

Kevin N. Alschuler, Aaron P. Turner,
and Dawn M. Ehde

Topic

Multiple sclerosis (MS) is a chronic and progressive central nervous system disease characterized by immune-mediated demyelination and neuronal damage within the brain, spinal cord, and optic nerves. While the exact cause of MS is unknown, it is thought to result from a combination of one or more environmental triggers and genetic vulnerability [1]. MS is characterized by significant variability in the type and severity of symptoms, as well as the pattern and rate of progression.

Individuals with MS experience a constellation of symptoms and co-occurring conditions,

including sensory problems, cognitive difficulties, weakness, spasticity, paresthesia, pain, visual disturbance, heat intolerance, fatigue, bowel/bladder dysfunction, and emotional changes. However, the specific symptoms and their severity differ widely among individuals:

A. **Key Concepts**

1. **Diagnosis**

Diagnosing MS is challenging: there is no one test that definitively diagnoses MS, and many of its symptoms are nonspecific and/or suggestive of other CNS disorders. Diagnosis of MS is often based upon the revised **McDonald criteria** [2] which specifies characteristics of the medical history, neurologic exam, and MRI that are indicative of MS. Occasionally, other tests, such as evoked potentials and spinal fluid analysis, are instrumental in differentiating MS from other conditions. Given that the individual symptoms experienced by a person with MS are not unique to MS specifically, diagnosis also involves ruling out other potential etiologies.

2. **Disease course**

MS is conceptualized in terms of four types of disease course [1]:

- a. **Relapsing-remitting MS (RRMS)** is the most common course, affecting an estimated 85 % of people with MS at time of initial diagnosis. RRMS is characterized

K.N. Alschuler, Ph.D. (✉)
Department of Rehabilitation Medicine,
University of Washington School of Medicine,
Seattle, WA 98133, USA
e-mail: kalschul@uw.edu

A.P. Turner, Ph.D., ABPP (R.P.)
Veterans Affairs Puget Sound Health Care System,
Seattle, WA, USA

Department of Rehabilitation, School of Medicine,
University of Washington, Seattle, WA, USA

D.M. Ehde, Ph.D.
Department of Rehabilitation Medicine,
University of Washington School of Medicine,
Seattle, WA 98108, USA

by distinct attacks or exacerbations of neurologic symptoms (relapses), followed by a return to prior function or partial recovery (remissions).

- b. The majority of individuals with RRMS eventually progress to **secondary progressive MS (SPMS)**, at which point their disease may progress with or without relapses. The prevalence of this conversion is unknown given the recent advances in disease management, as described below.
- c. **Primary progressive MS (PPMS)** affects approximately 10% of people with MS and is characterized by steady progression of neurologic symptoms from the onset of the disease.
- d. **Progressive-relapsing MS (PRMS)** is the least common disease course and involves a steady progression of disease from onset with episodic exacerbations (which may or may not result in some recovery).

Data on the natural history of MS suggest that at 15 years' postdiagnosis, approximately 50% of people will require an assistive device to walk, and 20% will require a wheelchair. However, current disease-modifying therapies are used in an effort to slow the onset of these symptoms.

3. Management of underlying disease

- a. Although there is no cure for MS, a number of **disease-modifying therapies (DMT)** are used to decrease disease activity and slow progression in individuals with relapsing forms of MS. To date, there are no approved DMTs for PPMS. Current medications come in three forms (oral, injectable, infusion,) and each comes with a profile of benefits and side effects. For the average patient with RRMS, early intervention with DMTs is associated with less disability over time relative to patients who do not take DMTs.
- b. To combat the inflammatory process that causes acute relapses and reduce

their duration, patients are often prescribed 3–5 day infusions of high-dose corticosteroids. Alternatives, such as oral steroids and an injectable gel (ACTH) are also emerging as alternatives to infused corticosteroids.

4. Symptom management

The remainder of medical treatment primarily focuses on managing symptoms and improving health-related quality of life via a range of interventions, including medications, behavioral interventions, and rehabilitation:

- a. **Medications** are available to alleviate the severity of many MS symptoms, such as pain, fatigue, and bladder/bowel dysfunction.
- b. **Cognitive and behavioral interventions** are recommended for the management of MS symptoms in an effort to maximize the individual's ability to engage in the activities that promote highest quality of life:
 - i. Rehabilitation psychology is frequently consulted to address questions related to adjustment to disability, depression, anxiety, cognitive assessment, cognitive rehabilitation, health behavior change, relationship conflict, and sexual functioning.
 - ii. Rehabilitation interventions, such as physical therapy, occupational therapy, and speech and language pathology, are prescribed when there are opportunities to improve or maintain physical or cognitive functioning.

