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RESEARCH ARTICLE

Managing the Symptoms of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that is characterized by recurrent bouts of acute neuroinflammation and chronic neurodegeneration. Treatments for MS are aimed at prevention of disability in the future or restoring function in the present. Prevention treatments disrupt the underlying disease pathology, whereas restorative treatments address not only the disease's primary effects on the central nervous system, but also secondary effects on other parts of the body and tertiary effects on each patient's psychosocial functioning. MS symptoms can have primary, secondary, and tertiary components, which can interlock and reinforce each other. Restorative treatment should tease apart these components and address them separately. In this article on symptom management, we focus on treatments that aim to maximize each component of function.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that is characterized by recurrent bouts of acute neuroinflammation and chronic neurodegeneration. Treatments for MS are aimed at prevention of disability in the future or restoring function in the present. Prevention treatments disrupt the underlying disease pathology, whereas restorative treatments address not only the disease's primary effects on the central nervous system, but also secondary effects on other parts of the body and tertiary effects on each patient's psychosocial functioning. MS symptoms can have primary, secondary, and tertiary components, which can interlock and reinforce each other.^{1, 137} Restorative treatment should tease apart these components and address them separately. In this article on symptom management, we focus on treatments that aim to maximize each component of function.

These different components require different specialists, including physical and occupational rehabilitation, cognitive therapy, urology, gynecology, psychiatry, pain management, and others. Although the following discussion focuses on the subtleties of pharmacotherapy, lifestyle modifications are equally important, both because they have their own dramatic effects that augment pharmacotherapy, but also because they promote each patient's sense of self-efficacy and outlook.⁸

To address symptoms, neurologists should take a full history with a targeted review of systems, proactively asking about "invisible" symptoms or other sensitive topics such as the patient's mental health.^{2,137} The initial clinical interview acts as a screening tool that prioritizes symptoms contributing to mortality or serious morbidity, after which neurologists can delve further into the symptoms that are most troubling to the patient.³ Patients may find it difficult to raise sensitive topics in the clinical setting due to concerns of being invalidated or misunderstood.¹³⁷ In addition, not all symptoms associated with MS are well-known and patients may not connect their experiences directly with their disease. Some symptoms may also be neglected as patients either ignore or adapt to them without intervention, despite interference in daily life. Providers should also be mindful of stigma relating to both the diagnosis and the symptoms and can discuss mitigation strategies with patients when addressing therapeutic options.^{3, 137} While detailed discussion of symptom management may seem like time-consuming, low priority compared to disease modification, it is essential to excellent MS care.¹¹

In this review, we describe management strategies for 11 common MS symptoms. Each section is intended to stand on its own, though some sections reference the topics of other sections when they overlap in constellations of symptoms.

Dysmobility and Gait

The quality of life of people with MS is affected by dysmobility more than any other factor.⁶ Dysmobility is a result of dysfunctional stance or gait, whose mechanics can be affected by weakness (especially with hip and ankle flexion), spasticity, decreased range of motion, pain, ataxia, and poor vision, each of which is addressed in other sections.^{12,13} The most serious immediate complication of dysmobility is falling, which can lead to further injuries, including orthopedic injuries.¹⁸⁰ It is important for physicians to evaluate pwMS for risk of falls by asking about recent falls or near-falls, and their circumstances. Once the causes of dysmobility are clear, neurologists can work with patients to craft a management plan that is tailored to each individual.

Physical therapy (PT) is the overarching treatment for dysmobility, but has many different modalities.¹¹ One important goal is to lessen secondary dysmobility through altered gait mechanics that worsen wear and tear on joints and contribute to painful arthritis. Cranial nerve non-invasive neuromodulation, such as the PoNS device,¹⁵⁹ has shown promise in augmenting PT: in clinical trials, it doubled the effect of PT on gait improvements and helped patients cross a clinical threshold associated with decreased risk of falls. Currently, it is only approved in Canada and the United States. Other non-invasive therapies have received inconsistent support.

Assistive devices can lessen dysmobility, render it more safe, or enable greater levels of activity or participation.¹⁵ One assistive device which can be a double-edged sword is wheelchairs,²³ which increase safety in the short-run, but can worsen deconditioning in the long-run. Therefore, they should be encouraged selectively in partially ambulatory patients. The visibility of assistive devices can provoke a variety of psychological reactions, some more helpful than others. Visible devices notify bystanders that the user is susceptible to falling so that bystanders take care to avoid jostling or bumping the user. At the same time, their visibility can prompt feelings of shame, vanity, denial, or defeat in users; physicians can emphasize that assistive devices are instruments that empower their user.

Prolonged-release dalfampridine^{17,18,19,20} (Fampyra, Ampyra) has been approved in Europe and the US for treatment of walking ability in patients with multiple sclerosis, with patients showing significant improvement in Multiple Sclerosis Impact Scale-29 scores after 12 months on treatment.¹⁵⁴ Contraindications for use include acute kidney injury or chronic kidney disease as the medication is renally excreted and can lower the seizure threshold. Patients' fear of falling can be worsened by sensations of dizziness or reduced cognition, and therefore medications that cause these as side effects should be discontinued or tapered when possible.²¹

Spasticity

Spasticity is the velocity-dependent resistance to muscle stretch, with two forms: *phasic* spasticity is paroxysmal and starts with painful cramps and spasms; *tonic* spasticity is chronic stiffness.^{24,25} The kind of spasticity determines medication selection, because each kind responds differently to different classes. Pharmacologic therapy should also be carefully selected based on the side effect profile in addition to potential treatment of comorbidities. Effective management will allow the patient to improve functionality, prevent contractures, and decrease pain.

