**Multiple sclerosis and implications for rehabilitation: a review of current literature**

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**Introduction**

Multiple sclerosis (MS) is a complex neurodegenerative disease which is progressive in nature and presents with a variety of symptoms. The research regarding MS treatments and diagnostics has developed tremendously within the last thirty years and continues to advance. For this reason, it is exceedingly important that clinicians evaluating and/or treating patients with MS stay up to date with the most recent literature. MS Standardized Training and Education Program with University Partners (MS STEP UP) is a unique program at the University of North Carolina Chapel Hill Division of Physical Therapy that provides specialized education in MS. The two-year program begins with self-directed educational modules in the first year. Since the program’s initiation in 2008, these modules have not been updated with the latest diagnostic criteria or other research regarding MS care. The program would benefit from additional resources and education regarding advanced cases of MS management. The primary purposes of this literature review are (1) to provide some of the diagnostic, evaluative, and treatment updates in MS to serve as a foundation for the advanced learning modules, (2) to provide necessary updates to the current content within MS STEP UP, and (3) to present brief summaries of relevant topics to help assess and respond to the associated forum prompts associated with the advanced learning modules.

**Diagnostics**

The 2017 McDonald Criteria are the most recent criteria for diagnosing MS.1 While there were many alterations made, only the most relevant ones will be discussed here as there are numerous changes that reside outside the scope of this review. The previous McDonald Criteria were established in 2010, but several issues regarding the 2010 criteria prompted the revisions established by the 2017 criteria.1,2 The primary changes put forth by the 2017 criteria relate to Clinically Isolated Syndrome (CIS), reducing the overlap between MS and other similar diagnoses such as neuromyelitis optica, the frequent and consequential false diagnoses of MS, and the advancements in magnetic resonance imaging (MRI) in MS.1 While the 2010 McDonald Criteria instituted the requirements of dissemination in time and space to confirm a diagnosis of progressive MS or non-CIS, the 2017 McDonald Criteria set forth to more accurately diagnose CIS as well as provide earlier diagnoses of MS. The 2017 criteria allow CIS to be diagnosed without sufficient MRI or clinical data if there is the presence of cerebrospinal fluid (CSF) oligoclonal bands. To allow for earlier diagnosis of MS, the 2017 criteria allow both symptomatic and asymptomatic MRI lesions to provide evidence for dissemination in time. In addition, cortical lesions as demonstrated by MRI, are sufficient evidence for dissemination in space, whereas the 2010 criteria only allowed juxtacortical lesions as evidence of dissemination in space.1,3

**Prognostics**

There are several factors that relate to prognosis in MS, some of which are related to clinical findings and others that are related to changes identified through imaging at diagnosis and over the course of the disease. Clinical findings that indicate a more negative prognosis include diagnosis at an older age, being male, delayed treatment initiation, longer disease duration at treatment initiation, primary symptoms affecting the efferent systems (motor symptoms rather than sensation changes), incomplete recovery after the first attack, and a higher frequency of relapses pre-treatment. 4,5 Negative prognostic factors related to imaging findings during the course of the disease include a faster loss in brain volume, a higher number of T2 lesions, a greater T2 lesion load, and lesions located in the spinal cord and cerebellum early on in the disease process.4,5 Grey matter atrophy occurs early on in the disease course, progresses over time, and correlates with disability and cognitive dysfunction.6,7 Grey matter atrophy is the most predictive measure of both physical and cognitive disability in MS. The combined measures of baseline central atrophy and lesion volume change are significant predictors of level of disability in 10 years, and level of cognitive deterioration.7

While several of these prognostic factors cannot be changed, such as primarily efferent symptoms at diagnosis, lesion locations at diagnosis, and sex, there are several factors that can be better controlled and accounted for with new disease-modifying therapies (DMTs) and the updated 2017 McDonald Diagnostic Criteria. With the new 2017 McDonald Criteria, MS diagnoses are being made earlier, which can reduce the age at diagnosis and galvanize disease-modifying treatments. In addition, improvements in DMTs have reduced the frequency of relapses early on in the disease course and delayed disease progression. While the MRI-related factors regarding prognosis in MS are able to predict relapse frequency and disease progression, they have not been researched as to their utility in predicting treatment response.4 In contrast, baseline MRI findings have proven significantly important in predicting disease progression especially regarding disability. Because of this, thorough and consistent MRI monitoring is recommended in order to better determine MS prognosis to help patients adapt and prepare for disease progression and to optimize treatment options.4

**Imaging Techniques and Analysis**

Currently, magnetic resonance imaging (MRI) is the gold standard for diagnosing MS, although it is not the only requirement for diagnosis as explained above. MRI uses radio frequency waves within a magnetic field to distinguish tissue types, which resonate at various frequencies in the neuromusculoskeletal system. For this reason, MRI is ideal for imaging soft tissues. It does not require radiation, reducing the negative side effects of radiation utilized by many other imaging types (e.g., x-ray and CT), it can take multiplanar images, and MRI has established typical findings associated with MS. While MRI is excellent for imaging soft tissues within the body, it has poor visualization of cortical bone because of the lack of water content and is extremely costly. Two of the most common types of MRI are T1-weighted and T2-weighted images. T1-weighted images highlight fat in bright white, while fluid appears grey, while T2-weighted images highlight fluid in bright white and the fat appears in grey. Therefore, MS lesions in T2-weighted MRIs are highlighted in white, and lesions in T1-weighted MRIs are highlighted in black and are sometimes referenced to as ‘black holes.’8 T2-weighted MRI images often show “Dawson’s fingers,” which are oval-shaped periventricular lesions perpendicular to medullary veins.6 Periventricular lesions along the fourth ventricle, temporal horns, in the midbrain, and in the cerebellar peduncle are also specific to MS. Other involved pathways include the corpus callosum, subcortical region, and the optic nerves and visual pathways.6 T1-weighted images are typically used to assess brain volume. The average brain volume reduction in MS is 0.7-1.0% per year.6

