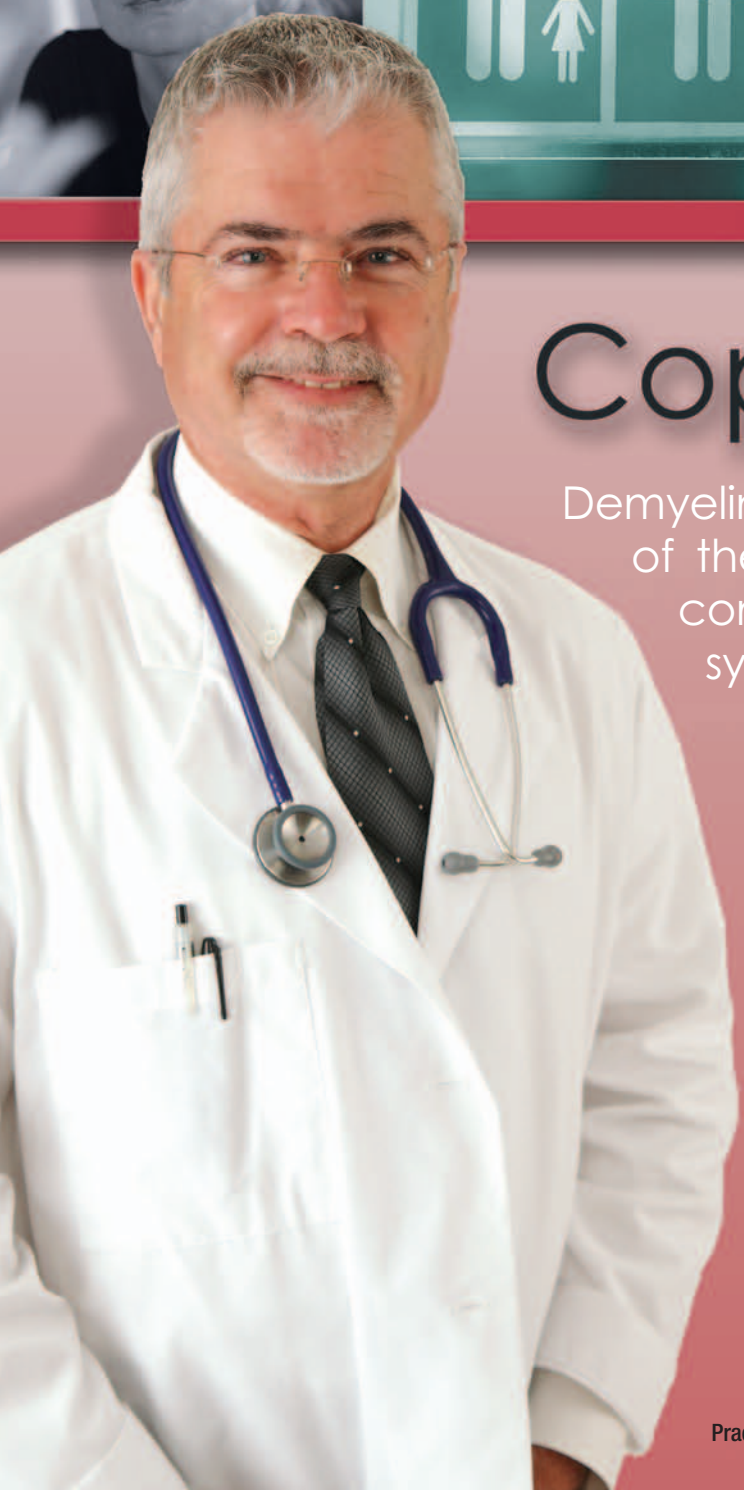
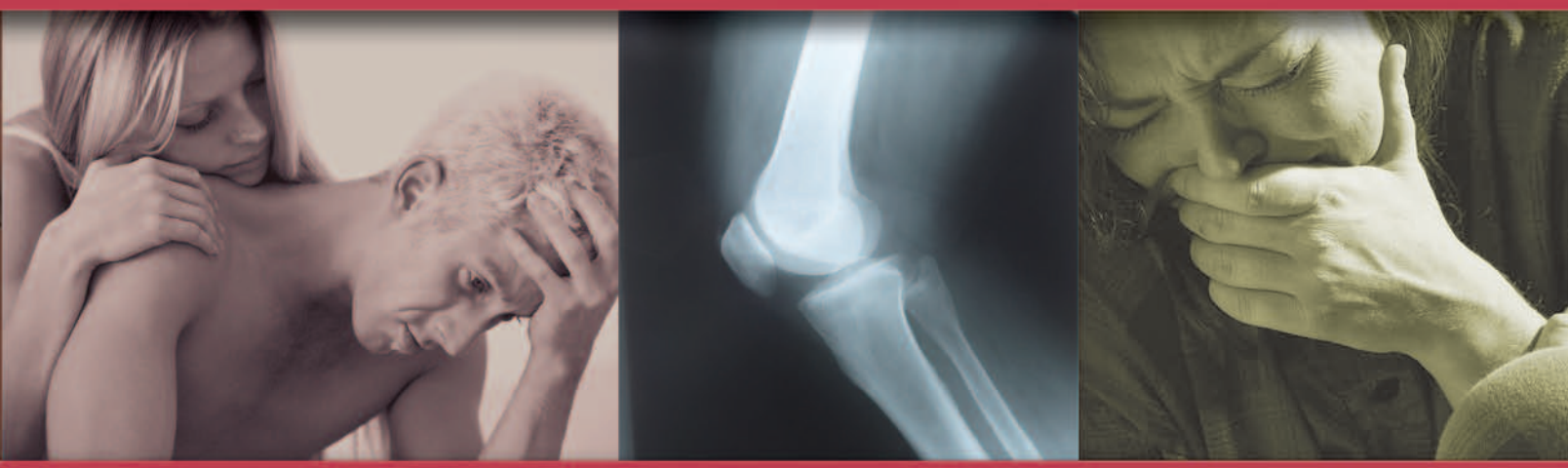