Spasticity and gait instability are closely related as patients with MS have been noted to have more lower extremity spasticity, specifically in comparison to patients with post-stroke spasticity (which is primarily in the upper extremities)¹³⁸. Ongoing tonic spasticity, in addition to pain, also slows movement and contributes to contractures. However, management of spasticity is a balancing act, as it also needs to avoid destabilizing weaker joints. Patients can be referred to physical rehabilitation, with targeted interventions such as stretching and pilates or yoga, which can improve patients stiffness and range of motion.

Phasic spasticity, due to its paroxysmal nature, can be difficult to distinguish from periodic limb movements. Trials of dopamine agonists are useful to distinguish dystonia from other forms of spasticity.^{26,27} Anticonvulsant drugs are efficacious, especially sodium-channel blockers such as carbamazepine, oxcarbazepine, lacosamide, and lamotrigine, as well as medications with other mechanisms of action, such as levetiracetam,¹⁶⁵ gabapentin, and pregabalin. Phasic spasticity can become cyclical due to ongoing pain acting as a trigger, so providers should work with the patient to remove other noxious stimuli (i.e. neuropathic pain).

Tonic spasticity is treated according to which muscles are affected, or according to the location of the CNS lesion. For patients with spasticity in proximal or large muscles, baclofen (for spinal cord spasticity), tizanidine (both cerebral and spinal spasticity), and dantrolene (primarily cerebral spasticity) are frequently used. All three are non-habit forming, although also require liver monitoring.³¹ In cross-comparison,, baclofen can assist with sleep or addiction,²⁸ dantrolene is less sedating, and tizanidine has less tendency to overshoot and weaken muscles. Oral cannabinoid extracts (OCEs) are effective at reducing patient-reported scores of spasticity, with studies showing it is likely ineffective at 12-15 weeks, but may show improvement after one year. OCEs have also been found to be effective in reducing painful spasms or central pain. Adverse effects include behavioral or mood changes, hallucinations, weakness, and fatigue.³² Tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (nabiximols) have also been approved in Denmark and in other countries as an add-on treatment for spasticity refractory to other treatments.¹³⁹ Benzodiazepines can provide additional relief, but generally should be reserved for refractory cases, due to their drawbacks, which include side effects like fatigue, cognitive blunting, and ataxia, as well as the challenges with discontinuation, which include their habit-forming nature and tendency to lower the seizure threshold when stopped abruptly. In patients with lower extremity spasticity, treatment with onabotulinumtoxin A injections using anatomical localization showed improvement in Disability Assessment scores (mobility subscale only). The most common botulinum toxin dosing for MS patients is 300U for equinovarus foot, followed by 150U for flexed knee, with minimal systemic side effects.¹³⁸ Refractory patients may also consider referral for implantation of a baclofen pump, which can provide steadier dosing and reduce systemic effects compared to orally dosed baclofen.

For patients with overlying musculoskeletal pain, muscle relaxants such as cyclobenzaprine, methocarbamol, carisoprodol, chlorzoxazone, and metaxalone are useful at low doses, either alone or in combination to address symptoms through multiple mechanisms.³⁴ Gabapentin can also be used in MS patients with simultaneous neuropathic pain and spasticity. Second-line agents for patients with spasticity include tiagabine (similar to baclofen) and clonidine (similar to tizanidine).³³

The goal of pharmacotherapy should be to facilitate daily function and reduce the risk of long-term complications, such as contractures. The

importance of stretching should be encouraged and reinforced frequently. Monotherapy dosage can be increased over time until efficacy reaches a ceiling or until side effects become intolerable, at which point additional medications with alternative mechanisms of action can be added and the original monotherapy titrated down. Multiplying mechanisms with different mechanisms of action and different half-lives can achieve a more satisfying balance between efficacy and side effects, but can also pose additional dangers related to polypharmacy.

Fatigue

'Fatigue' is a general and vague term that overlaps with similar terms like 'tiredness', 'brain fog', 'low arousal', and 'sleepiness'. Its general meaning reflects diminished spontaneous activity, reduced maximal effort, or waning performance with extended effort, and its meaning can be stipulated and operationalized in particular clinical contexts, such as with the Modified Fatigue Impact Scale (MFIS) in pwMS. Fatigue is associated with deconditioning, pain-limitations, sleep disturbances, depression, and many inflammatory diseases, including not only those of the central nervous system, such as MS and neuromyelitis optica,¹⁸¹ but also those of peripheral nervous system, such as chronic inflammatory demyelinating polyneuropathy,¹⁸² and even rheumatic diseases, such as rheumatoid arthritis.¹⁸³ Given the term's unclarity, and the different mechanisms underlying it, it is often difficult to tease apart MS fatigue's primary, secondary, and tertiary factors in particular cases. Nevertheless, some general differences provide guidance.