Proton density (PD) weighted images are another subtype of MRI, which allow for improved visualization of tendons and ligaments.8 Specifically within MS, PD-weighting identifies active inflammatory processes occurring within the brain, and can therefore determine the particular stage of demyelination for specific lesions within the brain. PD-weighting assists with establishing when patients are experiencing an MS relapse or exacerbation.9 Additionally, gadolinium chelate is a Gadolinium-Based Contrast Agent (GBCA) that is often administered approximately 5 minutes prior to a T1-weighted MRI. Gadolinium chelate detects blood brain barrier breakdown as caused by active inflammation. For about a month, new lesions caused by MS appear very bright, allowing for better identification of active disease processes. This is particularly useful during diagnostics and establishing dissemination in time.8,9 There are a couple of risk factors associated with the use of GBCAs including Nephrogenic Systemic Fibrosis (NSF) and GBCA retention. NSF causes thickening of the skin and damage to internal organs in people who take a GBCA with poor kidney function. The retention of GBCA has not been identified as harmful, but the potential subsequent effects remain unknown.10 Fluid attenuated inversion recovery (FLAIR) is a sequence utilized in T2 weighted MRI images of MS to improve visualization of periventricular lesions, which are often difficult to see due to the interference of the cerebrospinal fluid (CSF) located in the ventricles. The FLAIR sequence inhibits CSF interference while still maintaining signals from the MS lesions located in periventricular areas.9,10

**Medications**

Medications to treat MS are generally intended to either treat exacerbations, slow disease progression, or treat symptoms. A relapse or exacerbation is the spontaneous emergence of a neurologic symptom which lasts at least 24 hours.11 A pseudo-relapse or pseudo-exacerbation is brief and is typically caused by fatigue, infection, or other stressors such as heat. An acute relapse is typically treated with high-dose corticosteroids which can provide relief from symptoms, improve motor function, and shorten recovery time.11 Disease-modifying therapies (DMTs) are pharmacological treatments intended to reduce the clinical disease activity.11 DMTs may be delivered orally, via injection, or intravenously.11 There are a variety of DMTs that have been shown to be effective in reducing relapses, lesion accumulation, and disability in RRMS; however few if any are effective for progressive MS.12,13

One DMT that can be used for progressive MS is ocrelizumab (Ocrevus), which selectively targets B-cells and has been shown to delay disability progression.14  However, ocrelizumab is an emerging treatment and the majority of available evidence suggests that DMT use for patients with progressive MS and significant disability is typically not clinically effective.15 Many DMTs impact the function of the immune system and can lead to an increased risk of infection.16 Because DMTs may be associated with adverse events such as infections, have limited clinical utility in progressive MS, and are enormously costly, neurologists may recommend discontinuation for those with progressive MS.15,16 Rehabilitation plays a critical role in maintaining and restoring function in those with progressive MS particularly because there is so little effective, evidence-based pharmacologic intervention.

**Outcome Measures**

 The MS-EDGE task force provides recommendations for outcome measures to use with patients with MS in inpatient or outpatient rehabilitation.17 These recommendations were compiled in 2012 and provide a review of over 60 different outcome measures assessing a range of body structures and functions, activity, and participation.17 Although these EDGE documents are helpful in selecting an appropriate outcome measure to use with a person with MS, it is difficult to determine which measures may be appropriate for a person with a more advanced level of disability.18 A retrospective analysis published in 2018 suggests that the most commonly used outcome measures for patients with MS are inadequate for those with more severe mobility impairments.18 Many of the subjects with severe mobility impairments were unable to perform the tasks, or the measures were not responsive.18 This study highlights a need for improvement in assessments that are specific and validated for patients with more progressed MS.18

**Considerations for Pregnancy**

 Multiple sclerosis affects approximately 3 women to every 1 man, and onset is most typically in women of reproductive age.19 There are a variety of concerns, questions, and pregnancy-related issues that a patient with MS may be facing. Pre-pregnancy issues may include concerns about fertility, genetic risk, contraceptive use, DMT use, and impact of pregnancy on prognosis. MS does not have a significant impact on fertility or fetal development, and there also does not seem to be any impact of paternal MS on birth outcomes.19-22 In considering genetic risk, although having a first-degree relative with MS can increase disease risk by less than 2.5%, MS is not an inherited disease.19,23 Previous recommendations for women with MS were to avoid pregnancy due to potential worsening of disease; however, these recommendations were not evidence-based-- pregnancy has no negative long-term effect on prognosis and may actually be protective against developing MS.19, 24

 One of the major issues related to pregnancy is pharmacology, because none of the available disease modifying therapies (DMTs) for MS are recommended for use in patients who are trying to become pregnant, pregnant, or breastfeeding.19 It is unclear whether women who are trying to become pregnant would benefit from foregoing DMT until starting a family, or initiating DMT as soon as possible to control disease activity first.19 If a woman becomes pregnant while using a DMT, the standard of care is to stop DMT use immediately.19 It may be beneficial to start a DMT postpartum in order to reduce risk of postpartum relapse, particularly in women who are at higher risk which is associated with poor prognostic profile, relapse during pregnancy, no prior DMT use, and very active disease.25 The only DMTs that may currently be considered for use while breastfeeding are glatiramer acetate and interferon beta.19, 26

 MS disease activity is suppressed during pregnancy, especially in the third trimester. Clinical attacks are uncommon but possible in the first two trimesters, and are typically treated with short-term corticosteroids.19 Otherwise, pregnancy and delivery is not associated with any increased risk in women with MS.27 Patients should be aware that they are at risk of increased disease activity in the first three months postpartum.28 There is some evidence for prophylactic immunoglobulin and corticosteroids to reduce postpartum relapse.29,30 More research is needed to determine risks and benefits associated with pregnancy, and patients should be encouraged to discuss their concerns with their doctor.16