B. Terminology

1. Exacerbation or relapse

- Episode of new symptoms or a worsening of existing symptoms.
- To be considered an exacerbation, the symptoms must experience a minimum of 24 h and not occur within 30 days of a prior attack.
- Severity of exacerbations can vary in terms of severity, symptoms experience, and length.
- Individuals with MS also experience *pseudo-relapses*, which are temporary

worsening of symptoms due to physical and psychological stressors that resolve when the stressor is resolved. The variability in presentation of relapses, along with the presence of pseudo-relapses, makes the identification of relapses difficult.

- Relapses are followed by recovery, but the individual may or may not return to his or her prior level of functioning.

2. **Lesion**

- Hallmark characteristics of MS on MRI
- Areas where the myelin has been damaged (*demyelination*)
- May be present in the brain or spinal cord
- Sometimes quantified in terms of *lesion load*, such that individuals with more lesions are said to have higher lesion load.

3. **EDSS**

- The **Kurtzke Expanded Disability Status Scale (EDSS)** [5] is the most commonly used measure used to describe disability in individuals with MS.
- It has two forms, a provider-administered form [3] and a self-report form [4] which is highly correlated with the provider-administered form.
- The EDSS is scored on a 0 to 10 ordinal scale in 0.5 increments, with higher scores suggestive of greater disability.
- Individuals with scores <5.0 are fully ambulatory.
- Despite its frequent use, the EDSS has psychometric limitations; for a discussion of these, see [http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-\(FSS\)-and-Expanded-Disab](http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab).

4. **Other**

- For a list of additional terms commonly used in MS care, see <http://www.nationalmssociety.org/Glossary>.

Importance

- **Incidence and prevalence:** MS is the most common acquired neurologic disability found in young adults [5]. The estimated worldwide prevalence of MS is more than 2.3 million people, including more than 400,000 individuals in the USA [1]. MS is more prevalent among women (2–3 times more prevalent than in men), Caucasians, and individuals from northern latitudes [5].
- **Onset, duration, and lifespan:** The onset of MS is typically between the ages of 20 and 50 years [5], although it also occurs in children and older adults. As the lifespan of people with MS is only 5–10 years shorter than healthy adults [6], the typical person with MS faces many years of managing the disease and its effects.
- **Impact on functioning and quality of life:** Individuals living with MS often must make a number of lifestyle and behavioral changes to manage not only the effects of the disease but also its treatments (e.g., adapting to physical or cognitive impairments, adhering to disease-modifying therapies). As a chronic neurologic condition, many daily activities can be affected by MS, including physical functioning, activities of daily living, vocational functioning, role functioning, and leisure pursuits. The course, specific symptoms, and severity of disease progression vary considerably between and within individuals, making it an unpredictable chronic condition to manage. Health-related quality of life is significantly lower in patients with MS relative to healthy controls, the general population, and patients with other chronic diseases such as diabetes, hypertension, arthritis, and epilepsy [7].
- **Financial impact:** MS has been associated with substantial costs to individuals, their families, and society. As many as two-thirds of adults with MS are unable to maintain employment [8]. Uncertainty about the future, decreased independence, and financial hardship are common [9, 10]. Given that MS often occurs during child-rearing years, it may

affect parenting and performance of other family roles [11]. At a societal level, the economic costs attributed to MS in the USA have been estimated to be as high as \$13 billion per year [9]; costs include both direct costs for medical care and indirect costs such as lost wages, lost productivity (including sick leave), and caregiving costs.

Practical Applications

A. *Assessment and management of MS symptoms and associated concerns*

As with all medical conditions, the biopsychosocial model serves as a useful basis for the assessment and management of MS symptoms. Individuals with MS present with a constellation of symptoms that are primarily managed (versus eliminated). Treatment focuses not only on symptom severity but also symptom interference with functioning and quality of life. The following are common symptoms and associated concerns experienced by individuals with MS, along with recommendations for the assessment and management of those symptoms:

1. **Fatigue**

As many as 90 % of people with MS experience persistent fatigue, and 40–60 % report it as their most incapacitating symptom [12]. In MS, fatigue involves a lack of physical and/or mental energy; fatigue negatively affect activities of daily living, participation in valued roles, and quality of life [12].

