Symptomatic therapy in multiple sclerosis

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***Abstract*:** Multiple sclerosis is the most common disabling neurological disease of young adults. The ability to impact the quality of life of patients with multiple sclerosis should not only incorporate therapies that are disease modifying, but should also include a course of action for the global multidisciplinary management focused on quality of life and functional capabilities.

***Keywords*:** fatigue, neurogenic bowel and bladder, multiple sclerosis, spasticity, symptomatic therapy, visual symptoms

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Introduction

Multiple sclerosis (MS) is the most common disabling neurological disease of young adults [Sadovnick and Ebers, 1993]. The ability to impact the quality of life of patients with MS should not only incorporate therapies that are disease modifying, but should also include a course of action for the global multidisciplinary management focused on quality of life and functional capabilities.

Visual symptoms

Acute optic neuritis represents one of the signature clinical syndromes of MS, affecting about two-thirds of patients at some point during the clinical history [Balcer, 2006; Frohman *et al.* 2005]. Patients generally describe the onset of symptoms as evolving acutely to subacutely. They describe diminished vision, which can range from mild changes to complete blindness. As demonstrated in the Optic Neuritis Treatment Trial, over 90% of patients with optic neuritis describe pain in the affected side(s), which can manifest in a variety of ways [Optic Neuritis Study Group 2007; Beck *et al.* 2003, 1992; Keltner *et al.* 1993]. A number of visual illusions can be associated with acute optic neuritis and its aftermath, including micro- and macrosomia, scintillations, phosphenes, and light sensitivity changes. Once the diagnosis of acute optic neuritis has been confirmed, treatment can be initiated, typically with high-dose corticosteroids [Frohman *et al.* 2007; Balcer, 2006; Beck *et al.* 1992]. It is helpful to recognize that myopia, emerging presbyopia, astigmatisms and anisometropia (different corrections across the two eyes) can be corrected, at least partially, if identified. Such corrections not only help to optimize function but also can reduce eye strain induced headaches (asthenopia). For patients with light sensitivity and sluggishly reacting pupils, the use of high-quality sunglasses can be very helpful.

Eye movement abnormalities

Eye movement abnormalities produce some of the most frequent and disabling symptoms in MS [Frohman *et al.* 2005]. The most common abnormality of ocular motility is internuclear ophthalmoparesis, which is characterized by slowing of the adducting eye during horizontal saccades. Patients with internuclear ophthalmoparesis have a reduced synchronization of binocular movements, producing a position discrepancy between the eyes, which can result in double vision and the illusion of environmental movement (i.e. oscillopsia). The transient loss of coordinated eye movements also compromises accurate foveation (visual processing of information) and depth perception. Other ocular motor syndromes associated with MS include cranial nerve palsies (VI > III > IV), skew deviation (supranuclear vertical misalignment of the eyes secondary to otolithic dysfunction), all forms of nystagmus (e.g. gaze evoked, primary position, pendular) and saccadic intrusions (e.g. square wave jerks, saccadic oscillations, flutter, and even opsoclonus in rare cases) [Frohman *et al.* 2005]. All of these abnormalities result in displacing objects of visual interest off the fovea

centralis of the macula, thereby producing 'retinal slip' and a corresponding degradation in visual acuity. In selected cases, the application of prisms may help reduce diplopia in the primary position.

Perhaps the most disabling eye movement abnormality in patients with MS is acquired pendular nystagmus [Frohman *et al*. 2005]. This disturbance is characterized by a constant to and fro movement of the eyes in a number of possible planes (horizontal, vertical, or elliptical).When ocular motor syndromes first appear in those with relapsing MS, the primary treatment strategy is to intervene with high-dose corticosteroids [Frohman *et al*. 2007]. The most effective therapy for pendular nystagmus has been the use of memantine (10–20 mg three times daily as tolerated) or gabapentin (100–2000 mg three times daily as tolerated) [Strupp and Brandt, 2006; Starck *et al*. 1997]. We have also used these agents in combination with improved response rates when compared with using monotherapy.

Vestibular dysfunction

The most likely cause of vertigo in such patients is in fact the most common cause of vertigo in any clinic, benign paroxysmal positional vertigo [Frohman *et al*. 2000]. This disorder results in a highly characteristic nystagmus that can be easily identified at the bedside with a number of provocative techniques (e.g. the Dix-Hallpike maneuver) and treated effectively by attempting to reposition the otoconial mass onto the macular membrane (e.g. with the Epley maneuver) [Frohman *et al*. 2003]. The second most common cause of vertigo in MS is related to the development of demyelinating plaques, most commonly identified in one of two anatomic localizations; the medullary tegmentum (in the vicinity of the vestibular apparatus) and the root entry zone of cranial nerve VIII at the pontomedullary junction [Frohman *et al*. 2003, 2000]. In such cases, the rapid application of high-dose corticosteroids is highly appropriate treatment.

Fatigue

Fatigue has been identified as one of the most common symptoms for patients with MS. Many aspects of fatigue suggest that it may be related to the underlying demyelinating pathology. Demyelination causes slowing and desynchronization of nerve transmission or may even result in complete conduction block. Heat commonly worsens fatigue and is related to the instability of signal conduction in demyelinated nerves. Increased body temperature can induce conduction block in vulnerable axons, resulting in deterioration of neurological functioning, commonly known as Uhthoff's phenomenon. Depression may also increase fatigue and has a high prevalence in patients with MS, occurring in approximately 50% [Lapierre and Hum, 2007]. Many patients with MS and fatigue also complain of sleep difficulties. This may be secondary to intractable pain and/or spasticity, and nocturnal bladder dysfunction. Of course, some patients have concomitant sleep disorders such as apnea or restless leg syndrome (RLS). Other general medical conditions may also play a role in exacerbating fatigue. Infections, most commonly urinary tract or upper respiratory infections, can often worsen fatigue. Metabolic causes including thyroid disease, liver dysfunction and anemia (iron, drug related, vitamin B12 or folate deficiencies) should also be excluded when evaluating a patient with fatigue.