The paradigm of primary MS fatigue arises suddenly from a non-fatigued state ("crashing" fatigue), especially in response to high internal body temperature, which slows the conduction of demyelinated axons. For example, it is common for MS patients to feel energized upon awakening, but exhausted after a hot morning shower. By contrast, fatigue that is present upon awakening can be a mix, or hybrid, of primary and secondary factors. When lesions in the brainstem or spinal cord cause nocturia, restless legs, or painful spasms that interfere with sleep, these factors seem clearly secondary, whereas sleep disordered breathing due to lesions in the hypothalamus¹⁸⁴ and brainstem¹⁸⁵ seem primary, or at least straddle the line between primary and secondary, because of their intrinsic connection to sleep. Other causes of secondary fatigue which may be present on awakening have an insidious, progressive time course, such as deconditioning, muscle atrophy, and

obesity. Secondary fatigue from spasticity, pain, frequent toileting, and medications may fluctuate in severity as these factors wax and wane over longer durations. Tertiary MS fatigue from depression can be exacerbated or ameliorated in concordance with secondary factors, but may persist even when pwMS no longer acknowledge depressive feelings.³⁶ Accordingly, complaints of fatigue in pwMS should prompt a thorough review of physiological systems, including screening for comorbid conditions, especially depression and sleep disturbances. Interrogating the time course of positive symptoms helps distinguish their contributions to overall fatigue.

The simplest approach to managing fatigue is to start by optimizing sleep. The clinical goal of sleep is *restorative*; pwMS should awaken feeling *refreshed* and *invigorated*. The duration of sleep can be affected by trouble falling asleep or trouble staying asleep. Sleep hygiene can affect both factors and should be reviewed repeatedly over time. Cognitive behavioral therapy for insomnia (CBT-I) is first-line treatment, effective across multiple co-morbid medical conditions with improvements in sleep quality and efficacy with reduction in insomnia severity. However, ability to participate may be limited if patients have significant cognitive impairment. Various smartphone apps for patient self-management of fatigue using CBT-I are currently undergoing field trials and pilot studies. After sleep hygiene has been satisfactorily addressed, inquiry should be made into pain, stiffness, and nocturia; fortunately, many medications for these conditions promote somnolence and can aid in sleep initiation and even maintenance, though they can also overshoot and contribute to morning grogginess. Gabapentin lessens neuropathic pain and is one of the few medications that improves sleep quality by increasing sleep efficiency and reducing spontaneous arousal.¹⁸⁶ When sleep initiation and maintenance are satisfactory, then pwMS should have sufficient sleep duration for restorative sleep. Therefore, when fatigue upon awakening is out of proportion to sleep *quantity*, then long-acting medications should be reviewed and adjusted as necessary, and referral for polysomnogram should be considered to look for other causes of interrupted sleep that affect sleep *quality*.

Once restorative sleep has been achieved, subsequent interventions aim to extend this energy throughout daytime activities. When this is impossible, scheduled napping can be encouraged, with the caveat that longer naps can interfere with sleep at night. Extending energy throughout the day

involves a combination of energy conservation strategies to treat primary and tertiary MS fatigue, as well as strategies to treat secondary MS fatigue by augmenting reserve energy. Heat avoidance and aquatic therapy, which typically lowers internal body temperature, can preserve energy and improve primary MS fatigue. Programs in energy conservation and fatigue-self management (pacing strategies) improve quality of life, a reflection of tertiary fatigue. Diet and exercise are crucial to maintaining strength and cardiovascular fitness; in the short run, these lifestyle modifications can exacerbate fatigue, but in the long run, they improve endurance and maintain ideal body habitus. Some dietary changes have been associated with improved fatigue, but most results are preliminary.¹⁸⁷ Improving diet, exercise, and sleep hygiene all involve lifestyle modifications, which can take years to reach a satisfying equilibrium, even under conditions of MS quiescence. Consequently, the causes of fatigue are a moving target that requires a multidisciplinary approach with physical therapists, nutritionists, sleep neurologists, psychiatrists, and other specialists.

Patients whose MS fatigue is refractory to strategies for primary MS fatigue and the treatment of secondary and tertiary causes, can be treated with stimulants, which must be managed carefully, since they can interfere with sleep and thus worsen fatigue. Patients should be counseled to avoid taking stimulants close to bedtime and may need to reinforce sleep hygiene when using them. Stimulants should be considered for pwMS whose fatigue impairs their ability to drive an automobile safely or to maintain employment.

Caffeine can improve attention and concentration in patients with MS who can ambulate without a walking aid.¹⁸⁷ Other non-prescription stimulants such as B-vitamins and amino acids can also be considered.

For pwMS with ambulation problems, prolonged-release fampridine (Europe) and dalfampridine (USA) may improve fatigue. Presumably, the primary mechanism is by increasing gait endurance, but it also may speed up cognitive processing,¹⁸⁹ an effect similar to reducing cognitive fatigue.

Amantadine, modafinil, and methylphenidate (and other amphetamine-similars) may improve fatigue, but studies have found mixed effects in pwMS.¹⁹⁰ Such findings may be partly explained by an isolated effect on excessive daytime sleepiness, which shares some features with fatigue, and by

tachyphylaxis.¹⁹¹ Escalating the dose can overcome tachyphylaxis in the short run, but exposes patients to more long-term side effects, such as dehydration, mild anorexia, and insomnia, which worsen fatigue. Medication holidays offset tachyphylaxis, but can diminish these medications' appeal as a panacea for chronic fatigue. Because of these limitations, it is always important to introduce these medications alongside lifestyle modifications, and ideally only after sleep is optimized.