**Brain-Derived Neurotrophic Factor and Neuroplasticity**

Brain-derived neurotrophic factor (BDNF) has been gaining interest in the recent literature regarding its protective properties within the brain and its ability to elicit neuroplastic changes. BDNF improves brain function in the healthy population as well as those diagnosed with MS.31 It is of particular relevance to the MS population because of its control of development and repair of the central nervous system (CNS) and its responsiveness to a variety of stimuli. A few of those stimuli include aerobic exercise, resistance exercise, and the combination of the two31,32 MS is a chronic, neurodegenerative disease, and physical therapy targets preventive actions, restoration of previous or maintenance of current levels of physical function, and compensation for lost physical abilities. Neurologic rehabilitation also seeks to enhance positive neuroplastic changes in people afflicted by neurologic diseases, and BDNF plays an important role in both the goals of neurologic rehabilitation and neuroplasticity. Physical rehabilitation can address the symptoms related to MS but there is little evidence related to its effect on disease course. Recent studies analyzing the therapeutic effects of increased levels of BDNF have discovered positive changes regarding the pathogenesis of MS.31,32

Previous studies in healthy populations have shown that 10 minutes of moderate aerobic exercise is inadequate for achieving a significant increase in BDNF, but a high intensity bout of physical exercise is much more capable of achieving this. It has been shown that the increase in serum BDNF levels are directly related to the intensity of exercise.32 In addition, the baseline levels of BDNF are significantly different between the healthy population and those diagnosed with relapse-remitting MS (RRMS).32 This finding demonstrates the associated loss of neuroprotection in people with MS compared to those without MS. The levels of BDNF fluctuate in people with RRMS and are found to increase immediately after a relapse, indicating that BDNF plays a significant role during the remission phases of RRMS.32

Specifically within the MS population, 30 minutes of moderate exercise have achieved significant increases in BDNF over a course of 8 weeks, but these improvements have been transient, and returned to prior levels within 30 minutes after exercise completion.32 A recent study published in 2016 found that 24 weeks of moderate aerobic exercise was able to achieve significant increases in BDNF in persons with RRMS compared to sedentary controls with RRMS.32 While the exercise group demonstrated significant increases in BDNF, the control group experienced a decrease in BDNF, which speaks to the importance of regular aerobic exercise for brain function.32 Therefore, habitual aerobic exercise at higher intensities is much more likely to be effective in eliciting the neuroprotective and neuroplastic properties of BDNF. Based on these preliminary findings in MS and studies in the healthy population, BDNF is an important target in neurorehabilitation programs.31,32 While intense aerobic and resistive exercise may be more easily incorporated into physical therapy programs for people in mild to moderate stages of MS, we believe it should still be a consideration during the later stages of MS. Incorporating BDNF-targeted interventions into physical therapy practice and home exercise programs for individuals with MS may prove to be a reliable and effective method of improving the MS disease course through conservative treatment.

**Cannabinoids**

 In addition to the medications discussed above, many people with MS seek alternative methods of symptom management such as cannabis.33 Although cannabis is a Schedule I controlled substance federally, the majority of states have legalized cannabis for medical purposes.34 There are a variety of cannabinoid formulations and methods of administration, such as botanicals, tetrahydrocannabinol (THC) extract, cannabidiol (CBD) extract, THC:CBD extract, capsules, and oromucosal sprays, which have varying levels of safety and efficacy for persons with MS.33,35 There are several reviews supporting the use of cannabinoids for symptoms of pain and spasticity in MS, which are two of the most prevalent symptoms associated with MS.33 Results examining the use of cannabinoids to treat other common symptoms such as bladder dysfunction, ataxia, and tremor, are inconclusive.35 The majority of research conducted has used oromucosal sprays or extracts, and there have been very few quality studies examining the effects of botanical forms of cannabis.33

 Although cannabinoids may be effective in reducing pain and spasticity in people with MS, they are also associated with a range of potential adverse effects. The most common adverse events in patients with chronic pain were headache, nasopharyngitis, nausea, somnolence, and dizziness, which each occurred in 3-5% of participants.36 Adverse cognitive effects are possibly the largest concern with cannabinoid use for people with MS. In people with MS who have cognitive problems, cannabis use can worsen these deficits, particularly those in information processing speed, executive function, and working memory.37 The potential risks and benefits should be weighed for each individual patient, considering their most problematic symptoms and risk of adverse effects. Typically, adverse events and benefits associated with cannabinoids are observed in the first four weeks, so it might be beneficial for patients and their physicians to conduct a brief individual trial to determine whether the patient responds beneficially to cannabinoids.38

**Cognitive and Psychosocial Considerations**

Cognitive impairment affects 40-65% of people with MS, and is found with the highest frequency in those with secondary progressive MS.39 The most commonly affected domains are processing speed and memory, however deficits in attention, executive function, visuospatial perception, verbal fluency, and social cognition are also prevalent.40 Cognitive decline in MS typically progresses slowly and is strongly correlated with brain lesion count and location and brain atrophy.39 Cognitive deficits in patients with MS are associated with poorer adherence to treatment and potentially impact ability to make informed decisions about treatment. Care partners of people with MS report increased challenge, distress, and depressive symptoms, and reduced quality of life related to their partners’ cognitive deficits.40 Although some studies have found no correlation between depression and/or anxiety and cognitive dysfunction, many studies report that both anxiety and even mild depressive symptoms interfere with cognitive performance, particularly processing speed, in patients with MS.39 Although there is minimal evidence for pharmacological treatment (symptomatic or disease-modifying), there is some evidence that behavioral interventions may slow cognitive deterioration, improve cognitive function, and enhance memory.39 Cognitive rehabilitation and exercise are recommended interventions.