It is important to review the patient's medication profile for potential offending agents because many medications are known to be associated with increasing fatigue. Medications that frequently cause fatigue-related side effects include antispasticity agents (i.e. baclofen or tizanidine), narcotic analgesics, sedative–hypnotic or anticonvulsant agents. Patients can often report increased fatigue as a result of interferon therapy. This may be minimized by pretreating with nonsteroidal anti-inflammatory drugs prior to and often following interferon injection. We have observed the greatest success using a buffered, long-acting formulation of naproxyn. For headaches after interferon injections, we have found the most success using triptans at the time of the interferon injection.

Patients with MS often avoid physical activity because their symptoms may worsen with elevated body temperature or prolonged exertion. Therefore, many patients show a very low level of physical activity, which may subsequently worsen their weakness, fatigue and other health issues. Limited mobility can play a role in worsening spasticity, constipation, and may also contribute to bone loss. Nonpharmacological therapies include the use of local cooling devices, energy management strategies and focused rehabilitation. For alteration in gait mechanics related to pyramidal dysfunction, many patients benefit from the use of ankle foot orthotic (AFO) braces

in order to augment dorsiflexion during the swing phase of walking. More recently, the use of functional electrical stimulators have been used in a similar way and have the advantage of peroneal nerve stimulation induced foot dorsiflexion without the application of a cumbersome and restrictive orthotic. These assist devices improve gait mechanics, reduce pelvic obliquity and genu recurvatum (and thereby reduce knee pain), promote energy conservation, and improve the safety of walking. Several studies have shown a clear benefit for patients with MS in improving fitness levels and quality of life measures [Newman *et al.* 2007; Rampello *et al.* 2007; Rasova *et al.* 2006, 2005; Schulz *et al.* 2004]. Several medications have been found to be beneficial for reducing the severity of fatigue (Table 1).

Multiple sclerosis and pain

There are several different pain conditions associated with MS. One category of pain is central neuropathic pain, defined as pain in a neurologic distribution with altered sensation and no history or clinical evidence of peripheral neuropathy [O'Connor *et al.* 2008]. The most common central neuropathic pain conditions are extremity pain, trigeminal neuralgia and Lhermitte's phenomenon. Demyelination resulting in central hyperexcitability and disruption of the spinothalamic pathways may be a source of central extremity pain. While many MS-related syndromes result in a compromise or loss of neurologic function, pain syndromes are thought to signify a 'gain' of function secondary to exuberant ephaptic electrical discharges in central tract systems.

Gabapentin, pregabalin, lamotrigine and tricyclic antidepressants have each been recommended for the treatment of central pain based on efficacy in randomized control trials [O'Connor *et al.* 2008]. Carbamazepine (in its various formulations) is generally considered the first-line agent for the treatment of trigeminal neuralgia. Surgical neurovascular decompression can also play a role because it may be effective for decreasing pain for patients refractory to pharmacologic treatments. There have been several studies exploring the role of oral synthetic delta-9-tetrahydrocannabinol (dronabinol) in reducing MS-related pain and spasticity. It was suggested to reduce spasticity-related pain [Lienau *et al.* 2007].

Heat intolerance

It is estimated that 60–80% of the MS population experience transient increases in the

Table 1. Medications used to treat multiple sclerosis-related fatigue.

Medication	Effects in improving fatigue	Mechanism of action	Side effects
Amantadine	Widely used and moderately effective	Effect on fatigue is unclear, but known to have monoaminergic, cholinergic and glutaminergic effects	Neuromalignant syndrome Nausea Dizziness Sleep disturbance
Modafinil	Evaluated in several studies with varying results [Lapierre and Hum, 2007]. Although it is commonly used in clinical settings with good results	α-1 adrenergic properties It is widely used as a wake-promoting agent for the treatment of narcolepsy	Headache Nausea Dizziness Elevated blood pressures Tachycardia Sleep disturbance
Acetyl L-carnitine	Recently evaluated in a small study by Tomassini and colleagues who found it to be better tolerated and more effective than amantadine [Tomassini *et al.* 2004]	Carnitine is a cellular component involved in energy metabolism	Abdominal discomfort
Dalfampridine	Has been shown to be effective in reducing fatigue and may also improve weakness and heat sensitivity.	Potassium channel blocker intended to improve conduction in demyelinated pathways	May increase serum potassium level ECG changes were observed in clinical trials but were not felt to be significant Seizures

frequency or severity of clinical signs and symptoms as a result of elevated body temperature. Both physical (walking, running, driving, writing, reading, etc.) and/or cognitive (memory retrieval, processing speed, multitasking, etc.) functions can be impaired by heat exposure, greatly impacting overall patient safety as well as the ability of patients with MS to perform routine activities of daily living. The temporary worsening of neurological signs and symptoms of the disease in response to heat exposure can compromise activities of daily living and other functional capabilities of patients with MS, even those who are mildly affected. A small number of studies have reported potential benefits using cooling strategies that are convenient methods available to most patients with MS, such as cold showers, applying ice packs, the use of regional cooling devices, and drinking cold beverages. Drugs such as the potassium channel blocker, 4-aminopyridine, have been prescribed by physicians to treat heat sensitivity in patients with MS [Davis *et al*. 2010; Syndulko *et al*. 1996].

Spasticity

Spasticity is functionally significant because it can cause ambulation difficulty, decreased ability to complete activities of daily living, worsen fatigue, and increase the burden of care. In addition, it can negatively affect cardiovascular, sexual, endocrine, and pulmonary functions. For mild cases of spasticity, patients should be encouraged to stretch as frequently as possible. Patients with more severe spasticity can benefit from formal physiotherapy: strengthening exercises are targeted to restore strength to affected muscles so that the affected limb can be used effectively when increased tone has been reduced through other treatments. There are several oral medications available to treat spasticity (Table 2). Oral baclofen is reported to be the most commonly prescribed drug in patients with MS and spasticity [Rizzo *et al*. 2004]. Chemodenervation in the form of botulinum toxin and phenol injections are other modalities of therapy for spasticity. Patients exhibiting profound spasticity that are not sufficiently managed with oral, chemodenervation, or combinations of therapy may benefit from an intrathecal baclofen pump.