Coping with MS:

Demyelinating effects are but one aspect of the patient's plight. Here's how to combat the multitude of ancillary symptoms brought on by MS.

When caring for a patient who suffers from multiple sclerosis, the clinician must take a holistic view that encompasses both the direct and indirect symptoms that the condition—and in some cases, the immune-modulating therapies—inflict upon the individual. The goal of symptomatic treatment is to improve quality of life. In a condition where full restoration of function is generally not attainable, it is possible to help patients adapt to their impairments.

Concerned and careful listening will increase the likelihood that most of the patient's problems are addressed. This, however, has been challenging; Goodin found that for the six most common problems of multiple sclerosis patients (*i.e.*, bladder dysfunction, fatigue, spasticity, pain, depression and sexual dysfunction), only spasticity was treated in more than 40 percent of patients.[1] To be a skilled listener, the physician must let the patient tell his or her story. Observe the type of language the person uses to relate symptoms. If symptoms are described in emotional terms (*e.g.*, "My headache feels as if someone is ripping my brain apart."), it may indicate somatization of emotional distress. Such descriptions are common among patients with multiple sclerosis, who may be especially prone to emo-



How to Give Patients Their Lives Back

By Michael Kaufman, MD

tional distress on an organic basis. Being an effective listener does not mean being a passive listener. Many patients with multiple sclerosis have cognitive impairments that may make a concise history difficult to elicit. When the patient pursues a tangential topic, steer him or her back to the purpose of the visit. Careful listening also helps to establish a sense of trust that allows the patient to introduce critical, personal issues. This feature will offer practical suggestions on how to allow patients to preserve as much of their activities of daily living as possible.

Fatigue

MS patients identify fatigue as the most frequent and disabling symptom of the condition, and two-thirds list fatigue as one of their three worst symptoms. Seventy-five to 90 percent of multiple sclerosis patients experience unusual fatigue, compared to about 30 percent of the general population. Fatigue impedes mobility for 50 to 60 percent of patients and 40 percent describe it as their most disabling symptom.[2] Social Security Disability may be awarded on the basis of fatigue, and it is one of the two major reasons for unemployment among people with multiple sclerosis. Two monographs that are useful references for the management of fatigue have been published.[3,4]

MS-related fatigue includes a number of different syndromes that presumably have different etiologies and may respond to different therapies. Given the prevalence of this symptom in multiple sclerosis, it is surprising that no comprehensive study has been performed to define and differentiate the many theoretical causes of fatigue in this population. The most common include:

Spasticity. Deconditioning and spasticity may improve with an exercise program; however, patients should not exercise past the point of exhaustion because fatigue may persist. Lack of reciprocal innervation with spasticity may increase the energy required to move.

Sleep disorders. In a small study, disrupted sleep has correlated with fatigue measured by the Fatigue Descriptive Scale.[5] However, in another study of six relapsing-remitting MS patients with fatigue, no consistent polysomnographic evidence of disturbed sleep was found.[6] Almost half of all MS patients complain of sleep disturbances,[7] including periodic leg move-

ments of sleep and restless legs, hypersomnia, insomnia or disrupted sleep, delayed sleep phase syndrome and sleep apnea.

Insomnia, the most common complaint, has many potential causes. Conditions that are associated with fatigue may contribute to insomnia such as depression/anxiety, medications, pain, nocturia, restless legs, muscle spasms, inactivity and possibly alterations of the wake-sleep cycle caused by central nervous system pathology. In a group of 60 patients from London, insomnia in the middle of the night was most often caused by nocturia and was associated with daytime fatigue.[8]

Stimulants and insomnia-producing drugs should be avoided if possible, and regular sleep schedules established with sufficient "wind-down" time prior to sleep onset. Long-term treatment of insomnia using sleep-inducing pharmacological agents is generally discouraged. However, the melatonin receptor agonist ramelteon appears to decrease sleep latency without rebound in some patients with chronic insomnia. Some benzodiazepines may be effective for at least 24 weeks[9] and a 12-month open label study using eszolpiclone showed continued efficacy of treatment in primary insomnia.[10]

M***edications.*** Medications that inhibit neuronal function such as antispasticity agents, anxiolytics, antiepileptic drugs, and analgesics may cause sedation. Interferon-beta also may be associated with relatively persistent fatigue. If fatigue-inducing medications are essential, stimulants can be used to counteract this effect.

