diagnosed by a physician with the sleep disorder that was positive from their questionnaire. The authors concluded that sleep problems may be a hidden problem in the MS population, which is separate from MS-related fatigue.
Comorbid conditions in MS can have a significant impact on the disease course, the person’s quality of life, and on healthcare utilization. To appropriately address the comorbidities, clinicians must know which conditions to be aware of, how to recognize the comorbid condition (especially when there are overlapping symptoms with MS or confounding issues with MS), and how to effectively treat and manage the comorbid condition. With appropriate management, the effect of the comorbid condition on the person and on MS may be mitigated.
## For Healthcare Professionals

**Wellness Discussion Guide** – The National Multiple Sclerosis Society (United States) developed a discussion guide for healthcare professionals to use with persons with MS to help integrate lifestyle and complementary strategies into MS care; [http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Wellness-Discussion-Guide-for-ppl-wMS-and-HCPs.pdf](http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-Wellness-Discussion-Guide-for-ppl-wMS-and-HCPs.pdf)


**Assessment and Management of Psychiatric Disorders** – The American Academy of Neurology published an evidence-based guideline for clinicians regarding screening, diagnosing, and treating psychiatric disorders in individuals with MS. There is also a summary of the guideline; [https://www.aan.com/Guidelines/Home/GuidelineDetail/628](https://www.aan.com/Guidelines/Home/GuidelineDetail/628)

**Emotional Disorders** – The National MS Society published a guide for clinicians to diagnose and treat emotional disorders (i.e., depression, anxiety, bipolar disorder, PBA). There is also a related guide for how to discuss these topics with persons with MS; [http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical-Bulletin-Emotional-Disorders-5-5-14.pdf](http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical-Bulletin-Emotional-Disorders-5-5-14.pdf)

**Cardiovascular Disease Risk Calculator** – An online tool to estimate a person’s baseline risk of cardiovascular disease and stroke, from the American Heart Association; [http://static.heart.org/riskcalc/app/index.html#!/baseline-risk](http://static.heart.org/riskcalc/app/index.html#!/baseline-risk)

**Guidelines on the Go** – Available for iOS and Android operating systems, from the American Heart Association; [http://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp](http://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp)

## For Persons with MS and Caregivers

**Someone Like Me** – The Multiple Sclerosis Society of Canada offers a toolbox for managing the physical, emotional, and social aspects of MS; [https://someonelikeme.ca/toolbox/](https://someonelikeme.ca/toolbox/)

**Living with MS** – The National Multiple Sclerosis Society (United States) has examples of how a healthy diet, regular exercise, stress management, and other wellness strategies can help persons with MS manage their symptoms and comorbid conditions; [https://www.nationalmssociety.org/Living-Well-With-MS](https://www.nationalmssociety.org/Living-Well-With-MS)

**Understanding and Treating Depression in MS** – A resource guide to recognize the symptoms and learn about possible solutions from the Multiple Sclerosis Association of America; [https://mymsaa.org/PDFs/MSAA_Depression.0507.pdf](https://mymsaa.org/PDFs/MSAA_Depression.0507.pdf)

**Emotional Disorders** – The American Academy of Neurology published a fact sheet for persons with MS and their families, summarizing the main findings of their guideline on emotional disorders in MS; [https://www.aan.com/Guidelines/Home/GetGuidelineContent/630](https://www.aan.com/Guidelines/Home/GetGuidelineContent/630)

**Healthy for Good** – Create lasting change in your life, one small step at a time, by eating smart, moving more, and being well; from the American Heart Association; [https://healthyforgood.heart.org/](https://healthyforgood.heart.org/)
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