Gait mechanics and interventions

Patients with MS very often develop changes in the mechanics of ambulation that are most typically secondary to pyramidal distribution weakness, spasticity (tonic and phasic), diminished proprioception, and changes in motor integration. Those with weakness in the legs most commonly exhibit reduced hip flexion (due to iliopsoas paresis) with abnormal swing phase 'ignition', decreased dorsiflexion (due to tibialis anterior weakness), heel cord tightness and shortening (due to excessive gastroc-soleus complex action eclipsing the tibialis anterior; agonist–antagonist mismatch). This latter change increases the resistance that the tibialis anterior must work against during the swing phase of walking (and thereby increasing energy expenditure; and contributing to fatigue and reduced walking endurance). These changes make walking more energy consuming and typically slow gait speed and reduce the duration and distance of ambulation. A new drug that has been recently approved by the FDA in the USA to improve walking in patients with MS is dalfampridine (formerly called fampridine-SR and 4-aminopyridine). It is marketed under the name of Ampyra and is a potassium channel blocker that enhances conduction in damaged nerves [Goodman *et al*. 2010]. Pathophysiologic adaptation ensues that results in the cardinal features of upper motor neuron syndromes in general and include toe drag, circumduction and associated pelvic obliquity (leading to hip and pelvic pain), and excessive knee extension during the weight acceptance and single limb support phases of walking (so-called genu recurvatum). The latter can ultimately lead to erosive changes in the knee joint and concomitant pain, which can then compromise gait safety [Sabapathy *et al*. 2011; Gutierrez *et al*. 2005; Haselkorn *et al*. 2005; Rizzo *et al*. 2004; Barnes *et al*. 2003; Olggiati *et al*. 1988].

Falling, and associated bone fractures, is a common concern for patients with MS. The multidisciplinary approach to gait disturbances in MS involves the neurologist who characterizes the dysfunction, the physical therapist who formulates a plan to normalize mechanics (via stretching, conditioning, balance, trunk and postural training), and the orthotist who serves to custom mold AFO devices to improve dorsiflexion assist. In those with reasonably preserved dorsiflexion at rest, a hinged or articulated AFO device can be of great benefit with the advantage of allowing some dorsiflexion range of motion but without any plantar flexion capability (the foot 'stays' up during the swing phase of walking). In those with little to no residual dorsiflexion movement at rest, a single piece molded AFO device is preferred because such patients require

Table 2. Spasmolytic medications.

Medication	Recommended daily dosage	Half life	Metabolism	Site of action	Lab monitoring	Side effects	Notes
Baclofen	10–80 mg (in three to four divided doses)	2–6 h	Kidney, liver	CNS, GABA-B inhibition	LFT every 6 months	Somnolence, fatigue, constipation, nausea, vomiting	Only generic form is available
Cannabis	5–20 mg (in two to four divided doses)	19–36 h	Liver, renal	Unknown		Nausea, vomiting, somnolence, increased appetite	
Clonazepam	0.125–3 mg (max 3 mg/day) often dosed at night only	12 h	Liver	Benzodiazepine	LFT every 6 months	Drowsiness, sedation, ataxia	Preferred in phasic spasms, myoclonic movements or in RLS
Clonidine	0.1–0.4 mg oral/transdermal patch	5–19 h	Liver, kidney	Central alpha-2 agonist		Bradycardia, depression, syncope, fatigue, hypotension	
Cryproheptadine	4–16 mg (in one to two divided doses)		Renal	Serotonergic antagonist		Increased appetite, weight gain	Also helpful for patients with myoclonic movements or RLS
Dantrolene	25–100 mg (in four divided doses)	4–15 h (after oral dose)	Liver	PNS – inhibits Ca release at sarcoplasmic reticulum	LFT every 3–6 months	Most hepatotoxic, postural instability, slurred speech, diarrhea	No blood–brain barrier passage
Diazepam	2–40 mg (in two to four divided doses)	20–80 h	Liver	CNS, facilitates GABA-A agonist	Patient should not consume alcohol when using diazepam	Sedating, memory impairment	Used to treat oral and intrathecal baclofen withdrawal symptoms
Dalfampridine	10 mg BID			Potassium channel blocker; may increase central motor conduction	LFT every 6 months	Can cause seizures, nausea, tingling, distal artery vasospasm, hepatotoxicity	Seizures can occur with recommended dose or if stopped abruptly
Gabapentin	300–3600 mg (in three to four divided doses)	5–7 h	Excreted unchanged in urine	GABA analogue		Somnolence, dizziness, ataxia, fatigue	Safe for those with hepatic dysfunction
Levetiracetam	25–3000 mg (one to three divided doses)	7 h	Renal	Unknown; believed to work through GABA and glycine channels		Loss of appetite, mood disorder, fatigue, headache	
Piracetam	12–24 g (in one to three divided doses)	5–6 h	Excreted unchanged in urine	GABA derivative; nootropic agent	LFT every 6 months	Nausea, flatulence	
Tizanadine (capsule and tablet form)	2–36 mg (in one to three divided doses) – slow titration recommended	2.5 h	Liver	Central alpha-2 agonist, glycine facilitator	LFT every 6 months	Orthostatic hypotension, drowsiness, dry mouth, dizziness, patients with MS prone to muscle weakness	Recommend initiating at night

CNS, central nervous system; GABA, gamma aminobutyric acid; LFT, liver function testing; MS, multiple sclerosis; RLS, restless leg syndrome; PNS, peripheral nervous system.

greater support of the ankle–foot complex. AFO devices, when tolerated by the patient, can reduce toe drag, circumduction, pelvic obliquity, energy efficiency, and facilitate safety and greater speed and duration of walking. A major advance has been the development of functional electrical stimulation devices that stimulate the peroneal nerve at the fibular head in conjunction with a programmable capability to transmit such signals to the tibialis anterior only upon the swing phase of walking. Two such devices, the BioNess and WalkAide types, have been rapidly evolving as the preferred intervention for the most common walking derangements associated with MS. Patients have found these devices to be highly effective, more natural in effect with respect to molded and more restrictive AFO devices, and a remarkable achievement in terms of cosmetic factors.