Affective disorders. Depression, anxiety, and perceived poor health are all associated with fatigue, but fatigue can also induce social withdrawal and depression. Fatigue is worse for patients who tend to somaticize as well as those who feel that they have little control over their environment.[11]

Idiopathic lassitude. Lassitude is probably the most common and poorly understood form of multiple sclerosis fatigue. It may be the result of inefficient communication between areas of the brain that work together whenever the patient is active. Diminished neuronal integrity, as demonstrated by diminished cerebral metabolism, lowered N-acetylaspartate-creatinine ratio and greater brain atrophy, has been associated with high levels of subjective fatigue. Inflammation may also cause lassitude. Interleukin-1, released by inflammatory cells, can induce lassitude when injected into the ventricles of animals. A relapse of multiple sclerosis is often associated with severe fatigue, possibly due to this mechanism. Some patients report improvement in fatigue after initiation of immunomodulators. This type of fatigue may occur without preceding activity and may be helped by a brief nap.

Chronic lassitude may be helped by caffeine, amantadine and stimulants. The efficacy of amantadine is poorly supported at present. Although a recent well-controlled trial of modafinil showed no greater effect on fatigue in multiple sclerosis patients than placebo,[12] in the author's experience and in the experience of others,[13] some patients report dramatic response to it. Stimulants have also been used as adjuncts to treat depression and improve cognitive function after brain injury. Although controlled-release products are generally preferred, in some patients they interrupt sleep to a greater extent than immediate-release products. Recently, cases of sudden death have been tied to the use of stimulants in both adults and children, primarily among those with pre-existing structural heart defects.

The author has found bupropion, usually at high dose, to be occasionally helpful in treating fatigue albeit whether the effect is primary[14] or secondary due to amelioration of depression[15] is unclear. In a small, exploratory study, 240mg per day of ginkgo biloba had a modest effect on fatigue and sense of well being.[16] Acetyl L-carnitine has also been suggested as a treatment for fatigue. Iyengar yoga has been shown to be as helpful as regular exercise in combating fatigue.[17]

Overuse or failure of neuronal excitation. Uhthoff phenomenon is an example of this entity that may affect motor, cognitive and other functions. It is precipitated by emotional stress, a rise in body temperature, and activity. Presumably, increased recruitment of neurons or using the same neurons for multiple tasks makes them refractory to excitation. Any activity or condition that raises body temperature may result in fatigue and weakness. High body temperature shortens the duration of action potentials, leading to electrochemical transmission failure along demyelinated axons. Patients with MS have difficulty regulating body temperature, and this may be linked to fatigue severity.

This may also explain why a recent trial with 650mg of aspirin taken at morning and noon improved fatigue in multiple sclerosis patients.[18] Turning the thermostat to a temperature of 65°F to 68°F also may help. The Multiple Sclerosis Association of America offers cooling vests free of charge to patients with heat sensitivity. Some physicians have used compounded 4-aminopyridine to help patients with motor and other forms of overuse fatigue. Phase II and III studies suggest that sustained-release 4-aminopyridine may improve motor function in approximately one-third of moderately impaired patients.

Dysautonomia. Fatigue similar to that seen with beta-adrenergic blockers has been linked to sympathetic vasomotor insufficiency in multiple sclerosis patients. Studies have also shown that the amount of change in stroke volume and ejection fraction measured at rest when compared to hyperventilation is inversely correlated with fatigue, suggesting that abnormalities of vagal function may be a factor, resulting in fatigue.[19]

Spasticity

Spasticity, as applied to multiple sclerosis, describes increases in

tone at rest (rigidity), tone that increases with the speed of movement (spasticity), slow contraction of antagonistic muscles (dystonia), heightened tendon reflexes, and myoclonic jerks. Clinically, these forms of spasticity may occur independently or together. The functional consequences of spasticity range from mild impairment of running to increases in adductor tone that compromise genitourinary hygiene. In severely weak patients, spasticity may be useful in allowing them to stand, pivot and transfer.

Almost all patients with spasticity will benefit from an exercise program. Passive and active muscle stretching may reduce the amount of medication required to treat spasticity and can prevent contractures. Reduction of pain reduces spasms.

Because first-line agents baclofen and tizanidine have different mechanisms of action and toxicities, they can be combined to improve outcomes.[20] The use of ciprofloxacin is inadvisable in patients taking tizanidine because it may increase tizanidine blood levels dramatically. Some anticonvulsants and benzodiazepines have mild ameliorating effects on spasticity. Levetiracetam appears to modify phasic spasticity without inducing cognitive changes.[21] A number of patients report that cannabinoids are beneficial in the management of their spasticity, but objective improvement has not been satisfactorily demonstrated to date.

Intrathecal baclofen may benefit nonambulatory patients when spasticity is painful, interferes with skin care or hygiene, or makes transfer and positioning difficult. It occasionally provides dramatic benefit for patients with good strength but significant gait abnormalities due to spasticity. The systemic side effects of baclofen are minimal with this form of administration. Botulinum toxin injections can be used to relax single or small groups of spastic muscles. They are especially useful for patients with a painful, dystonic posture of a hand, foot and occasionally the neck, and in patients with compromised personal hygiene due to adductor spasm.