 There are a variety of tools to screen and assess cognition in patients with MS. The Symbol Digit Modalities Test (SDMT) is a simple, recommended tool to administer for baseline cognitive screening. There are several other tools that are similar to the SDMT, and many more comprehensive assessment batteries such as the Brief International Cognitive Assessment for MS (BICAMS) or the Minimal Assessment of Cognitive Function in MS (MACFIMS).40 It is also recommended that patients are screened regularly to identify any mood changes that may impact cognition. Recommended screening tools for depression include the Beck Depression Inventory or the Hospital Anxiety and Depression Scale (HADS).40 A 2016 systematic review concluded that the HADS, the one-item measure, and the two-item measure are the most sensitive and specific screening tools for persons with MS.41 The one- and two-item measures are particularly recommended for screening because they are quick and easy and do not contain overlap with somatic symptoms. The two-item measure assessed consisted of the following questions: “During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless?” and “During the past two weeks, have you often been bothered by little interest or pleasure in doing things?”41 These measures may be most appropriate for screening as physical therapists, particularly with patients with associated cognitive dysfunction.41 Unfortunately, less than 30% of individuals with depressive symptoms who are encouraged to receive treatment do so, so it is important that patients with depressive symptoms are not only identified and referred as is appropriate, but that there is also follow-up with the patient and identification of barriers to treatment.42

**Ankle-Foot Orthoses and Functional Electrical Stimulation for Gait**

Assistive devices and wheelchairs have advanced exponentially in a short period of time, during which functional electrical stimulation (FES) is being much more widely used and customized ankle-foot orthoses (AFOs) have largely become the new standard of care. Review of the newest technologies and advancements in both FES devices and AFOs will be discussed.

In terms of FES, there are currently two leading manufacturers including Bioness and WalkAide, which were first used clinically around 2004. While both companies provide FES devices, the respective means by which each device provides timely electrical stimulation differs. WalkAide devices elicit stimulation when triggered by a change in velocity as determined by an embedded accelerometer and a tilt sensor,43 while Bioness devices are stimulated by a tri-axis gyroscope and accelerometer that can sense movement in all three kinematic planes.44,45 Some of the benefits identified by use of FES devices include improved gait speed, improved gait biomechanics, reduced energy expenditure during ambulation, minimized muscle atrophy of the lower leg, and reduced frequency of falls.46-48 One study identified a decreased frequency in falls of 92%.46 Both the time required for each stride and the variability in lengths of time per stride are reduced immediately upon application of an FES device.46 A systematic review and meta-analysis by Miller et al. identified significant increases in gait speed in short-distance tests including the 10-meter Walk Test; however, the author states that the clinical benefits of these devices compared to AFOs must be compared to determine the cost-benefit ratio of FES devices.47 Similarly, another study comparing the effects of passive AFOs and powered AFOs was unable to identify an improvement in distance walking using a powered AFO, and actually observed the opposite: a significant decline in 6-minute walk test distance using the powered AFO.49

While FES devices have been shown to assist with improved gait mechanics and ease of ambulation while being worn, the effects have not been observed when the devices are not worn.47 Both WalkAide and Bioness hoped that therapeutic effects, or beneficial effects from device use, would carry over to elicit improvements in strength or motor control; these benefits have not been found in the research. Since there has not been any identified carry over effect from FES use, the devices have similar benefits as ankle-foot orthoses. A study by Renfrew et al. published in 2018 compared the effects of FES devices to AFOs on gait speed and oxygen cost during gait in people with MS.48 Results from the study indicate that there are minimal differences in orthotic benefits between the two. One finding of particular interest is that AFOs tended to slow the fast-walking group of individuals with MS, while this negative effect was not seen during FES use. Further high quality studies are needed in order for more definitive results.48,50 A 2019 RCT by Renfrew et al. identified similar improvements in ambulatory efficacy with use of AFOs or FES devices, and deemed the steep cost of an FES device ineffective in terms of cost when working to improve foot drop in MS at this time.48 The cost of an FES device is a substantial barrier to its implementation due to its lack of insurance coverage, while AFOs are typically covered by insurance providers.

There are several ankle-foot orthoses (AFOs) available for patients with lower extremity weakness. They range from isolated at the ankle to those that assist with knee function (KAFOs) and those with hip assistance (HKAFOs). Of those isolated to assisting the ankle, a few of the most frequently prescribed AFOs include the posterior leaf spring (PLS), articulated or hinged AFOs, and rigid AFOs. There are also varying types of materials used with AFOs including carbon, metal, and plastic. Typically, metal AFOs are worn by persons with sensory deficits and the light weight carbon material is prescribed for individuals with stable medial-lateral ankle control who may be seeking better gait efficiency.51 While many individuals with MS experience hip and knee weakness, the KAFOs and HKAFOs are not always recommended because of the significant increase in energy expenditure required by these orthoses.52 The primary benefit of KAFO use is the reduction in knee hyperextension or knee buckling due to quadriceps weakness. While this may enhance standing and gait stability for some individuals with MS, it may not be worth the steep increase in energy cost of walking for others. One consideration is hip flexion and extension strength, which if very weak, may help determine the practical utility and feasibility of a KAFO.52 Use of an AFO to assist with gait speed, foot drop, and gait biomechanics is evidenced in persons with MS and can be customized to the individual’s particular needs.49,51 While further evidence is needed to determine whether the utility of an AFO or an FES device is superior to the other, each patient’s optimal choice must be made on a case-by-case basis.