Physicians who manage MS must be familiar with the use of other assist devices for patients with changes in gait mechanics. Single and multiple prong canes can be very helpful and improve safety, however patients benefit when learning to correctly utilize these under the supervision of a physical therapist. In patients who require bilateral support, we emphasize lightweight walkers with three or four wheels that come with sit down planks and storage baskets.

Hand dysfunction

It is not uncommon for patients with MS to present with hand weakness, tremor, spasticity, or dystonia. Collaboration with an occupational therapist may be indicated in selected patients. We commonly recommend exercises for the hand extensors, given the mismatch of extensor–flexor weakness in upper motor neuron disorders. It is crucial to recognize the mismatch between the strength of the finger flexors and extensors and apply extensor bracing early in the course of the disease in order to avoid flexion contractures. Further, it is vital to think about the possibility of a concomitant nerve compression syndrome (median or ulnar) that might be a contributing factor to worsening hand and finger weakness.

Tremor has been enormously difficult to treat in patients with MS, particularly the highly disabling rubral outflow tremor. While we often try anticonvulsant agents and benzodiazepine agents, in general they only provide modest benefits in most patients. More recently we have observed more substantial benefit with the new slow inactivation sodium channel modulator lacosamide. While we have referred some patients for deep brain stimulation for severe and medication recalcitrant tremor, we have not found this procedure to be persistently mitigating over time.

Focal dystonias have been associated with MS (both hand and feet). Unlike tremor and weakness, this movement disorder is treated quite effectively in most cases with the application of membrane stabilizing anticonvulsants.

Seating and bed management

In patients who are unable to ambulate for more than a modest distance, even with these aids, a systematic evaluation for a wheelchair or scooter should be conducted. Seating should be individualized for every patient to ensure comfort, safety, attention to skin integrity, and whether manual or a power-operated mechanism is most appropriate.

In patients with significant leg weakness and spasticity, the care team must address the ability of the patient to drive safely using foot pedals. Modifications can be made to better utilize the leg, or hand controls and can be considered. We have numerous patients that drive expertly using hand controls, whereas we have others that have been trained to use their ‘other’ leg to control the accelerator and brake pedals of their vehicle. For patients who spend most of their time in a wheelchair, modification of their car, or a change to a disability van affixed with a chair lift and chair-locking capabilities, can facilitate mobility, continued independence and often gainful employment.

Loss of ambulation is often associated with reduced mobility in bed, which can compromise sleep hygiene, amplify pain and spasticity, and predispose our patients to skin conditions such as decubiti. As such, the discussion of bed types (manual *versus* electronic) and surfaces (with adequate pressure support to ensure skin integrity) can represent an important intervention with obvious ramifications. Collaboration between the patient and their family, the neurologist, case manager, and physiatrist can be very productive and alleviate significant suffering. In a similar way, we engage our case manager to conduct extensive home evaluations for our most disabled patients to assess their activities of daily

living (dressing, toileting, showering, cooking) and to ascertain whether particular assist devices or remodeling for accessibility will enhance independence, safety, and quality of life.

Skin integrity and rash in multiple sclerosis

Without doubt, loss of mobility in MS is linked with a markedly increased risk of skin breakdown, rash, decubitus, osteomyelitis, sepsis, pain, and overall demise. The principal factor that leads to these dermatological conditions is immobility with chronic compression of skin, particularly across bony surfaces (e.g. the sacrum). It is vital that providers ensure that patients who are chronically wheelchair bound are sitting on an appropriate cushion to offload and distribute buttock and leg pressure. Seating should be designed to accommodate the position of the back, buttock, and legs such that all contact surfaces are appropriately coupled to the patient's individual physical features. Patients with low back pain and appendicular edema often benefit from having a wheelchair (manual or electric) with pitch capability such that the legs can be elevated and pressure taken off the lower back from chronic upright positioning. Patients with compromised dexterity and in need of a power-operated chair or scooter should be carefully instructed on the safe operation of these mobility devices.

Speech, breathing, and swallowing dysfunction in multiple sclerosis

Albeit a less common manifestation of MS, it is important to recognize changes in speech and swallowing that can accompany the disease process. While life expectancy in MS is only slightly lower than in the general population, precocious mortality is most commonly related to infections (urinary tract and pneumonia). In patients with more advanced disability, there is a corresponding risk of reduced breathing capability, hypophonia, and weakness of the oropharyngeal apparatus. These changes increase the likelihood of dysphagia, aspiration, and ultimately infection and demise [Terre-Boliart *et al.* 2004]. We frequently collaborate with our colleagues in pulmonary medicine to consider respiratory interventions to improve speech, ease of breathing, and pulmonary toilet. Intermittent positive pressure breaths, bipap, incentive spirometry daily exercise, supplemental oxygen, and nebulization therapy may be indicated in some patients [Mutuay *et al.* 2007]. Dysphagia in MS is primarily associated with drinking thin liquids such as water, coffee, thin soup, and tea. Thickening of liquids and emphasis on a proper swallowing technique can mitigate the risk of aspiration. In some patients modified barium swallow under the supervision of a speech therapist can be practically useful in formulating effective and safe swallowing strategies. An alternative to the barium swallow studies is pharyngo–laryngeal videoscopy, which can be carried out without the use of X-rays and often provides better anatomic information. However, this technique is not useful in assessing the swallowing mechanism below the esophageal entrance. Unfortunately, some patients with advanced swallowing dysfunction are unable to adequately maintain their nutrition and hydration requirements, thereby mandating the placement of a feeding tube. Inadequate nutrition can lead to cachexia, elevated risk of decubiti, accelerated bone loss and fracture, and further fatigue, weakness, and immobility. We liberally utilize agents such as megestrol in order to augment anabolic mechanisms to maintain patients' weight. Alternately, in those who are obese, they are at risk of falls, provide greater challenges for overall care, including transfers, and catabolic agents such as topiramate or bariatric procedures can and should be considered as potentially helpful. Patients with MS who are obese and disabled are at risk of eventually being moved from home to an assistive care or nursing home facility. While care in a nursing facility can be excellent and fulfill the patient's medical, nutritional, and social needs, the loss of independence, dignity, and the family living environment can be devastating.