Bladder Management

Bladder dysfunction includes difficulties in storage and emptying of urine and the effects of inappropriately high pressures within the bladder. Urgency, caused by detrusor hyperreflexia, is often associated with frequency due to reduced bladder capacity. Difficulty initiating flow is usually the result of inability to relax the external sphincter. A low flow rate may result from increased external sphincter tone or loss of tone in the detrusor. The latter, often referred to as areflexic bladder, is usually associated with marked leg spasticity or weakness. Detrusor-sphincter dyssynergia is used to describe the combination of a hyperreflexic bladder with inability to relax the external sphincter. Many multiple sclerosis patients have this combination of symptoms resulting in urgency, hesitancy and incomplete bladder emptying. Urosepsis, once a major cause of mortality among patients with multiple sclerosis, usually can be avoided.

Table 1. Pharmacological Options for Treatment of Fatigue in Multiple Sclerosis Patients

Medication Class	Drug	Comment
Temperature modulator	Aspirin (650mg at morning and noon)	Single study suggests efficacy.
Generalized stimulants		
• First line	Amantadine (100 to 400 mg)	Has few side effects; works in less than half of patients.
• Second line	Methylphenidate (5 to 40mg or extended release)	Extended release formulations improve compliance; addictive, must rewrite prescriptions monthly.
	Mixed amphetamine salts (5 to 40 mg)	Activates tuberomammillary nucleus.
	Modafinil (100 to 400 mg)	Does not produce much anxiety; efficacy questioned.
Energizing antidepressants	Bupropion (100 to 300 mg)	May induce weight loss; contraindicated with history of seizures.
	Fluoxetine (10 to 40 mg)	
	Venlafaxine (37.5 to 225 mg)	Extended-release formulations are expensive.
Speculative	4-aminopyridine; extended release being studied	May cause seizures and hallucinations in patients with large juxtacortical lesions.
	Acetyl L-carnitine	

Note: Physicians assume liability for compounded substances when they are prescribed .

Three major risk factors for serious urinary tract complications are: (1) an indwelling catheter, (2) detrusor-sphincter dyssynergia in men, and (3) detrusor pressures less than 40cm of water. Aims of therapy should be to avoid these and to protect upper urinary tracts.

Initiation of therapy is aided by the ability to measure urine volume and by knowing the following facts about the bladder:

(1) The normal bladder can accommodate 450 to 500cc of urine before the urge to void.

(2) Normal volume of voided urine is 300 to 500cc, three to eight times daily.

(3) Post-void residual urine volume is normally only a few cc.

(4) The detrusor muscle is muscarinic (parasympathetic) and contracts in response to acetylcholine to empty the bladder.

(5) Adrenergic stimulation increases the tone of the external sphincter and inhibits the parasympathetic innervation of the detrusor, increasing the capacity of the bladder to store urine.

(6) The usual progression of bladder symptoms in multiple sclerosis is hyperreflexia of the detrusor muscle, then detrusor-sphincter dyssynergia, and then areflexia.

Evaluation of bladder function includes gathering information about the number of times the patient voids, the degree of urgency and hesitancy, severity of nocturia, the amount of fluid intake, the force and constancy of stream, the amount of urine voided, and the amount of and circumstances leading to incontinence. With only a clinical history, however, nearly 50 percent of patients are misdiagnosed.[22] A carefully recorded micturition diary describes urinary function more precisely than the history alone. Ultrasound urine volumes, ideally done at the time of first urge to void and after voiding (post-void residual), can be obtained non-invasively. Some patients may be managed initially with relative confidence based on history, micturition diary and pre- and post-void residual urine. The goals of therapy are to maintain a residual urine volume of less than 100cc, produce a ratio of residual volume to voided volume that is less than one third, and to prevent recurrent urinary tract infection.

A guide for the treatment of bladder dysfunction containing a number of algorithms is available.[23] In the case of hyperreflexic bladder, behavioral management includes reduced intake of substances that may irritate or stimulate the bladder such as caffeine or acids, reduced fluid intake when a lavatory will be unavailable or before sleep, and timed voiding. Timed voiding requires the patient to anticipate when the next need to empty the bladder will occur and void before the urge to urinate is felt. Over-the-counter calcium glycerophosphate (333mg, one to two doses with meals) can be useful in reducing urinary acidity and decreasing urgency. Pelvic muscle training and relaxation techniques may also be of some benefit.

Anticholinergics with strong antimuscarinic activity are the treatment of choice for a hyperreflexic bladder and for increasing bladder capacity. Oxybutynin, a commonly used and inexpensive agent, has potentially helpful weak muscle-relaxant and local anesthetic actions. Anticholinergic therapies are often associated with the unpleasant side effect of dry mouth. This may cause patients to drink more fluids, aggravating their frequency. Glycerine swabs or candies can occasionally be helpful in combating this problem. Blurred vision in bright light and acute angle closure glaucoma can be precipitated by anticholinergics because they cause papillary dilation.