**Assistive Devices and Wheelchair Considerations**

In addition to AFOs and FES devices discussed above, there are a variety of mobility assistive devices and technology which may be considered for individuals with MS throughout varying stages of disability. Canes are often used to maintain even weight distribution and to reduce walking effort and risk of falls when gait instability is mild. 53 Crutches, including lofstrand crutches, may be more appropriate for an individual with more balance needs, and those who need bilateral support and have good control of their upper extremities. Walkers, including rollators, are indicated for individuals with moderate deficits requiring an increased base of support and stability. Manual wheelchairs may be indicated for those experiencing frequent falls, severe balance difficulties, or for reducing fatigue with part-time use while still providing some level of physical activity.53 Manual wheelchairs have been consistently reported as the most common assistive device used by people with MS.53 Since upper extremity fatigue can be an issue when using a manual wheelchair, scooters may be a preferred mobility option for some; however, scooters may provide insufficient stability and have limited seating adaptations which would be available with power wheelchairs. In addition to being used for patients with more severe levels of disability, power wheelchairs should be considered as an option to address fatigue in those in less advanced stages of MS.53

 People often report viewing assistive device use as a symbol of disability; however, people who transition to using a power wheelchair report increased competence, adaptability, and self-esteem which significantly influences their perception of quality of life.53 Power wheelchairs with features such as tilt and recline reduce risk of pressure sores, enhance comfort, and reduce need for transfers through the day.53 The combination of tilt and backrest recline achieves greater pressure reduction than tilt alone, with the most pressure reduction demonstrated at a 45 degree tilt and 120 degrees of recline.53 There are a variety of risks related to disability and immobility including pressure sores, deep venous thromboembolism, coronary heart disease, osteoporosis, and weight gain and obesity, which should be screened for and considered especially in power wheelchair users.54,55

**ADA Regulations and Resources**

 The ADA, or the Americans with Disabilities Act of 1990, “prohibits discrimination against individuals with disabilities in all areas of public life, including jobs, schools, transportation, and all public and private places that are open to the general public.”56 In terms of employment, businesses or companies of “15 or more employees must comply with [ADA regulations],” which can include modifications to work environments that are within reason and allow an employee with a disability to “perform essential job functions.”57 Currently, for buildings open to the public, the 2010 Standards of the ADA require alternative and accessible routes to stairs such as a ramp. Ramps are required to have 12 inches of horizontal run for every single inch of vertical rise. Additional examples of ADA requirements are 2% of hotel rooms being ‘accessible’ and at least 2% of parking spaces in every lot being marked ‘handicapped.’57 There is a 20% cost limit on the amount of a single entity that can be spent on alterations to comply with the ADA Regulations. New designs and constructions must comply with ADA standards, but there are also certain standards that can be met in order for an entity to be ‘grandfathered’ in and not be required to maintain ADA standards.57

 For individuals struggling with employers, landlords, or others that are non-compliant with ADA regulations, there are several available resources. There are 10 regional ADA Centers in the United States that “provide local assistance and foster implementation of the ADA.”58 North Carolina is grouped in Region 4, the Southeast ADA Center. The ADA Centers offer support to individuals with disabilities and also provide free ADA training courses, webinars, and workshops. There are also several federal agencies that offer support to Americans with disabilities including the U.S. Department of Justice, U.S. Equal Employment Opportunity Commission, U.S. Access Board, U.S. Department of Labor, U.S. Department of Transportation, the Federal Communications Commission, U.S. Department of Housing and Urban Development, and the Federal Emergency Management Agency.59 There are links to these federal agencies and resources available on the adata.org website.

**Insurance Coverage**

 Medicaid is one of the national healthcare insurance programs that is specific to Americans with low-income, children, pregnant women, older adults, and individuals with disabilities. It is funded by both the state and federal government. Under Medicaid, there are both mandatory and optional benefits. The mandatory benefits include inpatient hospital services, outpatient hospital services, nursing facility services, home health services, physician services, labs and x-ray imaging, nurse midwife services, and transportation to medical care, among others. Some of the optional benefits include prescription drugs, clinic services, physical therapy, occupational therapy, speech and hearing services, respiratory care, dental services, optometry, podiatry, prosthetics, hospice, personal care, case management, and health homes for enrollees with chronic conditions, among others approved by the secretary. The mandatory services are required by the federal government, while the optional services are state-dependent and each state chooses whether or not to cover the listed services.60 Many of the listed Medicare services are important considerations for individuals with MS, especially due to the chronicity of the disease. Unfortunately, there are only three optional services covered for annual visits by the state of North Carolina’s Medicaid program, which include chiropractors, optometrists, and podiatrists. Outpatient specialized therapy services such as PT and OT require prior approval. Approval requests must be submitted through the Choice PA NC website where medical providers can register and track requests.61

 It is imperative that physical therapists understand the appropriate billing for therapy services as well. Rehabilitation has been differentiated by habilitation, in which rehabilitation is the return or reestablishment of previous skills to improve quality of life and physical independence. Habilitation is described as “services [to] help a person keep, learn, or improve skills and functioning for daily living,” and these skills often act as compensatory strategies and interventions to maintain a patient’s current level of function.62 Modifiers 96 and 97 should be included after the CPT code to identify services that can be qualified as either rehabilitative or habilitative. It is also important to note that the Jimmo Settlement deemed patients covered by Medicare and Medicaid who have chronic, progressive conditions eligible for skilled therapy services to maintain function or mitigate decline. The Jimmo Settlement was the outcome of the “Improvement Standard” lawsuit in 2013. With the ability to bill insurance for therapy for individuals with MS, it is important to take exceptional care and precision when documenting and billing, so that “skilled maintenance” is evidenced.63 Additional resources are available on the APTA website including frequently asked questions regarding both documentation and coding and billing for skilled maintenance.64

 States are also in charge of establishing alternative out of pocket costs for individuals covered by Medicaid whose income falls above the federal poverty line. These out of pocket costs are limited to 5% of family income. Should Medicaid enrollees fail to pay these out of pocket costs, additional services are subject to refusal.65 Additionally, the Community Living Initiative mandates that programs, activities, and other opportunities put forth by the state are offered in ways that allow individuals with disabilities to partake. It was set forth in order to promote equal rights and protection to persons with disabilities in public settings including employment and transportation, among others.66 This initiative and the offered community services such as medical transportation are critical for individuals with MS who are unable to drive, lack family or social support, and benefit from community program participation. Awareness of the available and covered programs in the local area can enhance both patients’ and providers’ awareness and knowledge of important resources.