Neurogenic bladder

Common bladder disorders in patients with MS include neurogenic detrusor overactivity, and detrusor sphincter dyssynergia. Detrusor hyporeflexia, or failure to empty, has been associated with brainstem/pontine lesions, and detrusor sphincter dyssynergia has been associated with the presence of cervical cord lesions [Araki *et al.* 2003]. The initial evaluation of a patient with bladder symptoms includes a history, physical exam, urinalysis, and uroflowometry with a postvoid residual (PVR). Interestingly, objective measurements of postmicturition residual volume were found to correlate poorly with subjective assessments [Kragt *et al.* 2004], suggesting that all patients may benefit from urinary screening and evaluation. The PVR evaluation assesses the amount of urine in the bladder wall after

urination, and can be performed by catheterization, or preferably by diagnostic ultrasonography. Patients with high PVR urine volumes ($>100\,cm^3$) are at risk of recurrent infections, risk of calculi, and in some cases, hydronephrosis.

Prior to initiating pharmacologic management, patients with MS should be encouraged to perform timed voiding. Pelvic floor exercises (e.g. Kegel's) have also been reported as effective in men and women with lower urinary tract symptoms, particularly urge incontinence [Vahtera *et al*. 1997]. Patients with failure to store disorders (typically neurogenic detrusor overactivity) often complain of urgency, frequency and nocturia, and have small volume bladders with a spastic detrusor muscle pattern on urodynamic testing. Treatment for this includes use of antimuscarinics, anticholinergics, mixed agents (e.g. oxybutynin) and the tricyclic antidepressant, imipramine (this agent is especially useful to reduce incontinence episodes). Patients with nocturia or nocturnal enuresis should be advised to empty their bladder prior to going to bed as well as to decrease their fluid intake about 2–3 h before going to bed. This can be challenging with patients who have medication(s) that are dosed in the evening. Spicy foods, caffeinated products and acidic foods can also result in bladder irritation and subsequent urinary frequency. Similarly, alcoholic beverages frequently have a diuretic effect and should be avoided prior to bedtime. If behavioral strategies are not effective, nocturia can be effectively managed with oral desmopressin.

Failure to empty is commonly due to an outlet disorder (e.g. overactive sphincter) or due to a hyporeflexic or areflexic bladder. Patients may complain of frequency, slow initiation of stream (hesitation), slow stream, prolonged voiding time, and dribbling of urine. Failure to empty due to detrusor sphincter dyssynergia may be managed with the alpha-antagonist class of medications (prazosin, terazosin, doxazosin, tamsulosin). In some cases, clean intermittent catheterization may be needed in patients with severely impaired emptying.

An additional emerging option for treatment of overactive bladder that has been refractory to oral pharmacotherapy treatments is the use of botulinum toxin type A injected into the detrusor muscle. Several systematic reviews have concluded that treatment with this agent is clinically effective in improving urodynamic parameters as well as urinary incontinence [Campbell *et al*. 2009; Karsenty *et al*. 2008, pp. 275–278].

Surgical options may need to be considered for patients with severe urinary incontinence unresponsive to medical therapies, or patients with recurrent infections resulting in MS exacerbations. For patients with incontinence related to overactive bladder, sacral neuromodulation has been found to be a very effective treatment alternative, though traditionally its use has been limited to patients with idiopathic overactive bladder. Augmentation cystoplasty, ileovesicostomy, and ileal conduit urinary diversion are all complex surgical procedures utilizing the bowel to either augment or replace the function of the bladder, and each may have a role in severely affected patients.

Neurogenic bowel

Similar to bladder dysfunction, bowel dysfunction is characterized as disorders of storage or elimination. In our MS clinic, constipation is the most common bowel dysfunction followed by poor evacuation and incontinence. The pathophysiology of constipation in patients with MS is poorly understood. The gut is influenced by neural, endocrine and luminal input and coordination. The neural system is composed of the intrinsic and extrinsic nervous systems. The intrinsic nervous system contains Meissner's and Auerbach's plexi. While it is well recognized that neurotransmitters play a role in this process, the physiological role of each is still unclear [Winge *et al*. 2003].

Sympathetic innervation consists of spinal levels T5–L2 and is largely inhibitory through noradrenergic input. Parasympathetic input consists of input from the vagus and sacral nerves. Stimulation of the parasympathetic nervous system promotes peristalsis, blood flow to the gut and intestinal secretion. The external sphincter receives innervations from the pudendal nerve (S2–S4). These same spinal levels are responsible for perineal sensation.

When a patient states 'I am constipated' they are frequently referring to straining, hard stools or inability to have a bowel movement. Constipation is defined as less than three bowel movements a week. However, stool frequency alone does not define constipation. Constipation can be caused by several factors.

A review of diet and fluid intake is recommended as first-line evaluation. Patients may limit fluid intake due to bladder dysfunction or dysphagia. The causes may be iatrogenic secondary to drugs used to treat spasticity, paresthesias, pain, or bladder dysfunction. Decreased physical activity and mobility can greatly impact bowel movement frequency. Secondary medical causes that may or may not be related to MS require screening.