Another concerning side effect of anticholinergic medication is impaired cognition. In addition to traditional anticholinergics, many other drugs (antihistamines, cimetidine, prednisolone, theophylline and digoxin) can have detectable antimuscarinic effects, potentiating the problem in older and cognitively impaired patients. In such patients, physicians may wish to use darifenacin for its M3 selectivity or trospium chloride, tolterodine or solifenacin, which have low lipid solubility limiting their entry into the brain. M3 receptors are found in gastrointestinal smooth muscle, salivary glands, iris sphincter and bladder but not in CNS tissue. It also may be advisable to combine these medications with newer, and unfortunately more expensive, therapies to substitute for drugs with anticholinergic effects in order to reduce the "total cholinergic burden" in patients susceptible to confusion.

Alpha-blockers are used to treat difficulty initiating a urinary stream (hesitancy) initially. Care must be exercised to avoid induction of hypotension when these agents are used. Botulinum injections into the external sphincter may also be effective treatment for hesitancy due to inability to relax the external sphincter. Saw palmetto, an herbal preparation available without prescription, has been used to alleviate symptoms of hesitancy in association with benign prostatic hypertrophy, but in a well-controlled and adequately powered study, one preparation performed no better than placebo.[24]

An areflexic bladder may respond to muscarinic agonists. Double-voiding, a Credé maneuver that applies pressure on the bladder, or a vibrator placed over the lower abdominal wall may improve emptying of an areflexic bladder. A permanent intraurethral catheter is rarely appropriate and usually only used for patients with immobility and limited surgical options.

Referral to a urologist should be considered if a post-void residual volume is greater than 200cc. Volumes in this range can be associated with chronically elevated pressures (greater than 30cc of water) in the bladder that lead to reflux of urine into the ureters and, in the setting of bacteriuria, infection of the urinary tract. If urinary pressures are high, intermittent catheterization is needed to prevent recurrent urinary tract infections, albeit improper catheterization can also lead to recurrent infection. Females have a short urethra, as compared to males, that pro-

vides less resistance to the contraction of the detrusor muscle. Changes in the pelvic floor induced by surgery and childbirth and the thinning of the vaginal mucosa with menopause make women more likely to be incontinent, although these changes also lead to low bladder pressures.

Avoidance and prompt treatment of bladder infections is paramount to the care of multiple sclerosis patients. A urine analysis should be obtained in the setting of new urgency to look for infection. Patients with altered bladder sensation, however, often do not have typical symptoms in the setting of a urinary tract infection. Reliance on a urine analysis to screen patients using two of the most sensitive indicators of infection, (1) leukocyte esterase and (2) moderate bacteriuria by microscopy, can overlook about 14 percent of infections.[25] Therefore, a urine culture is advised for MS patients with a decline in neurologic status or a change in bladder function.

A three-day course of trimethoprim-sulfamethoxazole as initial therapy is sufficient for uncomplicated urinary tract infections in patients with early multiple sclerosis and minimal bladder symptoms. If resistance to these drugs is high, antibiotic choice is based on susceptibility testing. Patients with high residual urine volumes and high bladder pressures or who are taking immunosuppressive therapy require longer periods of treatment (seven to 10 days) to eradicate infection.[26] Patients taking immunosuppressive therapy should undergo a repeat urine analysis at five days after initiation of therapy to ensure an appropriate response and a culture 10 days after the completion of therapy to verify complete resolution of the infection.

Elevated white blood cell counts (equivalent to a positive leukocyte esterase) are not a definite indicator of infection when patients have urinary catheters. Patients with Foley catheters and more than 100,000 CFUs by urine culture should be treated only if symptomatic.

More than three urinary tract infections per year is reason for referral to a urologist. Patients who self-catheterize may be more susceptible to infection and may benefit from suppression of bacteria with uroquid acid (methenamine/sodium biphosphate) or methenamine and vitamin C QID. Suppression with antibiotics can be done by alternating treatments using one month of nitrofurantoin, 50mg per day, followed by one month of trimethoprim-sulfamethoxazole or trimethoprim alone, 400mg per day. More aggressive suppression can be accomplished by irrigation of the bladder with gentamicin 240mg in 500ml of normal saline with one ampoule of sodium bicarbonate daily for seven to 10 days. Irrigation is performed after changing the bladder catheter. Initially, 60ml of normal saline is used to irrigate the bladder via catheter, then 30ml of gentamicin solution is placed into the bladder, and the catheter is cross-clamped for 30 minutes. The gentamicin mixture is drained through the catheter.

Bowel Dysfunction

Constipation historically has been defined as 12 weeks or more of symptoms per year, hard stools, straining, incomplete evacuation, use of manual maneuvers to pass stool or a sense of difficulty passing at least one in four stools or/and less than three bowel movements per week. Because patients tend to underestimate their stool frequency, a bowel diary may clarify the history. Any patient with blood in the stool, weight loss or whose onset of symptoms occurs at an advanced age should be referred to a gastroenterologist. Multiple sclerosis patients in particular are vulnerable to constipation resulting from medications (anticholinergics, nonsteroidal anti-inflammatory agents, calcium supplements and amantadine), decreased mobility and dehydration.[27]

The treatment of constipation begins with behavioral therapies. Bowel entrainment can be fostered by timing elimination 30 to 60 minutes after the same daily meal. Regular exercise, dietary fiber and fruits, and good hydration all contribute to good bowel function. One half cup of a mixture of one-third prune juice, one-third apple sauce, and one-third bran cereal ingested once or twice daily is well tolerated and beneficial when symptoms are mild. Pineapple also seems to be particularly useful as a food that promotes regularity. Some patients have reported that the use of bifidobacteria-containing yogurt has been helpful for them.