- **Assessment:** The severity and impact can be obtained using a 0–10 numerical rating scales or by measures such as the Fatigue Severity Scale [13] and Modified Fatigue Impact Scale [14].
- **Interventions:** Medications such as amantadine hydrochloride and modafinil are sometimes used for fatigue; evidence of their benefits is mixed. Rehabilitation approaches including energy conservation [15], heat management, and physical activ-

ity [16] have some evidence for decreasing fatigue and its negative impact in MS. Treatment of comorbid factors that may exacerbate fatigue, such as depression or insomnia, is also indicated.

2. **Pain**

Approximately 50–65 % of adults with MS experience chronic pain [17–19]. Although pain can be widespread, it is most commonly found as affecting the legs, hands, and feet. Pain may be musculoskeletal, neuropathic, or both. In MS, chronic pain has been associated with poorer health-related quality of life, including greater interference with daily activities, vitality, emotional health, and social functioning [20]. Pain-related cognitions and coping behaviors and social variables have been strongly associated with pain intensity, physical functioning, and psychological functioning in MS samples [21]. (Individuals may experience acute pain, particularly during an exacerbation, but the more commonly experienced pain in MS is chronic.)

- **Assessment:** Pain intensity is typically measured via 0–10 numeric rating scales. Pain interference can be measured simply with a similar 0–10 scale or via the interference scale of the Brief Pain Inventory [22]. Assessment of potentially modifiable behaviors impacting pain such as activity level, pain catastrophizing (unhelpful thoughts about pain), and coping skills is also recommended for treatment planning.
- **Intervention:** Anticonvulsants such as gabapentin or pregabalin are commonly prescribed for neuropathic pain; nonsteroidal anti-inflammatory medications and antidepressants such as duloxetine may also be used. Behavioral interventions—including cognitive behavioral therapy, hypnosis, and mindfulness—are recommended to

decrease pain and its negative effects on functioning, mood, and quality of life [23].

3. **Cognition**

Cognitive deficits are observed in 43–70% of individuals with MS [24]. Cognitive problems are variable in presentation, severity, and impact. Most commonly, individuals with MS present with difficulties in attention, learning/acquisition of new information, speed of information processing, and executive functioning; however, there is some variability in presentation related to MS disease course [24]. Individuals can have cognitive impairment in the absence of or minimal physical disability. As with most symptoms of chronic disease, cognitive concerns are often noted when symptoms begin to interfere with functioning, often in the work, school, or home setting.

- **Assessment:** Historically, the primary modality for assessment has been the comprehensive neuropsychological evaluation, which focuses on functioning across commonly effected cognitive domains (e.g., memory, processing speed, attention), as well as the intelligence, academic achievement, and personality domains. More recently, MS-focused researchers have focused efforts on shorter batteries, such as the Minimal Assessment for Cognitive Functioning in MS [25] that focuses specifically on processing speed, working memory, learning and memory, executive function, visual-spatial processing, and word retrieval.
- **Interventions.** The most common interventions for areas of cognitive weakness focus on the identification and implementation of compensatory strategies to accommodate deficits in the context of the patient's life (e.g., memory notebooks, organization systems, reminder prompts).

Recent preliminary evidence suggests certain skill training practices (teaching imagery and story context) may also improve deficits in memory [26]. Such “cognitive rehabilitation” interventions are most commonly provided by rehabilitation psychologists, neuropsychologists, or specially trained speech-language pathologists.

4. **Depression**

The lifetime prevalence of concurrent depressive disorders and MS is 25–50% and 2–3 times that of the general population and other chronic diseases [27]. Biologic (e.g., brain pathology, immunologic) and psychosocial (e.g., stressors) factors contribute to depression [28]. Major depression is associated with fatigue, poorer neuropsychological functioning, pain, lower quality of life, vocational disruption, social disruption, poorer health, and possibly greater disease progression [29]. Depression is too often underdiagnosed and undertreated in MS mood [30].