The American Academy of Sleep Medicine clinical practice guidelines (aasm.org) strongly recommend modafinil, pitolisant, sodium oxybate, and solriamfetol in treating patients with narcolepsy. Modafinil was conditionally recommended specifically for patients with multiple sclerosis and hypersomnia, but data quality was considered poor. Post-hoc analysis of randomized placebo controlled trials of pitolisant showed NNT of 3-5 for excessive daytime sleepiness. In narcolepsy patients, solriamfetol lessens excessive sleepiness. Both pitolisant and solriamfetol are therapeutic options for MS patients with these conditions.

Visual Impairment

Visual impairment for MS patients can impact various aspects of quality of life and can be the most troubling symptom after dysmobility, as it can contribute to falls and injuries as well. Due to adverse effects such as difficulties with driving, or even inability to use devices such as computers and smartphones,¹⁵² visual impairment contributes to social isolation and unemployment, and therefore should have regular monitoring.

The most common forms of impairment for MS patients include optic neuritis, which can lead to scotomas or reduced visual acuity, ocular motility disorders such as internuclear ophthalmoplegia (INO), isolated cranial nerve palsies of III, IV, or V, or saccadic dysfunction such as nystagmus. Even when present, some types of visual impairment such as visual field deficits, may go unreported by patients as they may not be immediately obvious to patients (or attributed to another cause), and therefore need to be asked about specifically.¹⁵² Ocular motility disorders are more likely to cause persistent visual symptoms such as diplopia or reduced depth perception compared to near-complete resolution following optic neuritis.

Medication lists should be extensively reviewed when patients are reporting visual symptoms, as some disease-modifying drugs used for primary MS treatment are known to cause adverse effects, the most well-known being S1P modulators like

fingolimod, siponimod, ozanimod, and ponesimod (natalizumab's label also includes a warning about the risk of retinal necrosis) . S1P modulators can cause macular edema, which is painless, and therefore patients should be evaluated periodically, especially within the first 6 months after initiating treatment. For patients on several DMTs, especially natalizumab, the most concerning potential adverse effect is progressive multifocal leukoencephalopathy (PML), which can present as hemianopic visual field loss, and therefore should prompt further investigation and neuroimaging.¹⁵² Other medications such as anticholinergics (for urinary incontinence) can cause blurry vision or dry eyes. Findings of nystagmus should prompt reassessment of use of anticonvulsants for pain, such as gabapentin, carbamazepine, phenytoin, or lamotrigine.⁴¹

Patients reporting visual symptoms should be referred to ophthalmology for detailed assessment in addition to management. Part of ophthalmological assessment would include assessment of ocular motility, visual acuity and color vision, as well as perimetry testing to measure the visual field. Following optic neuritis, patients should have evaluation for visual acuity, color vision (Ishihara's test), and contrast sensitivity, as these modalities can influence face recognition, reading and activities of daily living. Optical coherence tomography (OCTs) or visual evoked potentials (VEPs) can also be useful tests for diagnosis and follow up of patients with optic neuritis. In cases of diplopia, prosthetics such as eye patches or prism glasses can be useful for minor cranial nerve paresis or nystagmus. More severe palsies can be treated with Botox injections or strabismus surgery.

Tremor

Tremor in patients with MS does not usually occur at rest, but instead is usually kinetic or postural due to lesions in the cerebellum or connecting circuits. Prevalence in MS can be high, between 25-60%,^{42,43} with patients reporting it as one of the most bothersome symptoms. Generally, tremor in areas of frequent movement such as the dominant hands or head are a higher priority for treatment, although more severe or high amplitude tremors in other areas can be equally prioritized due to impact on quality of life. Prior to starting pharmacotherapy, patients should also become aware of exacerbating factors such as stress and anxiety, allowing them to use coping mechanisms in response.³¹ Referrals to cognitive behavioral therapy may be useful in scenarios in which a tremor has a strong emotional component. Medications like propranolol can improve the underlying

exacerbating factors, even when they do not directly address the underlying mechanism.³¹

Currently, only case series provide options for treating tremor in MS patients, with little high quality evidence available. These papers have examined the use of carbamazepine⁴⁵, topiramate⁴⁶, primidone⁴⁷, dalfampridine, isoniazid, ondansetron, trihexyphenidyl, buspirone, acetazolamide, gabapentin, and hydroxyzine.⁴⁸ If these medications are being used in patients to treat other MS symptoms (for example, neuropathic pain), a strategy for use can be to increase the dosing to see if they are effective on tremor as well. Cannabis has shown mild to no improvement in MS tremor, despite benefits for spasticity.¹⁹²⁻⁴ Open label studies for levetiracetam showing improvements on daily living questionnaires are promising, although crossover trials are currently showing inconsistent results.¹⁵⁹ Patients with rubral tremor in the general population have been shown to respond to levodopa,⁴⁹ but patients with MS typically have been noted to have poor response to anti-parkinsonian medications.¹⁵⁹