Concentrated fiber preparations increase the bulk and water content of stool. Colonic bacteria metabolize natural fiber sources such as psyllium, oat bran and fruits, which results in the release of gas. This phenomenon does not occur with synthetic or insoluble fibers such as methylcellulose (Citrucel) and polycarbophil (Perdiem, Fibercon) or wheat bran/dextrin (Benefiber). Stool softeners can be added to fiber. Softeners include docusate sodium (Colace) and docusate calcium (Surfak)

Hyperosmolar agents, such as sorbitol, lactulose and polyethylene glycol (listed in order of increasing cost), may also cause bloating. The American College of Gastroenterology Chronic Constipation Task Force (2005) has made a Grade A recommendation for both lactulose and polyethylene glycol for improving stool consistency and frequency. Pyridostigmine 30-60mg or erythromycin 333-400mg taken before meals may increase peristalsis.

A number of relatively inexpensive stimulants (bisacodyl, senna, cascara, and phenolphthalein) and saline laxatives are available for intermittent use. Some "natural remedies" contain significant amounts of senna and cascara. Decreased absorption of fats and fat-soluble products and induction of refractory constipation limit the use of all stimulants. Glycerin suppositories used every other day or bisacodyl suppositories every third day may also help.

Gastrointestinal propulsives include cisapride, domperidone and metaclopramide. Cisapride and domperidone both have cardiac toxicity while metaclopramide can induce parkinsonism. Lubiprostone is a chloride channel activator that increases intestinal fluid secretion. It has low systemic absorption, but can cause nausea. Trials using 24mcg twice a day appear to show benefit in chronic constipation.

Sexual Dysfunction

Sexual dysfunction generally affects patients with spinal cord symptoms of multiple sclerosis. During intercourse, multiple and easily perturbed neural networks on both conscious and unconscious levels coordinate to reach a successful culmination. Decreased libido, numbness and dysesthesias, vaginal dryness, autonomic dysfunction, vascular insufficiency, emotional and cognitive impairment, spasticity, bladder dysfunction and side effects of medications all can contribute to unsatisfactory intercourse. Most antidepressants affect sexual function, although bupropion and mirtazapine generally spare the ability to achieve orgasm. Alpha-adrenoceptor antagonists, frequently used to treat hesitancy, can lead to disorders of ejaculation. Marital discord can cause sexual dysfunction, but nearly 25 percent of patients believe that the lack of sexual fulfillment has contributed to marital problems. Surprisingly, corticosteroid treatments sometime improve sexual function.[28]

Fifty to 75 percent of men with multiple sclerosis report erectile dysfunction. This has become much easier to treat with the development of oral phosphodiesterase inhibitors sildenafil, vardenafil and tadalafil. These medications should be used with caution or not at all when patients are taking other vasodilators. Medications that inhibit the P-450 system such as statins, protease inhibitors, and systemic tiazole antifungals increase the plasma levels of the oral phosphodiesterase inhibitors and increase side effects. Vacuum devices and alprostadil urethral suppositories can be used alone or added to phosphodiesterase inhibitors. Intracavernous injections of prostaglandins E1, papaverine and phentolamine in different concentrations can be effective as well. As many as 25 percent of men with multiple sclerosis have premature ejaculation. This generally responds well to selective serotonin reuptake inhibitors taken an hour before intercourse.

Testosterone levels have found to be slightly lower in MS. Despite this, the author has rarely found a low testosterone level when searched for. Other endocrine causes of erectile dysfunction are hyperthyroidism and prolactinomas. The vascular risk factors of inactivity, diabetes, hypertension and dyslipidemia are associated with restricted pudendal artery flow and erectile dysfunction. Patients with Pyronie disease develop pain and penile curvature with erections that results in dysfunction.

Treatment of women with sexual dysfunction often is more difficult than treatment of men. The most common complaints of women are inadequate lubrication, anorgasmia or hypoorgasmia, reduced libido and diminished perineal sensation. An association of cerebellar disturbances and orgasmic dysfunction has been found.[29] Vaginal creams and water-soluble lubricating jellies can be used to treat vaginal dryness. Petroleum-based jellies should be avoided because they can leave residues that promote bacterial vaginitis. Patients experiencing diminished sensitivity often respond to vibrators. Oral sildenafil may be an adjunct to sexual arousal, but small studies have shown only a limited effect on lubrication. This agent has also been compounded as a cream, sometimes combined with L-arginine, and applied to the clitoris with anecdotal success.