- **Assessment.** Ideally, all patients with MS should be routinely screened for depression as part of their specialty or primary care. Screening measures validated for use in MS include the Patient Health Questionnaire-9 [31], Hospital Anxiety and Depression Scale, and the Beck Fast Screen for Medically Ill Patients. No one measure is clearly superior to the others, however [32].
- **Interventions.** Multimodal treatment is typically recommended, particularly for moderate or severe depressive episodes [28]. Antidepressants are commonly used and presumed to be beneficial, although they lack evidence refuting or supporting their use in MS [33]. Research supports the use of cognitive behavioral therapy delivered in person or by phone in people with MS and depression [33].

Other behavioral interventions used for treating depression in other populations (e.g., behavioral activation, mindfulness-based interventions, acceptance, and commitment therapy) have not been studied in MS depression but merit consideration in treatment planning.

5. **Anxiety**

Anxiety disorders are present in as high as 40% of individuals with MS [34], and may take many forms, including generalized anxiety disorder, health-related anxiety, or injection phobias. In MS, in particular, anxiety often centers around the uncertainty that is central to the condition, as the perceived uncontrollability often becomes a focus for worry. The implications of anxiety are significant, as anxiety has been associated with poorer medication adherence [35], higher pain intensity and interference [36, 37], lower quality of life [38], and suicidal intent [34].

- **Assessment.** Measures such as the HADS-A and the GAD-7 are validated measures of anxiety symptoms in MS [39, 40]. More formal measures, such as the SCID or MINI, are available to provide diagnostic assistance. Clinical interviews are effective in identifying the cognitive, behavioral, and physiologic correlates of anxiety.
- **Interventions.** There are a number of effective anxiety interventions that are well known to mental health professionals, but relatively little has been done to evaluate these interventions for anxiety experienced by individuals with MS. Commonly used interventions include cognitive behavioral therapy, exposure therapy, and acceptance and commitment therapy. In some cases, medication may also be helpful.

6. **Adherence to DMTs**

Despite the importance of DMTs in slowing MS progression, nearly one-half

of individuals who begin a course of DMT discontinue at some time, and overall past-month adherence has been estimated at roughly 75% [41, 42]. Numerous medical and psychosocial factors, including side effects, depression, social support, perceptions of medication efficacy, and cognitive difficulties impact adherence over time [35, 43–45].

- **Assessment.** Self-report of missed doses over a fixed time period retrospectively or with medication diaries, electronic pill container devices, or administrative reviews of pharmacy data.
- **Intervention.** Motivational interviewing and care coordination promoting self-management have been shown to improve adherence over time [46, 47].

7. **Exercise/Activity**

Levels of physical activity among individuals with MS are generally low [48]. However, mounting evidence suggests that physical activity has substantial benefits for individuals with MS, including improvements in physical health (e.g., strength, balance, endurance, and ambulation) [49, 50] and mental health (e.g., fatigue, depression, and quality of life) [51–53].

- **Assessment.** Exercise testing (e.g., VO₂ max), physical activity monitoring (e.g., accelerometer), global functional tests (6 min walk), and self-report (e.g., 7-day physical activity recall).
- **Intervention.** Group-based exercise programs and individual counseling delivered in person [52], via telephone [51], or with web-based education support [54] have all demonstrated improvements in physical activity levels and corresponding physical and mental health outcomes.

8. **Alcohol use**

Current rates of hazardous alcohol use among individuals with MS typically range from 14 to 18% [55, 56].

Hazardous consumption may compound MS-related disability by impairing sleep, exacerbating fatigue and cognitive difficulties [57, 58], and contributing to depression, anxiety, and suicidal ideation [55, 59].

- **Assessment.** Assessment typically addresses use and use-related problems. The Alcohol Use Disorders Identification Test (AUDIT) is one of the many brief and well-validated options [60].
- **Intervention.** Individual brief advice, cognitive behavioral therapy, motivational interviewing and group-based cognitive behavioral treatment, and 12-step programs as well as pharmacologic interventions including acamprosate, naltrexone, and disulfiram under supervision have all been shown to reduce hazardous alcohol use [61]. Little is known about the efficacy of specific interventions among individuals with MS.