DBS and thalamotomy are effective in reducing limb tremor in MS patients,⁵¹ with responder rate to DBS of approximately 60-70%.¹⁵⁹ Stimulation targets for DBS include ventral intermediate nucleus of the thalamus [VIM] (the majority of studies), ventral oralis nucleus of the thalamus [VO], ventral caudal nucleus of the thalamus [VC], zona incerta [ZI], with studies showing improvement in the Hedges standardized mean tremor score by 2.15, although number of patients in these studies were usually small with no randomized allocation or unmasked evaluation of outcomes.¹⁶⁰ When considering DBS as an option for patients, providers should consider the 1.7% risk of post-op hemiparesis or decreased consciousness, as well as a 5% risk of hardware disruptions.⁵³ Botulinum toxin is also a potential treatment for tremor in MS patients, with one study showing improvement in tremor severity of the upper limb at 6 and 12 weeks, although a significant minority of patients reported weakness in the affected muscles.⁵⁰

Cognitive Impairment

Cognitive impairment occurs frequently in patients with MS,^{55,56,57} even at disease-onset and in otherwise asymptomatic patients,¹⁹⁵ for whom it indicates a poor prognosis.¹⁶² Slowed information processing speed is the hallmark cognitive deficit in MS, with additional deficits in memory,⁵⁴ complex attention, executive functioning, and verbal fluency.¹⁶¹ Impairment will eventually affect the

majority of untreated MS patients as the disease worsens over time.

Regular cognitive screening of patients allows providers to detect early disease activity, assess for treatment effects, evaluate progression, and screen for new-onset cognitive issues later in the disease course. Early baseline screening is possible with the Symbol Digit Modalities Test (SDMT) or similarly validated testing, with annual reassessment with the same test. Adults require more comprehensive neuropsychological assessment if they test positive during cognitive screening tests in the clinic or show significant decline. Patients are also recommended to get yearly screening for depression as mood changes may negatively impact cognition.¹⁶¹ Limiting factors for regular cognitive assessment include lack of time, trained personnel (such as neuropsychologists), or equipment.¹⁶²

Patients showing signs of cognitive decline may have some benefit from referral to cognitive rehabilitation⁵⁸, which has a low risk profile. Clinical trials for neuropsychological intervention for cognitive impairment have mostly shown inconclusive evidence due to methodological limitations, although other types of studies have shown positive effects on performance. Comparison of different strategies is difficult due to the heterogeneity of rehabilitation interventions.¹⁶² Overall MS treatment with DMTs is beneficial for cognitive deficits due to reduction of lesion burden in the brain.¹⁶⁴ Smaller studies are currently investigating non-invasive brain stimulation technologies such as transcranial Direct Current stimulation (tDCS) and trans-cranial magnetic stimulation (TMS) and their uses in management of MS symptoms. In regards to cognitive impairment, these techniques are meant to induce increased plasticity, which may act therapeutically when used in conjunction with cognitive rehabilitation.¹⁶³

Emotional Disorders

Emotional disorders are highly prevalent in patients with MS and require careful monitoring and treatment.⁴ Psychiatric disorders are commonly linked with decreased quality of life,^{62,63,64,65,66,67,68} functional status, or even non-adherence to medications.¹⁶⁴ Common conditions such as depression and anxiety are often considered to be precipitants of relapse in patients and worsening of symptoms. While neurobiological studies have found some associations between increased lesion load or cortical atrophy in certain areas of the brain and increased incidence of emotional disorders in MS patients, the likely cause is multifactorial. Secondary and tertiary factors

should always be considered in a patient reporting signs of an emotional disorder, such as the psychosocial context or side effects of medications, such as interferons.

Current guidelines recommend screening for depression and its outcomes in MS patients,¹¹ which can be extended to other emotional disorders as well. Identifying an emotional disorder may be challenging, especially if the patient does not independently bring it up during a clinical encounter. Screening tools may be useful, such as the General Health Questionnaire for emotional disturbances.⁶⁰ An additional challenge is that other MS symptoms also have significant overlap with emotional disorders (i.e. fatigue or cognitive dysfunction), and should be evaluated simultaneously when a psychiatric disorder is suspected. Given that many psychiatric disorders are comorbid or can have similar diagnostic criteria to each other, referral to psychiatry is useful for complex cases.

Pharmacotherapy should not be used as monotherapy for patients with MS.⁸⁰ In the daily clinical setting, encouraging a sense of self-efficacy can improve negative affect in MS patients due to feeling empowered to achieve control over their symptoms.⁸ Referrals to cognitive behavioral therapy and other forms of psychotherapy are encouraged,^{75,76,77} as it has been shown to be effective in patients with MS. In sessions, cognitive reframing has been shown to lower depression levels. However, thought processes such as escape avoidance and emotional respite are shown to worsen levels of depression and should be carefully avoided.¹⁶⁴ Local support groups are available as well for patients to seek out the experiences of other people experiencing the same disease.^{78,79}