Ten percent of women with MS have painful perineal dysesthesias that may be manageable with carbamazepine or gabapentin or the local application of 2% xylocaine gel. Women with incontinence should empty the bladder prior to intercourse, and those with high residual volumes should empty afterwards. Intercourse for patients with urinary catheters and spasticity may be possible with proper positioning and treatment of spasticity.

Pain

Pain is common in multiple sclerosis. Over half of the subjects in a cross-sectional study described acute or chronic pain syndromes during the course of the disease.30 Nearly a quarter of patients take analgesics daily, compared to less than 10 percent of a control population; 19.3 percent of MS patients reported that pain interfered with daily life "all the time" versus 7.4 percent of controls.[31]

One of the most difficult problems in multiple sclerosis management is to differentiate pain caused by tissue damage from behaviorally-associated pain. Although both can be difficult to treat, the latter may be characterized by confrontation between patient and caregivers. Other causes of pain should always be considered when a patient develops a new pain syndrome. Chronic neurogenic dysesthesias are commonly experienced in patients with secondary progressive multiple sclerosis.[32]

Pain can be classified into categories that aid in the selection of treatments:

Paroxysmal neuralgic pain. This phenomenon is variably described as sharp, stinging, burning, shocking or by an equivalent phrase. In one study, this was the most common type of pain experienced.[33] These paroxysmal pains may be atypical in patients with multiple sclerosis when compared to "idiopathic" cases. Paroxysmal neuralgic pain includes trigeminal neuralgia, glossopharyngeal neuralgia, occipital neuralgia, pseudoradicular pain, and Lhermitte phenomenon.

Chronic neurogenic pain. Chronic neurogenic pain involves the feet and legs more commonly than the hands.

Although chronic neurogenic pain is not associated with quantitative sensory threshold changes, mechanical or thermal hyperalgesia is common.[34] If the pain is well localized, application of a 5% lidocaine patch is sometimes helpful. Up to three patches may be apply for up to 12 hours within a 24-hour period. The long lasting effects of short-term intravenous lidocaine therapy have been reported as treatment for chronic neurogenic pain as well as for musculoskeletal pain.[35] Tricyclic antidepressants and anticonvulsants are the mainstay of treatment, but many therapies have been used when the pain is intense. To minimize side effects, the author may start with gabapentin and, if a partial response is obtained, add carbamazepine. A tricyclic antidepressant then can be added, and finally a narcotic, often oxycodone.

Duloxetine HCl and venlafaxine, selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors, have been shown useful in diabetic neuropathy and in some forms of myofascial pain. If pain is severe only at night, a hypnotic may be helpful. Capsaicin cream applied three to five times daily may be an adjunct to other therapies. Doses of narcotics necessary to control pain vary greatly, although keeping the dose of these addictive medications low is desirable. Clonidine or tizanidine can be used as an adjunct to narcotic use. Intrathecal morphine (800-10,000µg per day) and clonidine (400-750µg per day) can be used if a continuous infusion pump is implanted.[36]

Headache or back pain. Headache or back pain can be a sign of a relapse. In some situations, such as retrobulbar neuritis, pain may be well localized. Treatment of chronic headaches in multiple sclerosis patients is not different than for idiopathic headaches. The relatively recent additions of topiramate and botoxulinum toxin have made treatment easier, but one must be careful not to add to cognitive disturbances of multiple sclerosis patients with topiramate.

Musculoskeletal pain. Musculoskeletal pain can be caused by ligamentous and bursal inflammation from inactivity, overuse of muscle groups, improper mechanics of joint movement, muscle spasms, pressure sores and syndromes of undefined etiology. Most neurologists will defer to orthopedic and rheumatologic consultants to manage these diverse problems. Due to the association of avascular necrosis of the femoral head and other bones with corticosteroid administration, neurologists should be familiar with its symptoms and differential diagnoses. The absence of pain with flexion and extension of the hip (Patrick-Fabere test) is useful in differentiating trochanteric bursitis from intra-articular hip disease.

The basis of treatment for most musculoskeletal pain is the application of heat, stretching and strengthening exercises, body mechanics, bracing, and nonsteroidal anti-inflammatory drugs. Therapies that are useful in chronic pain syndromes may be of use in this setting.

Cognitive disorders

Between 40 and 65 percent of MS patients have measurable cognitive disorders by neuropsychological testing. Cognitive impairment appears early in the course of MS, affecting over half of patients with clinically isolated syndromes.[37] Interestingly, cognitive abnormalities were found in patients with spinal cord, optic nerve, and cerebral localizations for their symptoms. Although cognitive impairment is common, it appears to change slowly, at least in treated patients.[38]

Clinically, the author has found variability in whether memory or executive functions are most affected. Formal neuropsychological testing suggests that measures of information-processing speed,[40] word list generation and verbal memory[39] are the earliest markers of impairment. Correlation with gait impairment is poor, and cognitively impaired patients may appear otherwise relatively well. Although cognitive dysfunction is not usually severe, even mild impairments greatly disturb people with high baseline ability.