9. Smoking

Current rates of smoking among individuals with MS typically range from 18 to 36% [62]. In addition to being the leading cause of preventable death among the US population in general [62], smoking also provides specific challenges for individuals with MS. Smoking is associated with a greater likelihood of developing MS [63]—possibly even by second-hand exposure [64]—disease progression [65, 66], increased CNS lesion activity, and in some studies increased disability over time [42, 66].

- **Assessment.** Current use. Readiness to quit. Past quit attempts. Dependence [60].
- **Intervention.** Brief advice during a medical appointment (5 or 10 min), motivational interviewing, nicotine replacement therapy, tobacco quit lines, and smoking cessation classes have all been shown to reduce smoking [67]. Little is known about

the relative effectiveness of smoking cessation interventions among individuals with MS.

10. Additional important symptoms and concerns

- **Sleep disorders**, as well as **sleep interrupted due to disruptive symptoms**, are more common in MS than in the general population and warrant assessment and treatment.
- Common changes in physical functioning and sensation include **sensory changes** (e.g., numbness or tingling, heat sensitivity), **spasticity** (e.g., **involuntary muscle contractions, stiffness**), **weakness (neurologic and deconditioning)**, mobility impairment, and **falls**.
- A high percentage of patients experience **bowel and/or bladder dysfunction** (retention or incontinence), as well as **disrupted sexual functioning**, all of which may be underreported due to embarrassment, but all of which can be highly interfering with quality of life
- In a portion of patients, **visual changes**, including changes in visual perception, may occur
- As MS often presents during the prime years of **employment, childbearing, and family/relationship building**, it is common for patients to have concerns in one or more of these areas
- While onset of MS symptoms most commonly occurs in early to middle adulthood, an estimated 2–5% of individuals with MS have an onset of symptoms prior to age 18. According to the National MS Society, most individuals with **pediatric MS** have relapsing-remitting disease course. Given the relatively low prevalence and difficulty distinguishing pediatric MS from other childhood medical conditions, research on pediatric MS is relatively sparse; more research is needed to understand prognosis and treatment for this subpopulation.

Tips

- a. **Focus on improved management of symptoms and reduced interference.** MS is largely a disease that requires effective management of multiple symptoms, as opposed to a focus on the elimination of symptoms.
- b. **Acknowledge the discomfort associated with uncertainty.** A hallmark symptom of MS is the constant presence of uncertainty regarding prognosis, progression of symptoms, and impact on quality of life. Patients can learn to cope effectively with the presence of uncertainty, but it is a source of discomfort for most patients.
- c. **Normalize fears of disability.** Patients often have fears of increased disability, including requiring a wheelchair for ambulation, given the progressive nature of MS. This is a real, understandable, and common fear of individuals with MS.
- d. **Utilize community resources.** A positive for individuals with MS is that there is a strong support network provided by national organizations, including the National MS Society (NMSS). They provide opportunities for community support, assistance with case management, and reliable educational resources about MS.

References

1. National Multiple Sclerosis Society. www.nationalmssociety.org
2. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.
3. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444–52.
4. Bowen J, Gibbons L, Gianas A, Kraft GH. Self-administered Expanded Disability Status Scale with functional system scores correlates well with a physician-administered test. *Mult Scler*. 2001; 7(3):201–6.
5. Stern JA, Sorkin L, Milton K, Sperber K. Aging with multiple sclerosis. *Phys Med Rehabil Clin N Am*. 2010;21(2):403–17.
6. Ragonese P, Aridon P, Salemi G, D'Amelio M, Savettieri G. Mortality in multiple sclerosis: a review. *Eur J Neurol*. 2008;15(2):123–7.
7. Wu N, Minden SL, Hoaglin DC, Hadden L, Frankel D. Quality of life in people with multiple sclerosis: data from the Sonya Slifka Longitudinal Multiple Sclerosis Study. *J Health Hum Serv Adm*. 2007;30(3):233–67.
8. Honarmand K, Akbar N, Kou N, Feinstein A. Predicting employment status in multiple sclerosis patients: the utility of the MS functional composite. *J Neurol*. 2011;258(2):244–9.
9. Bennett SE, Coyle PK, Conner CS. The Clinician's primer on latest advances in improving quality of life for patients with multiple sclerosis. Consensus Medical Communications. Littleton (CO): 2010.
10. Beiske AG, Naess H, Aarseth JH, Andersen O, Elovaara I, Farkkila M, et al. Health-related quality of life in secondary progressive multiple sclerosis. *Mult Scler*. 2007;13(3):386–92.
11. Pakenham KI, Tilling J, Cretchley J. Parenting difficulties and resources: the perspectives of parents with multiple sclerosis and their partners. *Rehabil Psychol*. 2012;57(1):52–60.
12. Finlayson M, Johansson S, Kos D. Fatigue. In: Finlayson M, editor. Multiple sclerosis rehabilitation: from impairment to participation. Boca Raton: CRC Press; 2012. p. 69–100.
13. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121–3.
14. Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Mult Scler*. 1999;5(4):251–9.
15. Blikman LJ, Huisstede BM, Kooijmans H, Stam HJ, Bussmann JB, van Meeteren J. Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2013;94(7): 1360–76.
16. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbin KA, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013;94(9):1800–28.
17. Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. *Mult Scler*. 2006; 12(5):629–38.
18. Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. *Pain*. 2007;127(1–2):35–41.
19. Khan F, Pallant J. Chronic pain in multiple sclerosis: prevalence, characteristics, and impact on quality of life in an Australian community cohort. *J Pain*. 2007;8(8):614–23.
20. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple

- sclerosis: systematic review and proposed classification. *Pain*. 2008;137(1):96–111.
21. Jensen MP, Moore MR, Bockow TB, Ehde DM, Engel JM. Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: a systematic review. *Arch Phys Med Rehabil*. 2011;92(1):146–60.
 22. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med*. 1994;23(2):129–38.
 23. Ehde DM, Kratz AL, Robinson JP, Jensen MP. Chronic pain. In: Finlayson M, editor. *Multiple sclerosis rehabilitation: from impairment to participation*. London: Taylor & Francis; 2013. p. 199–226.
 24. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol*. 2008;7(12):1139–51.
 25. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol*. 2002;16(3):381–97.
 26. Chiaravalloti ND, Moore NB, Niekshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: the MEMREHAB trial. *Neurology*. 2013;81(24):2066–72.
 27. Patten SB, Metz LM, Reimer MA. Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Mult Scler*. 2000;6(2):115–20.
 28. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. *Nat Rev Neurol*. 2014;10(9):507–17.
 29. Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler*. 2005;11(3):328–37.
 30. Mohr DC, Hart SL, Fonareva I, Tasch ES. Treatment of depression for patients with multiple sclerosis in neurology clinics. *Mult Scler*. 2006;12(2):204–8.
 31. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
 32. Amtmann D, Bamer AM, Johnson KL, Ehde DM, Beier M, Elzea J, et al. A comparison of multiple patient reported outcome measures in identifying major depressive disorder in people with multiple sclerosis. Under review.
 33. Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, et al. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82(2):174–81.
 34. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Mult Scler*. 2007;13(1):67–72.
 35. Turner AP, Williams RM, Sloan AP, Haselkorn JK. Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. *Rehabil Psychol*. 2009;54(1):116–21.
 36. Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. *Mult Scler*. 2005;11(3):322–7.
 37. Bruce JM, Arnett P. Clinical correlates of generalized worry in multiple sclerosis. *J Clin Exp Neuropsychol*. 2009;31(6):698–705.
 38. Garfield AC, Lincoln NB. Factors affecting anxiety in multiple sclerosis. *Disabil Rehabil*. 2012;34(24):2047–52.
 39. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler*. 2009;15(12):1518–24.
 40. Terrill A, Hartoonian N, Beier ML, Salem R, Alschuler K. The GAD-7 as a tool for measuring generalized anxiety in multiple sclerosis. *Int J MS Care*. 2015;17(2):49–56.
 41. Devonshire V, Lapiere Y, Macdonell R, Ramo-Tello C, Patti F, Fontoura P, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2011;18(1):69–77.
 42. Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to glatiramer acetate therapy in individuals with self-reported progressive forms of multiple sclerosis. *J Neurosci Nurs*. 2003;35(3):163–70.
 43. Mohr DC, Goodkin DE, Likosky W, Gatto N, Neilley LK, Griffin C, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. *Mult Scler*. 1996;2(5):222–6.
 44. Turner AP, Kivlahan DR, Sloan AP, Haselkorn JK. Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: utility of the health beliefs model. *Mult Scler*. 2007;13(9):1146–52.
 45. Siegel S, Turner A, Haselkorn JK. Adherence to disease modifying therapies in multiple sclerosis: does caregiver social support matter? *Rehabil Psychol*. 2008;53:73–9.
 46. Turner AP, Sloan AP, Kivlahan DR, Haselkorn JK. Telephone counseling and home telehealth monitoring to improve medication adherence: results of a pilot trial among individuals with multiple sclerosis. *Rehabil Psychol*. 2014;59(2):136–46.
 47. Stockl KM, Shin JS, Gong S, Harada AS, Solow BK, Lew HC. Improving patient self-management of multiple sclerosis through a disease therapy management program. *Am J Manag Care*. 2010;16(2):139–44.
 48. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler*. 2005;11(4):459–63.
 49. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. *Arch Phys Med Rehabil*. 2004;85(2):290–7.
 50. Dettmers C, Sulzmann M, Ruchay-Plössl A, Gütler R, Vieten M. Endurance exercise improves walking distance in MS patients with fatigue. *Acta Neurol Scand*. 2009;120(4):251–7.
 51. Bombardier CH, Ehde DM, Gibbons LE, Wadhvani R, Sullivan MD, Rosenberg DE, et al. Telephone-based physical activity counseling for major depression in