**Osteoporosis and MS**

 MS places individuals at a higher risk for acquiring osteoporosis at a younger age and increased risk of osteoporosis-related fractures. The development of osteoporosis among individuals with MS is due to an accumulation of factors including reduced time spent standing or walking, general physical inactivity, low vitamin D levels associated with MS diagnosis, and use of medications commonly used to treat MS relapses such as glucocorticoids.67 The prevalence of low bone mass in MS has been estimated at 27.2% and osteoporosis at 15.4%. Similarly, it has been found that 22% of individuals with MS suffered fractures compared to only 2% of their age-matched controls.68 Another study identified 80% of men with MS with low bone mass in either the femoral neck or lumbar vertebrae. The age range of the participants was 55 to 64 years, which is still younger than the typical definition of an older adult of 65 years old.69

 Osteoporosis can be considered a secondary symptom of MS. Primary symptoms of MS are those that are directly caused by the disease process such as demyelination of the central nervous system (CNS) leading to muscular weakness and incoordination. Secondary symptoms of MS are those that are indirectly caused by the disease and can be avoided or minimized. While spasticity and demyelination of the CNS are primary symptoms of MS, weakness can be both a primary and secondary symptom. The increased energy expenditure associated with standing and walking when one is experiencing muscle weakness due to MS can significantly limit one’s time spent exercising or being physically active, further increasing their physical inactivity and subsequently reducing their physical fitness. Reduced time spent standing, walking, and exercising decreases the mechanical load on their bones, thereby decreasing osteoblastic activity and increasing osteoclastic activity. Osteoblasts are responsible for forming new bone and are activated by mechanical stress on the bones.67

 Vitamin D has a well-established effect on bone density including control of calcium homeostasis. There is a known link between low Vitamin D levels and MS diagnosis.68 This could contribute to early-onset osteoporosis; however, it is unlikely to be the sole contributor. In addition, medication use such as glucocorticoids has known negative effects on bone density.69 Glucocorticoids are most commonly utilized during acute MS relapses. Two of the negative side effects associated with glucocorticoids are inhibition of osteoblast differentiation and increased osteoclast activity leading to increased bone resorption. Since these steroids are usually taken for short periods of time, their effects are typically transient, and therefore, cannot be the sole contributors to osteoporosis in MS. Antidepressants and anticonvulsants are frequently prescribed medications in the MS population and are usually taken on a long-term basis and are likely associated with decreased bone density.67 There is a long list of potential contributors to osteoporosis in MS, and it is likely a combination of these risks and factors that lead to the actual diagnosis and any subsequent fractures.

 The FRAX model, created to objectify fracture risk in the general population, has been expanded upon by Bazelier et al. to include additional risks specific to the MS population such as antidepressant and anticonvulsant use, falls history, and history of fatigue.70 The other factors taken into account in the FRAX model are the age, sex, body mass index (BMI), and fracture history, among others.70 Following the modified FRAX model created by Bazelier and colleagues, treatment for osteopenic and osteoporotic patients with MS should be multifaceted, targeting nutrition, physical activity, and lifestyle changes.70 Several important lifestyle changes include smoking cessation and reduced alcohol intake. Physical activity measures that can be taken to offset osteoporotic processes include resistance training and aerobic exercise that includes impact training to induce increased muscle strength and bone remodeling. Vitamin D supplementation and increasing sun exposure can also assist with immunomodulatory effects that affect bone density. In terms of pharmacologic interventions, there are several drugs including bisphosphonates, parathyroid hormone, and denosumab. Dual x-ray absorptiometry (DXA) scans are the gold standard for measuring bone density levels and are recommended frequently for high risk populations such as women who are post-menopause. Among the MS population, individuals unable to ambulate without assistance (EDSS 5.0 or higher), men over 40 years old, and women post-menopause should receive regular DXA scans to objectively track changes in bone density and treat osteoporotic changes appropriately.67 Currently, there are no specific standards for treating low bone mineral density in the MS population, therefore, further research is required to determine the best methods for reducing early onset and eventual diagnosis of osteoporosis in MS.67

**Wellness Considerations**

There have been several advances in the pharmacologic treatment of relapsing MS, however this is not as true for progressive MS.71 Disease-modifying therapies for progressive MS in particular are associated with inadequate efficacy and substantial side effects, which has prompted increased interest in lifestyle and wellness behaviors. Despite wellness being a high priority for those living with MS, there is little quality evidence related to wellness interventions for people with progressive MS.71 A review published in 2018 considering 21 articles examining wellness interventions for people with progressive MS found four main types of intervention: exercise training, emotional well-being therapies, dietary modifications, and a combined wellness intervention.71 Based on this evidence, there are possible benefits with exercise training and mindfulness therapies, but there is inconclusive evidence for dietary modifications or combined wellness intervention.71 This review again suggests the need for additional research focused on interventions for patients with progressive MS.71