Depression is the most prevalent psychiatric condition in patients with MS, approximately 2-5 times greater than the general population in their lifetime. Suicidal ideation is 2.3 to 1.4 times higher compared to the general population, with relative suicide risk higher in the first five years after diagnosis.^{69,70,71,72,73,74,75, 164} Guilt and self-esteem are less common depressive symptoms in MS patients, with irritability, memory/concentration, fatigue, and discouragement being more common.¹⁶⁴ Given symptom overlap between depression and multiple sclerosis, the Beck Depression Inventory is useful for screening and assessment.^{60,164} The preferred pharmacotherapy for depression in MS patients is similar to first-line treatments in the general population, with SSRIs and SNRIs as a starting point.^{84, 164} Clinicians should

select medications that are individually tailored to the patient and their MS symptoms, specifically in regards to their side-effect profile. A drug should not be selected if it is thought to exacerbate a patient's already existing symptoms. SSRIs can worsen sexual dysfunction and insomnia even if they are effective for depression.⁸⁴ Mirtazapine can be a helpful alternative for patients who have concomitant nausea, insomnia, sexual dysfunction, or anorexia.^{85,86,87} Bupropion can be used in patients with sexual dysfunction or fatigue and can be used in combination with SSRIs to mitigate the side effect of lowered libido.^{90,93} Varenicline, bupropion, venlafaxine, and nortriptyline can also be useful in patients with substance abuse or for smoking cessation.^{96,97,98,99,100,101}

Pseudobulbar affect (PBA) is considered to be an affect disorder, sharing a category of euphoria or apathy as a disorder that can affect patients with MS in particular.⁸² Pharmacotherapy for PBA has been extensively studied, with first-line treatment of dextromethorphan with quinidine, which is effective but may require 4-5 weeks for effect.⁸¹ Comparatively low doses of SSRIs or TCAs are effective as well. For refractory patients, lamotrigine, venlafaxine, mirtazapine, methylphenidate, or amantadine can be tried.⁸³

Pharmacotherapy in patients with MS and other emotional disorders is less well-studied, with the general approach to treat MS patients similarly to members of the general population. Anxiety disorders, bipolar disorder, psychotic disorders, or personality disorders are also linked to lower quality of life and should be evaluated if patients show concerning signs. Providers should be cautious about steroid therapy precipitating manic or depressive episodes in patients with MS and bipolar disorder, but should avoid steroid discontinuation when it is medically indicated, instead giving smaller doses or giving lithium prophylaxis.¹⁶⁴

Pain

Pain experienced by MS patients can be divided into multiple categories, such as continuous central neuropathic pain, intermittent central neuropathic pain, musculoskeletal pain, and mixed neuropathic and non-neuropathic pain.¹⁶⁷ Treatment should ideally be targeted towards the specific modality experienced by the patients. Indirect or secondary causes of pain such as spasticity, alteration of gait mechanics, or fatigue should be managed separately (and are addressed in other sections of the paper).

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Neuropathic Pain Questionnaire (NPQ), Douleur Neuropathique 4 Questions, and painDETECT are all options as diagnostic tools for screening for neuropathic pain.¹⁶⁸ Initial treatment options for neurogenic pain include gabapentin, pregabalin, tricyclics, carbamazepine, SNRIs, or lamotrigine.¹⁰² Some studies indicate that gabapentin may be effective for phasic spasticity in addition to neuropathic pain, and that levetiracetam has shown some efficacy in treating neuropathic pain.¹⁶⁵ Pain associated with optic neuritis can be resolved with a steroid course early in the disease, which is also effective in cases of optic neuritis in the setting of other demyelinating diseases besides MS.¹⁶⁵

Oral cannabinoids such as Dronabinol or Nabilone, in addition to Nabiximols (an oromucosal spray with THC and CBD) are effective in treating MS spasticity and pain in multiple studies.¹⁶⁷ Adverse effects of cannabis are mild-to moderate and usually involve the nervous system or gastrointestinal system, such as dizziness and fatigue/weariness, as well as dry mouth.¹⁶⁷

Trigeminal neuralgia is 20-400 times more frequent in the MS population, usually attributed to a plaque in the root-entry zone of the trigeminal nerve. Treatment initially begins with analgesia and membrane-stabilizing agents, usually sodium-channel blockers, which may attenuate ephaptic transmissions.¹⁶⁵ Topical lidocaine and hot compresses to slow nerve conduction are also helpful. In refractory cases, surgical treatments include vascular decompression, gamma knife, and rhizotomy. Similarly, ephaptic discharges caused by a plaque in the CN IX and X region can cause glossopharyngeal neuralgia (GN) and glossopharyngeal-vagal neuralgia (GVN), requiring topical anesthetic sprays in addition to anticonvulsant medications. Lhermitte's phenomenon, while a common sensory disturbance in MS, is rarely painful, but a handful of studies show improvement in symptoms with lidocaine injections or oral mexiletine.¹⁶⁵

There is moderate evidence for exercise as a complementary therapy to alleviate intensity of neuropathic pain in multiple sclerosis patients, with specific modalities of aerobic exercise, resistance training, and aquatic aerobic exercise showing improvements in pain scores compared to placebo.¹⁶⁹ Unfortunately, there is only very low-level evidence for other non-pharmacological interventions for chronic pain such as transcutaneous electrical nerve stimulation (TENS), Ai Chi,

transcranial direct stimulation (tDCS), tRNS, telephone-delivered self-management program, EEG biofeedback and reflexology in pain intensity, with current studies primarily involving small groups of patients and other methodological weaknesses.¹⁷⁰ For patients with moderate pain related to MS, Cognitive Behavioral Therapy (CBT) treatment in addition to standard care did not show any difference in pain severity, pain interference, or depressive symptom severity compared to patients who received MS-related educational materials as adjunctive therapy.¹⁶⁶