- people with multiple sclerosis. *J Consult Clin Psychol*. 2013;81(1):89–99.
52. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol*. 1996;39(4):432–41.
 53. Turner AP, Kivlahan DR, Haselkorn JK. Exercise and quality of life among people with multiple sclerosis: looking beyond physical functioning to mental health and participation in life. *Arch Phys Med Rehabil*. 2009;90(3):420–8.
 54. Pilutti LA, Dlugonski D, Sandroff BM, Klaren R, Motl RW. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. *Mult Scler*. 2014;20(5):594–601.
 55. Bombardier CH, Blake KD, Ehde DM, Gibbons LE, Moore D, Kraft GH. Alcohol and drug abuse among persons with multiple sclerosis. *Mult Scler*. 2004;10(1):35–40.
 56. Turner AP, Hawkins EJ, Haselkorn JK, Kivlahan DR. Alcohol misuse and multiple sclerosis. *Arch Phys Med Rehabil*. 2009;90(5):842–8.
 57. Davies SJ, Pandit SA, Feeney A, Stevenson BJ, Kerwin RW, Nutt DJ, et al. Is there cognitive impairment in clinically ‘healthy’ abstinent alcohol dependence? *Alcohol Alcohol*. 2005;40(6):498–503.
 58. Parsons OA, Nixon SJ. Cognitive functioning in sober social drinkers: a review of the research since 1986. *J Stud Alcohol*. 1998;59(2):180–90.
 59. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. *Neurology*. 2002; 59(5):674–8.
 60. Abrams DB, Niaura R, Brown RA, Emmons KM, Goldstein MG, Monti PM. *The tobacco dependence treatment handbook: a guide to best practices*. New York: Guilford Press; 2003.
 61. Berglund M, Thelander S, Salaspuro M, Franck J, Andréasson S, Ojehagen A. Treatment of alcohol abuse: an evidence-based review. *Alcohol Clin Exp Res*. 2003;27(10):1645–56.
 62. Vital signs: current cigarette smoking among adults aged ≥ 18 years—United States, 2005–2010. *MMWR morbidity and mortality weekly report*. 2011;60(35):1207–12.
 63. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. *PLoS One*. 2011;6(1):e16149.
 64. Hedström AK, Bäärnhielm M, Olsson T, Alfredsson L. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. *Mult Scler*. 2011;17(7):788–93.
 65. Healy BC, Ali EN, Guttman CR, Chitnis T, Glanz BI, Buckle G, et al. Smoking and disease progression in multiple sclerosis. *Arch Neurol*. 2009;66(7):858–64.
 66. Pittas F, Ponsonby AL, van der Mei IA, Taylor BV, Blizzard L, Groom P, et al. Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis. *J Neurol*. 2009;256(4):577–85.
 67. Lemmens V, Oenema A, Knut IK, Brug J. Effectiveness of smoking cessation interventions among adults: a systematic review of reviews. *Eur J Cancer Prev*. 2008;17(6):535–44.