 Observational studies suggest that vascular comorbidities are associated with increased risk of disease activity and disability, vitamin D levels are inversely correlated with MRI markers of disease activity, and smoking tobacco is associated with increased risk of disability.72 Smoking cessation should be encouraged for all patients with MS, because it has been shown to decrease the risk of worsening disability.72 Several studies suggest the importance of stress management and management of psychiatric comorbidities in MS.72 In a review examining 16 complementary and alternative treatments of MS, the interventions most strongly supported by evidence were cannabis extract (discussed further in another section), physical activity, and cognitive behavioral therapy.73 Yoga was not shown to have significant effects in the two studies examined, and there is insufficient evidence for treatments like relaxation techniques, reflexology, acupressure, and amphetamine salts.73

 There have been a variety of epidemiological studies linking diet to incidence of MS, and theoretical considerations of the effects of diet at the molecular level; however, there are limited clinical, quality studies examining nutritional guidelines for people with MS.74 Vitamin D is often recommended based on epidemiological studies indicating lack of vitamin D may be associated with risk of MS, disease activity, and disease progression, however a Cochrane meta-analysis indicates the evidence to support vitamin D supplementation is not reliable.5 If vitamin D deficiency is demonstrated, as is common in people with MS, oral supplements are then recommended.74 In general, it is recommended that people with MS maintain a low-calorie diet with balanced nutrition that provides fiber, anti-oxidants, unsaturated fats, unrefined carbohydrates, and supplements vitamin deficiencies.74,75 In addition, nutritional counseling should be encouraged for individuals with MS because comorbidities such as malnutrition, metabolic syndrome, and cardiovascular disease may be impacted by diet and are correlated with decline in physical condition and quality of life.74

**Caregiver Considerations**

30% of people with MS require assistance from caregivers, with more than 80% of that care being provided informally rather than through professional services.76 Informal care is often provided by a spouse or family member, and can have negative effects on the person providing care. Caregiver burden can be related to strain on mental and physical health, loss of employment due to the time demands of providing care, and lack of appropriate knowledge or training for caregiving.76 Caregiving can be very time consuming, with those with severe levels of disability often requiring between eight to 12 hours of care per day.76 A 2013 study found that 51% of care partners interviewed reported reducing their employment hours in the past year due to the increased time demands of caregiving.76 Caregiver burden has been found to be mediated by the disease severity of the person being cared for, the availability and reliance on support networks, participation in respite and self-care activities, and participation in other or conflicting roles outside of caregiving.76 Twenty-five to 55% of caregivers for those with MS report that they would personally benefit from counseling services, however only 35% of those actually seek treatment, citing financial barriers.76 Healthcare providers are encouraged to acknowledge both the caregiver and the patient, to encourage caregivers to engage in self-care practices, and to recommend respite or other community resources as is needed.

**Innovative Interventions**

The two innovative interventions highlighted in this review are evidenced conservative treatments for MS that have recently gained momentum in the literature. Central vestibular dysfunction, differentiated from peripheral vestibular dysfunction, is oftentimes overlooked and undertreated in the MS population. The other intervention is High Intensity Interval Training (HIIT) a recently studied form of exercise in MS. Both interventions will be reviewed in depth to provide insights regarding the pathophysiology and/or physiologic benefits, risks, evaluative methods, and appropriate dosing specific to the MS population.

In addition to these two innovative interventions, additional literature was reviewed related to recommended interventions for patients with advanced MS. The majority of the evidence related to exercise and rehabilitation for individuals with MS has been focused on those with mild-to-moderate levels of disability (typically with an EDSS of less than 5.5).77 A 2017 review examined the effects of conventional aerobic and resistance training and adapted exercise modalities on outcomes related to physical fitness and function, fatigue, mobility, and quality of life in people with MS with an EDSS of greater than or equal to 6.0.77 Although aerobic exercise training was shown to be safe and feasible, there were no significant results reported in the studies analyzed in this review. Conventional resistance training may illicit benefits for those with severe mobility disability, and may be easily adaptable to those who are using a wheelchair or require other modifications.77 There is also evidence that progressive resistance training combined with neuromuscular electrical stimulation may contribute to significant improvements in endurance, fatigue, balance, and quality of life in persons with advanced MS.77 There were several types of adapted exercise training which were shown to be beneficial for this population such as body-weight supported treadmill training, electrical stimulation assisted cycling, and total body recumbent stepper training; however, additional studies are needed to examine the effects and clinical feasibility of these interventions.77

1. **Central Vestibular Dysfunction in MS**

Due to the number of contributing factors to balance dysfunction in MS, central vestibular dysfunction specifically within the MS population lacked sufficient evidence.79,83-85 In recent years, this undertreated condition in individuals with MS has gained momentum in the literature including several high quality RCTs.81-87 Unlike peripheral vestibular dysfunction, central vestibular pathology is not caused by disturbances of the inner ear such as unilateral vestibular hypofunction or benign paroxysmal positional vertigo (BPPV). Rather, central vestibular dysfunction occurs due to a central disturbance such as a lesion within the cerebellum or brainstem. Lesions located in the brainstem have been identified in approximately 68 to 72% of the MS population.78 Additionally, up to 70% of individuals with MS present with cerebellar dysfunction.78 These statistics demonstrate the high probability of a significant prevalence of central vestibular dysfunction among people with MS. Even when vestibular rehabilitation is included in MS rehabilitation, it lacks standardization and individualization due to the current lack of research regarding specific guidelines.78,79 While there are medications that seek to ameliorate the complaints related to central vestibular dysfunction, they simply mask the symptoms and my further prolong the underlying dysfunction due to failure to target the actual source of dysfunction.80