There are several interventions for constipation. Bulking agents are effective, and common forms include psyllium (from the ispaghula husk), bran and calcium polycabophil. Osmotic agents usually contain magnesium and are available as magnesium oxide and magnesium sulfate. Magnesium oxide is primarily used in mild to moderate severity constipation. Magnesium sulfate is dosed similarly to magnesium oxide but can cause bowel movements that are more explosive and have a liquid-like consistency. Magnesium sulfate should be avoided in older people. Poorly absorbed sugars, lactulose, polyethylene glycol and sorbitol, are effective in patients with more chronic constipation. Polyethylene glycol is now available over the counter as liquefied glycerine with docusate sodium and is approved for use in children. The most common adverse effect with polyethylene glycol is abdominal cramping. Stimulants are agents that increase intestinal motility and secretions. Common agents include senna, cascara and castor oil. They work rapidly and can occasionally lose their effect if abused. Senna is generally preferred over the other stimulant agents due to increased tolerability. Stool softeners can be used to treat constipation. Docusate sodium is dosed at two 100 mg tablets daily, and in combination with a stimulant (senna) quite effectively treats mild to moderate constipation in patients attending our clinic. Prokinetic agents can also be used: lubiprostone is a fatty acid in the prostone class. It is a chloride channel activator and increases intestinal fluid secretion. Tap, saline and soapsud enemas work quickly and effectively to soften stools and assist in expelling the contents of the rectum. Saline enemas are reported to be the safest of the three [Feldman, 2006]. Several types of enemas are available and physicians are encouraged to monitor what type a patient is using and with what frequency in order to prevent electrolyte imbalance. For those with rectal pain, a similar formulation can be utilized that also includes the local anesthetic benzocaine. Rectal pain can also be effectively treated by the use of belladonna and opium (B&O) supprettes. These small suppository-like devices are highly effective rectal analgesic agents. Bisacodyl and glycerin suppositories stimulate the rectal wall through stretch mechanisms. They are safe and effective in patients suffering from symptoms of dysphagia, nausea or vomiting. Surgery may be indicated in refractory cases, to ease the burden of care for severely debilitated patients. Often quality of life does improve in patients with colostomies because constipation can cause pain, discomfort and embarrassment.

Patients with bowel incontinence may be more reluctant to report symptoms to their physician compared with patients with constipation because there may be discomfort or feelings of humiliation. Fecal incontinence is defined as an involuntary loss of stool per rectum usually caused by reduced anal squeeze pressures. A diet and fluid history should be evaluated in patients with incontinence. Treatment will be targeted at the underlying cause. Drug therapy with loperamide can be used in patients with chronic diarrhea with fecal incontinence. This is not recommended for use in patients with symptoms of diarrhea and constipation. Biofeedback training is utilized to improve pelvic floor muscles and improve rectal sensory perception. Surgical repair is indicated for medically refractory or trauma cases. There are several techniques available, including pelvic floor muscle repair, forming a new external anal sphincter via muscle transposition, and even development of a 'false' anal sphincter using hydraulic rings. Fecal diversion with colostomy is used when the above options fail or are not feasible.

Sexual dysfunction

Sexual dysfunction is a common symptom in patients with MS. It is highly conspicuous that in one study as many as 94% of women reported that sexuality has never been discussed in the context of their office visits [Hulter and Lundberg, 1995]. Sexual dysfunction is linked to a reduced quality of life and is a principal cause of marital instability and other relationship problems. Not surprisingly, relationship partners may not fully recognize or fully understand the link between their partner's fatigue or decreased libido and the MS disease process. Common symptoms of sexual dysfunction in women with MS include difficulty achieving orgasm/climax,

decreased sexual libido, increased or decreased vaginal sensation, lack of sufficient lubrication, and dyspareunia [Borello-France *et al*. 2004; Zivadinov *et al*. 2003; Yang *et al*. 2001, 2000; Zorzon *et al*. 1999; Mattson *et al*. 1995; Chancellor and Blaivas, 1994]. Common symptoms of sexual dysfunction in men include erectile dysfunction, loss of early morning erection, ejaculatory dysfunction and/or orgasmic dysfunction, reduced penile sensation and reduced libido. There is no consensus on the effects of age, disease duration, disability and education level on sexual dysfunction.

In setting up a discussion with patients on sexual dysfunction it is strategically useful to inform patients that a substantial percentage of the MS population have this problem, and that in many cases it is a derivative of the disease process affecting the physiology of sexual functioning. Further, we have found that a series of objective and targeted questions can facilitate open and honest discussion of sexual dysfunction. These include the following:

1. Describe changes in your sexual interest and desires that have occurred since your diagnosis.
2. Are you having difficulty with sexual arousal, and/or achieving orgasm?
3. Male specific: are you having difficulty achieving or maintaining erection or with ejaculation?
4. Female specific: are you having difficulty with painful sex or lubrication?

Once sexual dysfunction is established, the clinician is encouraged to rule out underlying medical causes as the etiology. Reviewing cardiovascular, endocrine, and other neurological disorders and screening for thyroid function, fasting glucose and hemoglobin A1c are recommended. Testosterone levels have been studied in the general population. Low levels of testosterone are not consistently correlated with sexual dysfunction in men or women [Traish *et al*. 2007]. Diagnosis and treatment are recommended to be coordinated in conjunction with a neurourologist, endocrinologist or gynecologist. Each patient should be screened for depression [Beck *et al*. 1961]. The selective serotonin reuptake inhibitor (SSRI) class of antidepressants, while very effective, frequently cause decreased libido as a side effect. Bupropion is an antidepressant that is being studied for its effect on improving libido and orgasm enhancement. In cases of well controlled depression with an SSRI, when reduced libido is reported, we will often add a daytime dose of bupropion to counteract these effects. Many of our patients subsequently indicated important restoration of libido and sexual satisfaction. A patient's cultural or religious background may influence their attitudes about sex and should be taken into consideration [Schmidt *et al*. 2005].