Bowel and Bladder Dysfunction

Despite occurring in the majority of patients with MS and causing significant frustration and morbidity, patients and care providers can be reluctant to discuss bladder or bowel symptoms. Up to 90% of patients experience incontinence or voiding dysfunction, although symptoms primarily occur 6-8 years after the initial diagnosis.¹⁷¹ The topic is important to discuss during regular visits as prompt treatment can reduce feelings of social isolation, improve sleep quality, and prevent UTIs, which account for 30-50% of hospitalizations in patients with MS.¹⁷¹ It is important to distinguish symptoms of storage failure, like urgency, frequency, and nocturia, from symptoms of voiding failure, like hesitancy, double-voiding, bladder-insensitivity, and poor force of stream. Most patients with MS have storage-phase symptoms, but some will eventually develop voiding phase symptoms as well.¹⁷¹ If symptoms remain persistent despite initial medical management, patients should be referred to urology for post-void residual measurement, urodynamic studies, and further symptom management.

Therapy for urinary dysfunction is preferably conservative and initially reversible due to the waxing and waning nature of symptoms.¹⁷¹ Pelvic floor therapy provided exercises to enable relaxation or to defer urges to urinate. Patients should be started on lifestyle modifications to allow them to avoid situations of increased urgency and frequency, such as scheduled voiding, avoiding excessive fluid intake and caffeine, and bathroom mapping. Clean intermittent catheterization can also be used in order to assist with scheduled voiding. When symptoms are more severe, patients can be encouraged to wear pads or diapers, and carry a change of clothes when out for longer periods of time.

For patients with primarily voiding dysfunctions, such as the majority of patients with progressive MS,

first line treatment includes alpha-1 antagonists like doxazosin, terazosin, and tamsulosin, which are specifically aimed towards improving detrusor-sphincter dyssynergia, which can also contribute to increased rate of UTIs.^{105,171} Side effects to be aware of in these patients are orthostasis, overflow urinary incontinence, and abnormal ejaculation.¹⁰³ These patients would also benefit from intermittent clean catheterization, and indwelling catheters should be avoided whenever possible.¹⁷¹ Medications can be combined if there is concern for adverse effects of monotherapy at higher doses.

In patients with primarily storage-phase symptoms, PVR should be checked prior to starting therapy. If elevated, patients should start with self-intermittent catheterization prior to medications, while patients with low PVR can go directly to pharmacologic options.¹⁷¹ First-line therapy is anticholinergic drugs such as oxybutinin, tolterodine, flavoxate, hyoscyamine, and propantheline, which target parasympathetic activity of the bladder and reduce detrusor hyperreflexia.¹⁰⁵ Patients with neurogenic bladder who still have the ability to void (with elevated PVR) are at increased risk for urinary retention, which can be a side effect of ongoing anticholinergic therapy.¹⁷¹ Other adverse effects of anticholinergics to specifically be aware of in MS patients are sedation and cognitive impairment, in addition to more common side effects such as dry eyes, blurry vision, or constipation. tadalafil (phosphodiesterase inhibitor), mirabegron (beta-3 agonist), can all be used to counteract detrusor hyperactivity, though side effect profiles of each should be carefully reviewed prior to and after initiation.^{103,104,105} Desmopressin, a vasopressin analogue, can be a useful adjunctive therapy to reduce nocturia (and corresponding night-time awakenings) and enuresis.

Refractory cases can be referred to urology for Botulinum toxin injection, which is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity.¹⁷¹ Another option for patients with advanced cases include bladder stimulators, including both sacral and tibial stimulators,^{107,109} which can improve both storage phase and voiding phase dysfunctions. However, not all stimulators are MRI-compatible, and so the implantation of such devices should be considered alongside other therapeutic goals. Urologists may also consider augmentation cytoplasty for motivated patients with refractory symptoms. Otherwise, patients should be considered for suprapubic catheters in cases refractory to even Botox injections, with adjunct treatment with anticholinergics.¹⁷¹

Bowel dysfunction in patients with MS is difficult to localize or categorize in the same manner as urinary dysfunction, and does not seem to correlate with duration of MS or degree of disability.¹¹⁰ Diarrhea and constipation in patients with MS can be attributed to autonomic dysfunctions, primarily deterioration of the pyramidal tract and secondary immobility, although they do not seem to contribute to fecal incontinence.¹⁷² Management of these symptoms is similar to other patients in the clinical setting without multiple sclerosis. In cases of constipation, patients can be encouraged to increase their intake of both soluble and insoluble fibers, as well as general fluid intake.¹¹¹ Additional medication therapy such as softeners and stimulants can be prescribed but should be used as needed. Patients with fecal incontinence or diarrhea can have reduction of symptoms with timed evacuations after eating and general bowel training, with bulking agents as useful medical therapy.¹¹¹

Sexual Dysfunction

Part of the definition of sexual dysfunction (SD), which can encompass multiple symptoms, is that it is a condition that causes anxiety or interpersonal dysfunction for six months.¹⁷³ However, it can still be considered a “hidden” symptom of MS, with estimates of prevalence ranging up to almost 80% of MS patients.^{112,113,114,115,116} Sexual dysfunction may be underreported as neurologists do not address it with even a general question in half of cases, and patients may not independently address the topic with their neurologists if not asked. Therefore, assessment of sexual dysfunction primarily involves a semi-structured clinical interview, with focus on identification followed by assessment of severity and impact on quality of life. Since sexual function is influenced by psychological, social, and cultural factors in addition to biological factors, a conceptual model can help to divide concerns into primary, secondary, and tertiary dysfunction.