 The RCTs examining vestibular rehabilitation in MS have identified both statistically significant and clinically significant improvements in balance, fatigue, and dizziness when compared to respective control groups.81-87 One of the interesting findings from an RCT that stratified its participants by presence of a cerebellar and/or brainstem lesion is that both groups, those with identified lesions indicating potential central vestibular dysfunction and those without lesions in those two areas, demonstrated similar improvements during the first 6 weeks of the program.81 During the latter 8 weeks of the program, individuals with cerebellar and/or brainstem lesions continued to see significant improvements, while those without lesions in those locations did not. Overall, vestibular training has proven beneficial for individuals with and without cerebellar or brainstem lesions, but those with specific lesions may benefit to a greater degree, especially in the long-term.81 When comparing vestibular rehabilitation to a conventional balance and exercise program, balance improvements were also significantly improved in the vestibular group.82 From the RCTs81-87 and a cross-over study80 identified examining vestibular rehabilitation in the MS population, several patterns of results can be emphasized. Primarily, it can be determined that combined vestibular rehabilitation and conventional balance training allow for greater and more efficient improvements in balance and vestibular impairments than either intervention performed in isolation.81-83 Additionally, individualizing vestibular rehabilitation regimens to person-specific deficits has been found to assist with maximizing participant improvements.82 The studies generally occurred over a short period of time, a mean of 4 weeks, which was sufficient to provide significant improvements in vestibular function and balance.82,84-87 It is also important to note that individuals with MS who were moderately to severely disabled also benefited from vestibular rehabilitation to address fatigue, balance, and ADL performance.80,81 Many individuals with moderate to severe MS are unable to participate in balance training because of difficulties standing and walking, but vestibular rehabilitation offers static and less dynamic exercises that can still reduce complaints of dizziness and instability.81-83 Therefore, vestibular interventions performed in sitting and static positions that target eye, head, and neck movements can provide important improvements for individuals with MS with a higher level of disability.80,81

 The various protocols and equipment used during the interventions studied are feasible within typical outpatient clinical settings with the exception of the Balance Manager, a product of NeuroCom Systems not readily commercially available. The Balance Manager is used to perform the Computerized Dynamic Posturography Sensory Organization Test, which examines differences in visual, somatosensory, and vestibular function as they interact to promote upright balance. The Balance Manager is an expensive piece of equipment not commonly found in general outpatient clinics, but the Sensory Organization Test can be performed using less expensive materials. Aside from the Balance Manager, all other interventions and assessments are feasible and efficient in a typical outpatient physical therapy session. Additionally, many of the interventions provided in clinics can be carried over to the home setting, so patients can continue with their therapy independently.81 While the results from recent RCTs appear promising, there is still a great deal of heterogeneity among the studies examining vestibular rehabilitation in persons with MS.82 Continued research into standardizing these training regimens and identifying how particular lesions respond to specific interventions will help optimize rehabilitation protocol creation and patient outcomes.

1. **High Intensity Interval Training (HIIT)**

In the past 20 years, exercise has transitioned from being controversial and considered potentially dangerous for people with MS to being an important contributor to their health and wellness.88 Moderate intensity exercise is recommended for improving fitness in those with MS, however, high intensity exercise was still not yet considered until recent years.89 High intensity interval training (HIIT) has been repeatedly shown to be more efficient at improving VO2maxand reducing cardiovascular risk factors in healthy people than continuous moderate training.89 It is also beneficial for patients with neurologic conditions such as Parkinson’s disease or chronic stroke.89 HIIT is speculated to be particularly beneficial for those with MS due to its inherent incorporation of intervals, which are comparable to energy-conserving rest breaks. It is hypothesized that this may allow for increased intensity and volume of work without increased thermosensitive responses which may trigger pseudoexacerbation.89, 90

Although HIIT for people with MS is a new topic--the earliest applicable article found was published in 201591 --with limited high-quality evidence at this time, high-intensity interval training has been shown to be a safe and effective intervention for patients with relapsing-remitting MS of low levels of disability.89 A systematic review published in 2018 included 11 articles describing seven studies of HIIT for people with MS.89 These studies primarily used cycle ergometry in intervals at a targeted range of 85 to 100% of an individuals’ maximum heart rate (HRmax), or a range of 80-110% peak power, with target range varying for individual studies. The intervals ranged from 30-90 seconds of work with 30 seconds to three minutes of complete or active rest.89 Frequency was two to three times per week for a range of three weeks to 12 weeks, with most of the studies progressing target intensity throughout. Some of the studies examined HIIT as a stand-alone intervention, but many included HIIT in combination with either moderate aerobic training, resistance training, or inpatient rehabilitation.89 The majority of participants included in this review had RRMS with a moderate to low level of disability as indicated by an EDSS of 4.0 or less.89 This review provides limited evidence that HIIT can improve VO2peak and VO2max, HRmax, peak power, muscle strength, and decrease matrix metalloproteinase(MMP)-2 levels in those with MS who have low to moderate levels of disability. MMPs are believed to play a substantial role in the pathogenesis of MS by disrupting the blood brain barrier, recruiting inflammatory cells into the CNS, and enhancing the demyelination process.92 When compared with moderate continuous training, HIIT requires fewer and shorter sessions to achieve similar if not better results. Moreover, studies report high adherence to HIIT.

There is very little evidence available regarding how HIIT may impact quality of life or symptoms such as fatigue. In a small pilot study with 40 total participants with RRMS, participants in both the moderate training and HIIT groups who were in a subgroup with high baseline fatigue scores demonstrated significant reduction of fatigue after eight weeks of training.93 However, the lack of significant difference between moderate and HIIT groups may be because the HIIT in this study was using a peak power output of 70% which is relatively low compared to other HIIT interventions.93 Future research will hopefully assess the impact of HIIT (at a peak power of at least 80%) on fitness, fatigue, and quality of life in individuals with MS, and will consider the efficacy of HIIT compared to moderate continuous exercise for patients with progressive MS or higher levels of disability. HIIT using cycle ergometry appears to be safe and at least as effective as continuous moderate training for individuals with MS with a low to moderate level of disability.89

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