Few studies have characterized the types of cognitive deficits multiple sclerosis patients experience. Although it is commonly believed that most of the intellectual decline is subcortical, cortical demyelination can be severe and subpial lesions found in the infoldings and sulci of the brain may be the cause of cognitive defects, particularly in patients with progressive MS.[41] Both cognitive decline and physical disability appear to correlate more closely with MRI evidence of progressive brain atrophy than with increasing T2 lesion burden.[42] A number of batteries are available to diagnose cognitive decline. A practical 15-question survey, the MS Neuropsychological Screening Questionnaire, appears to provide reasonable sensitivity for the detection of cognitive impairment when completed by a non-patient informant.[43,44]

Occasionally, patients respond to cholinesterase inhibitors, the NMDA inhibitor memantine and, rarely, stimulants. The caregiver may be the most reliable observer when measuring response to therapy. When using cholinesterase inhibitors for cognitive dysfunction, one should remember that they can increase the frequency and urgency of urination and defecation.

Depression and Anxiety

Emotional distress occurs commonly in multiple sclerosis. A Canadian population-based study has found major depression to be about 2.3 times more prevalent in persons with than without multiple sclerosis, affecting approximately 26 percent of patients between 18 and 45 years of age.[45] The lifetime prevalence of depression in MS appears to be about 50 percent. Those with left anterior temporal or parietal lesions by MRI scan may be at a slightly increased risk.[46]

Although it has been difficult to establish, many experienced clinicians feel that interferon-beta therapy may bring out

depressive symptoms in MS patients. Patients with multiple sclerosis have a higher incidence of bipolar disorder than the general population.[47] Anecdotal evidence links emotional stress to a poor prognosis for multiple sclerosis. In support of this observation is evidence that interferon-gamma production by peripheral blood mononuclear cells falls with the treatment of depression.[48]

Exercise has been reported to be beneficial in improving depression in multiple sclerosis.[49] In addition to being less depressed and angry, patients were stronger, were slimmer, displayed more cardiovascular fitness, exhibited less fatigue, had more positive social interactions, and reported better bowel function. Antidepressant treatment may prevent loss of hippocampal cells in patients with recurrent depression.[50]

Drugs blocking the reuptake of both 5-HT and NE (SNRIs) produce a high rate of treatment response for depression and anxiety, generally showing a slight superiority to SSRIs, but they also have more side effects. Unlike SSRIs, SNRIs are helpful in relieving pain.

Osteoporosis

Clinicians should expect patients with multiple sclerosis to have osteoporosis, which seems to be linked to inflammation found in a number of chronic disease states. Dual-energy X-ray absorptiometry (DXA) scans can be useful in following the efficacy of therapy for patients with bone loss. Because of the variability in measurements, the recommended interval is generally between two and five years, although this can be done more frequently in patients at high risk for fracture while on aggressive therapy.

Multiple sclerosis patients lose bone mass more rapidly and experience more fractures than age- and gender-matched controls. They also may have low levels of vitamin D. Immobility causes loss of bone, and bed rest for one year results in loss of more than 10 percent of bone density. The use of glucocorticosteroids demineralizes bone. Bone loss can be minimized by weight bearing, cessation of smoking, avoidance of high alcohol intake, ingestion of 1500mg of calcium (in three divided doses) and 600 to 800 IU of vitamin D daily for both men and women. Calcium carbonate is less expensive than calcium citrate but requires stomach acid for absorption.

Patients with T or Z scores below -2.0 or with scores below 1.5 and additional risk factors or previous vertebral or hip fracture should be treated with pharmacological intervention.

Bisphosphonate therapy can be undertaken using alendronate, risedronate or ibandronate. The first two come in sustained-release formulations that can be given once weekly. Ibandronate can be taken once monthly. Patients must take these medications 30 to 60 minutes before the first morning meal, with a full glass of water and remain erect for 30 minutes after taking them. They should not lie down until they have eaten breakfast. Bisphosphonates should not be used, or should be used cautiously, in patients with hypocalcemia, renal insufficiency, esophageal irritation, or trouble swallowing.

Other treatments include raloxifene, nasal calcitonin and teriparatide. The selective estrogen modulator raloxifene avoids some of the cardiac and breast cancer risks of estrogen. It is contraindicated in patients with a history of venous thromboembolic events. Nasal calcitonin is administered as one dose in alternating nostrils daily. It does not appear to be as potent as the other therapies and is generally considered second-line therapy. Teriparatide is a recombinant human parathyroid hormone analogue. It is the first anabolic drug approved for the treatment of severe osteoporosis. Although it is a potent drug, it must be given subcutaneously at a dose of 20 micrograms once daily and has significantly more side effects than the other compounds. It also is currently five to eight times more expensive than the other drugs.

Common correctable causes of osteoporosis may be sought through relatively simple testing such as: serum calcium and phosphorous; 24-hour urine calcium and, if elevated, parathyroid hormone level; liver function panel; creatinine; serum protein electrophoresis to exclude multiple myeloma; thyroid panel; and hormone levels.[51]

Conclusion

Except in newly diagnosed patients, treating symptoms generally consumes more time than slowing progression of multiple sclerosis. Often, comfort and improvement in the quality of life is all the physician can provide. Interventions as described above that help patients to forget or overcome their MS symptoms, however briefly, are well worth the effort. **PN**

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