Scales for evaluation of sexual dysfunction in patients with multiple sclerosis can provide an opportunity to discuss the topic as well as assessment of specific complaints, with the Female Sexual Function Index, initially developed in a non-neurological context, as the most widely used scale for assessment of sexual dysfunction for MS patients.^{173,174} Other useful assessments include Szasz Sexual Functioning Scale, International Index of Erectile Function, Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19) or MSISQ-15.¹⁷³ For complete evaluation of SD, patients should also be assessed on mood, urodynamic function, and overall quality of life.¹⁷³

Primary sexual dysfunction is caused directly by lesions and can primarily be localized to the spinal cord, although can also result from peri-insular injury, similarly to bowel and bladder complaints in patients with MS.^{117,118} In women, this can manifest as concerns about pain, numbness, or paresthesias during vaginal intercourse, lubrication, sexual satisfaction and orgasm. Patients can be referred to pelvic floor therapy exercises in conjunction with use of devices (i.e vibrators).^{119,120,121} Lubricant and topical estrogens can be used for vaginal dryness as well as clitoral sensitivity.⁴ For male patients, problems can include erectile dysfunction (ED) as the most commonly reported sexual problem, ejaculatory dysfunction, and orgasmic dysfunction. First-line treatments are phosphodiesterase inhibitors, but persistent ED can also be treated with intracavernous prostaglandin injections, which may be more effective for patients with lower motor neuron lesions. Patients with spinal cord injury and ejaculatory dysfunction have also shown effective management with penile vibratory stimulation and midodrine, with potential for use in patients with MS in the future.¹⁷⁴ Bupropion can also be used in both genders for medical management of low libido.⁴

Secondary sexual dysfunction occurs due to interference from physical symptoms of MS, as opposed to direct sequelae of lesions in the nervous system. Examples of these include pain, spasticity, bowel/bladder problems, or fatigue, and are reviewed earlier in the paper.¹¹⁹ Under circumstances of secondary sexual dysfunction, strategies can include planning of sexual activities in order to avoid fatigue, changing sexual position to reduce difficulty and pain, or performing bladder catheterization prior to activity to avoid incontinence.¹⁷⁴ Tertiary sexual dysfunction primarily addresses psychological or social factors of MS that affect patient’s sexual function and expression.¹¹⁹ Sexual and relationship therapy, behavioral approaches, or general counseling can help patients work through negative self-images, depression and anger, loss of confidence, or social isolation.^{122,174}

Swallowing and Speech Dysfunction

Patients with MS will often benefit from referral to speech language pathologists (SLP), who can provide individual therapy for both dysphagia and dysarthria. Dysarthria is reported by MS patients as one of the most bothersome symptoms and can significantly affect quality of life, especially when it affects ability to express their needs.⁶ It can be classified into three types: spastic, ataxia, and mixed, with mixed being the most common in MS

patients due to involvement of multiple systems including corticobulbar tracts and cerebellar pathways.⁴ If classified as primarily spastic, dysarthria may improve with general treatments for spasticity in MS patients, although ataxic or mixed is harder to treat.

Paroxysmal dysarthria and ataxia consists in multiple, brief episodes (seconds to minutes) of slurred speech and dizziness or lack of coordination. It usually result from lesions to cerebellar pathways in the thalamus and midbrain near the red nucleus, and is thought to be related to ephaptic transmission.¹⁹⁶ Consistent with this hypothesis, it is responsive to sodium channel blockers,¹⁹⁷ and other anti-epileptics such as levetiracetam¹⁹⁸.

Dysphagia is estimated to affect one-third to 43% of patients with MS, leading to complications such as aspiration pneumonia, dehydration, or malnutrition. Prior to referral in the clinic or the hospital setting, an MS-specific dysphagia tool for evaluation is the self-administered Dysphagia in Multiple Sclerosis Questionnaire (DYMUS), with the Mann Assessment of Swallowing Ability (MASA) as a clinical swallowing assessment that can be

performed at bedside.¹⁷⁵ If initial results are indicative of advanced dysarthria, instrumental testing such as Modified Barium Swallow performed by SLP can provide objective data. In addition to individualized therapy, SLP can provide recommendations for dietary changes (primarily texture restrictions), though this can meet barriers including patient resistance, insufficient knowledge, and lack of time for caregivers. Specific gaps in caregiver knowledge can be addressed by speech language therapy.¹⁷⁶

Conclusion

Multiple treatment options exist for symptom management in patients with MS. In clinical encounters, MS providers should address “invisible” or neglected symptoms, identify self-reinforcing symptom clusters, and tease apart underlying primary, secondary, and tertiary factors. Once comfortable with treatment options, neurologists can break these vicious cycles. Ongoing symptom management and its evolution over time can be challenging. However by addressing them, patients with MS can have hope and increased functionality in their daily lives.

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