General treatment recommendations applicable for both sexes include adequately treating neuropathic or visceral pain and spasticity because both can impede sexual performance and cause fatigue. Also, energy-conserving positions are recommended. Assessment and treatment of neurogenic bladder or bowel dysfunction is crucial. Patients with bladder dysfunction/retention should be advised to empty their bladder with the use of a Foley catheter prior to engaging in sexual activities. Sexual activities may need to occur in the morning as several patients with MS have disabling fatigue late in the day.

The introduction of sildenafil, and similar agents, has revolutionized the treatment of erectile dysfunction in men. A double-blind, placebo-controlled study on the effects of sildenafil *versus* placebo in men with MS reported 90% of patients experienced improved erections compared with 24% of those on placebo [Green and Martin, 2000]. Newer, longer-lasting agents including vardenafil and tadalafil have emerged but have not been specifically studied in patients with MS.Other treatments for men with erectile dysfunction include vacuum pump devices (not accepted by most), injection therapy (with intracavernosal alprostadil), and implantation of penile prostheses [DasGupta and Fowler, 2003; Litwiller *et al*. 1999]. For these interventions to be effective, some degree of manual dexterity is required by the man or his partner. It is important to remember that erectile dysfunction is just one of several possible symptoms of sexual dysfunction in men. The clinician is encouraged to screen for decreased libido or ejaculatory problems.

Sildenafil in women with MS and sexual dysfunction resulted in significant improvement in lubrication but not in other areas, including desire or ability to achieve orgasm [Brady *et al*. 2004]. Hormone replacement treatment can aid in lubrication. For patients who cannot take hormone

replacement treatment, water-soluble lubricants are recommended. Decreased sensation or difficulty to achieve orgasm can be aided with the use of vibrators. In general, effective vibrator stimulation involves high-intensity, high-frequency, wall-powered devices that are applied to the region just above the clitoris in women and to the ventral aspect of the penile corona in men. Recently, the US Food and Drug Administration approved the first device for sexual dysfunction in women, EROS (NuGyn Inc., Spring Lake Park, MN, USA). This device promotes vascular engorgement, lubrication, and improved sexual satisfaction. Other forms of treatment being studied include cognitive behavioral therapy, testosterone transdermal patch treatment, and also medications including tadalifil, ropinirole and bupropion XL.

Autonomic derangements: edema, acrocyanosis, neuropathic causalgia

Very common accompaniments of pyramidal distribution weakness in MS include limb discoloration (red to blue), acrocyanosis of the hands and feet often with associated neuropathic causalgia, reduced skin temperature (with patients frequently complaining of cold limbs), and edema (most commonly pedal and pretibial). Perhaps the latter is the most disabling, given that increased tissue water adds substantial weight to the legs, which compounds already evident weakness (particularly hip flexion), increases the energy demands of movements, and impairs walking. In patients with severe leg weakness, this process is compounded by reduced muscular action upon veins, thereby reducing the normal mechanisms of venous return. With age, valvular incompetence within veins and immobilization worsens edema and increases varicosities. The increased hydrostatic pressures of sitting for prolong periods also eventually provokes changes in skin integrity (stasis dermatitis) with greater risk of breakdown and infection. The temperature changes in the limbs along with neuropathic pain can adversely affect sleep hygiene and thereby worsen fatigue.

Our approach to patients with severe leg weakness and associated changes is to begin by educating them on the importance of leg elevation periodically throughout the day and at night. We also strongly encourage that patients perform leg exercises each day that are focused on promoting muscular activity and improved venous return of tissue fluid. We also liberally recommend the use of compression stockings (most commonly below the knee). We typically suggest starting with 8–12 or 15–20 mm Hg compression in order to ensure that patients or carers can apply the stockings. Doing so early in the morning upon arising, when leg edema is reduced, is a practical suggestion that makes the use of compression therapy more comfortable for the patient and carer. In general we recommend that patients purchase their stockings through online vendors, given the wider variety and cheaper cost compared with medical supply stores (discountsurgicalstockings.com is a particularly good source).

For patients who have darkened hands, feet, or digits, we consider whether Doppler studies are indicated to exclude peripheral vascular insufficiency. Over the years, we have found this to be exceedingly rare in patients with MS, particularly in nonsmoking women. Once this consideration has been addressed, we discuss the use of cilostizol, an agent with antiplatelet and smooth muscle relaxation properties. We have found this agent to be highly effective in reducing acrocyanosis and pain. However, slow titration is necessary to avoid intolerance (generally headache). Some recent reports indicate that the proerectile agent sildenafil may also represent an effective therapy for acrocyanosis and limb pain.

Cognitive and intellectual changes

While treatment advances have resulted in decreased sequelae in a variety of neurological domains in MS, the incidence of neurocognitive impairments in MS is steadily increasing, with estimates ranging from 40 to 70% [Benedict *et al.* 2006]. The nature and degree of these deficits have been found over time to lead to significant disability, contributing to unemployment and impaired quality of life. The most common cognitive deficits detected have been in attention, executive functioning, processing speed, and memory, with the typical presentation consisting of a specific impairment in one of these functions. The occurrence of dementia, a progressive cognitive decline in multiple cognitive domains, in patients with MS though is uncommon [DeLuca *et al.* 2004; Fischer, 2001, pp. 233–256; Rao *et al.* 1993].

As the initial occurrence of these deficits can be subtle at times, neuropsychological batteries with sensitive measures are often required to delineate these impairments. Extensive neuropsychological

testing not only provides markers of cognitive dysfunction but aids in identifying other factors that could amplify the deficits including depression, fatigue, and associated motor impairments. Assessment for the presence and contribution of these factors to cognitive dysfunction, particularly depression, is essential to not only obtain an accurate determination of the etiology of the deficits, but also for treatment options. While treatment for fatigue and depression can produce reversal of cognitive dysfunction, there has been less success in directly treating cognitive impairments associated with MS. Cognitive rehabilitation programs have shown only inconsistent improvements in performance, although this field is in the early stages of development and still may prove effective particularly if used with pharmacotherapy [Lincoln *et al.* 2002]. Pharmacological treatment of the cognitive symptoms themselves has shown some success. Donepezil, in particular, has demonstrated some improvements in memory deficits in MS [Christodoulou *et al.* 2006; Krupp *et al.* 2004]. Amphetamines have been associated with improved cognitive performance but as to whether this was related to improved fatigue or mood change requires further investigation. Amantadine and gingko biloba were not effective [Morrow *et al.* 2009].

Psychiatric mood disorders

Patients with MS can be afflicted with a wide range of psychiatric disorders. However, most commonly depression is associated with the illness. In such patients, agitation, reduced initiative, sadness, demoralization, loss of self worth and esteem, and sleep and eating derangements can markedly impact upon quality of life, compromise relationships, reduce adherence to treatment and rehabilitation strategies, and ultimately promote worsening of the disease. We carefully and systematically discuss the features of depression with patients and their family members. When identified, we discuss the range of both pharmacologic and counseling options.

Often the most effective approach is a combination of a mood stabilizer agent in conjunction with a period of psychological counseling. Funding limitations often preclude the latter, however the neurologist and other members of the care team (nurses, social workers, and physician extenders) can play a pivotal and productive role in encouraging patients to remain positive and committed to their care plan. We can educate patients on the progress that has already been achieved in understanding the mechanism of disease, and how this has translated into the approval of disease-modifying and symptomatic agents that both alter the course of the disease and quality of life.

Sleep medicine and multiple sclerosis

Cross-sectional observational studies indicate that the majority of patients with MS experience unsatisfactory sleep [Merlino *et al.* 2009; Bamer *et al.* 2008; Clark *et al.* 1992]. The presence of sleep complaints is associated with lower quality of life scores and an increased likelihood of depression. Insomnia, defined as difficulty initiating or maintaining sleep, comprises the largest category of sleep complaints, affecting up to 40% of patients [Tachibana *et al.* 1994]. Reported causes include muscle spasticity and spasms, nocturia, depression, anxiety, and medication side effects [Fleming and Pollak, 2005]. A variety of specific sleep disorders may occur in patients with MS, and may contribute to insomnia and disturbed sleep. RLS and periodic limb movement disorder are more frequently found among patients with MS than among healthy controls [Manconi *et al.* 2008]. Obstructive and central sleep apnea, and circadian rhythm sleep disorders have not been found to occur more frequently in MS, but are not uncommon and should therefore always be considered in the evaluation of patients with sleep-related complaints [Wunderlin *et al.* 1997].

Polysomnographic study of patients with MS conducted in the sleep laboratory reveals reduced sleep efficiency with an increased number of awakenings compared with controls [Tachibana *et al.* 1994]. A few studies have attempted to correlate disturbed sleep with the location of demyelinating lesions in the brain. Patients with sleep complaints have been shown to have a significantly higher frequency of lesions in the motor association areas of either cerebral hemisphere [Tachibana *et al.* 1994]. Periodic limb movements identified on polysomnography appear to correlate with lesions in the brainstem and cerebellum [Kato *et al.* 2003]. Narcolepsy with low hypocretin-1 levels in the cerebrospinal fluid has been diagnosed in patients with MS and plaques involving the hypothalamus [Oka *et al.* 2003; Plazzi and Montagna, 2002]. Rapid eye movement sleep behavior disorder has been reported in association with demyelinating disease in the

pontine tegmentum [Plazzi and Montagna, 2002].

Successful treatment of sleep disturbances in patients with MS is dependent on the clinician's awareness of the typical features and presentations of common sleep disorders, and on the ability to obtain a careful sleep history, often including the bed partner's report of observed habits and phenomena before and during sleep. Supplemental questionnaires, such as the Epworth Sleepiness Scale, the Berlin Questionnaire, and the Pittsburgh Sleep Quality Index, can help to focus and clarify the sleep history to aid diagnosis [Buysse *et al*. 2008; Chung *et al*. 2008; Johns, 1991]. Referral to a comprehensive sleep center for consultation, testing, and treatment is available in many communities, and is often appropriate when specific sleep disorders are suspected.

Bone and mineral and vitamin D

Factors thought to account for the high incidence of accelerated bone loss in MS have included the higher sex predilection for women to develop MS and to have a higher risk of bone loss, avoidance of the sun due to heat sensitivity (Uhthoff's phenomenon), the use of corticosteroids for treating and preventing MS attacks, living at paraequitorial latitudes where sunlight exposure is less, and vitamin D deficiency [Sioka *et al*. 2009]. Studies have suggested that greater sunlight exposure in early life, along with living closer to the equator, may represent important factors that reduce the risk of developing MS. Further, vitamin D has been shown to augment the clonal frequency of regulatory cells that may also help to regulate the immune system [Correale *et al*. 2009]. The colocalization of the vitamin D binding protein and the HLA-DR2, B1-1501 genetic polymorphism, may further intensify efforts to understand the relationship between vitamin D and the development of immune tolerance mechanisms [Handunnetthi *et al*. 2010; Ramagopalan *et al*. 2010]. In the interim, we know that most patients with MS are deficient in vitamin D, and more attention in clinics has turned to monitoring blood levels of this important vitamin. In our clinic, we target for a D total level of 60–80 ng/ml, and thereby utilize vitamin D3 (cholecalciferol) for replacement, given that it appears to be more potent than vitamin D2 (ergocalciferol) [Holick, 2007].

Conclusion

The ability to recognize and manage the multitude of symptoms that patients with MS are faced with can have a significant and beneficial impact on their quality of life. Clinicians should actively screen for, address, and educate patients, their families, and caregivers about the myriad of ways this disease affects the person and the potential therapeutic strategies available to them.

Conflicts of interest statement

None declared.

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