Multiple sclerosis: Managing the whole patient
American Pharmacists Association

Multiple sclerosis
Multiple sclerosis (MS) is an autoimmune, neurodegenerative disorder that affects approximately 400,000 people in the United States, with 200 people newly diagnosed every week. It is one of the major causes of neurologic disability in young and middle-aged adults; the mean age of onset is approximately 30 years.1 Women are affected two to three times as often as men.2 The impact of MS on patient function can range from relatively mild to somewhat disabling to devastating.

The term “multiple sclerosis” refers to two characteristics of the disease: (1) the numerous affected areas of the brain and spinal cord producing multiple neurologic symptoms over time and (2) the characteristic plaques, or sclerosed areas, that are the hallmark of the disease.3 These plaques, also known as lesions, are associated with symptoms in systems innervated by the affected neuronal pathways.

In MS, the immune system attacks the myelin sheath that protects the axons of neurons, leading to demyelination and subsequent axonal damage. The exact causes of MS are not fully understood. Evidence suggests that MS is caused by a combination of genetic, environmental (e.g., virus exposure, vitamin D levels, smoking, excess weight), and immune system factors.

Diagnosis of MS is based on the presence of lesions in the central nervous system that cannot be attributed to another disease process and occur in different parts of the central nervous system at least 3 months apart.4 Magnetic resonance imaging is typically used to identify lesions.

Patients may initially present with “clinically isolated syndrome”—a single symptomatic neurologic episode consistent with MS, such as optic neuritis. Other common presenting symptoms include paresthesias, weakness, and impaired coordination.

Symptoms that frequently occur in patients with MS include bladder dysfunction, constipation, sexual dysfunction, fatigue, depression, diplopia (double vision), gait and limb ataxia, Lhermitte’s sign (electrical sensation down the spine during neck flexion) numbness and tingling, speech impediments, tremors, dizziness, hearing loss, and cognitive impairment.5 Most MS patients experience muscle weakness and difficulty with coordination and balance. These symptoms may impair walking or even standing and can eventually lead to paralysis.

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Learning objectives
At the conclusion of this application-based activity, the pharmacist will be able to:
- Discuss disease-modifying therapies that are commonly used in treating multiple sclerosis (MS) and their impact on patient outcomes.
- Explain strategies for promoting patient adherence, managing adverse events, and assisting patients with medication administration.
- Describe the REMS programs for medications used in the treatment of MS.
- Describe symptoms that are commonly associated with MS and the pharmacologic options for managing them.
- Discuss the use of biomarkers in research for new therapies for MS.
Symptoms typically resolve spontaneously, but relapses may occur within months or years. However, in some patients, MS is progressive from the initial presentation of symptoms. MS is categorized into four specific subtypes (Table 1).^

No cure exists for MS. The ultimate goal in the long-term management of MS is to prevent or delay the progression of axonal damage that leads to permanent neurological disability. Disease-modifying therapies (DMTs) are partly effective in achieving this goal. DMTs can reduce the number of exacerbations, reduce the duration and severity, slow disease progression, and reduce the relapse rate.^

The various pharmacologic therapies used in managing MS have unique management considerations and safety profiles that require careful patient education and management. Numerous other agents are available for managing symptoms associated with MS or in managing the adverse effects of other MS medications.

The DMTs currently approved for use in relapsing forms of MS in the United States include the following:
- Interferon beta (Avonex—Biogen Idec, Betaseron—Bayer HealthCare, Extavia—Novartis, and Rebif—EMD Serono)
- Fingolimod (Gilenya—Novartis)
- Glatiramer acetate (Copaxone—Teva)
- Natalizumab (Tysabri—Elan Pharmaceuticals)
- Teriflunomide (Aubagio—Genzyme)
- Mitoxantrone (Novantrone—OSI) (used rarely)

This article will focus on managing adverse events associated with these products. A thorough review of the agents approved before 2012 can be found in the recent issue of Pharmacy Today.^

Pharmacists’ role in managing patients with MS
Pharmacists play a key role in assisting patients with MS to improve outcomes. Pharmacists can review patients’ complete medication regimens to assess whether they are receiving appropriate medications in the correct dosages and educate them to take medications correctly. Pharmacists can discuss the risks and benefits of early treatment of MS with patients, screen for associated symptoms that may be suboptimally managed, and discuss appropriate treatment measures with other members of the health care team. In addition, they have key roles to play in supporting adherence, promoting appropriate injection techniques, and implementing risk evaluation and mitigation strategy (REMS) programs.

Promoting adherence to pharmacologic therapy of MS
Adherence to treatment and persistence with therapy (i.e., maintaining adherence) is critical for reducing disease progression and maximizing long-term benefits of therapy. However, adherence is a challenge for many MS patients as a result of adverse effects, lack of immediate observable benefits, and issues related to administering medications, many of which must be injected. Patients’ feelings about them-
including injections, over the long term. Pharmacy-based pharmacists, are critical to improving adherence to therapy, and support from multiple health care providers, including for addressing this barrier. Individualized patient education lapse are lower if they stay on the medication is important for treatment and informing them that the chances of a re-

treatment is a perception that the treatment is not work-

can also affect adherence. Educating patients to establish realistic expectations that the treatment is not work-

versus effects. Further, patients require initial education to minimize, monitor, and manage these adverse effects in several ways.18

A recent study by Clerico et al.16 showed that the most common reason for people on MS therapies to discontinue treatment is a perception that the treatment is not working. Educating patients to establish realistic expectations for treatment and informing them that the chances of a relapse are lower if they stay on the medication is important for addressing this barrier. Individualized patient education and support from multiple health care providers, including pharmacists, are critical to improving adherence to therapy, including injections, over the long term.17 Pharmacy-based disease management programs for patients with MS have been found to significantly improve patient adherence to injectable medications and result in fewer MS relapses.18

Many of the agents used to treat MS are associated with adverse events, some of which are major and require close monitoring. Health professionals can work with patients in several ways to minimize, monitor, and manage these adverse effects. Further, patients require initial education to ensure that they understand and accept the risks associated with treatment, monitoring parameters that must be fol-

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Features</th>
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<tbody>
<tr>
<td>Relapsing-remitting multiple sclerosis (RRMS)</td>
<td>RRMS is the most common initial phase of MS, representing approximately 85% of patients at the time of diagnosis. In RRMS, patients experience acute episodes of neurologic decline (i.e., “attacks”), followed by full or partial recovery with little or no progression. This phase can last for many years.</td>
</tr>
<tr>
<td>Secondary-progressive multiple sclerosis (SPMS)</td>
<td>Many patients with RRMS develop SPMS, which is characterized by slow, steady, irreversible neurologic dysfunction occurring with our without attacks. Many patients with RRMS eventually develop SPMS.</td>
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<tr>
<td>Primary-progressive multiple sclerosis (PPMS)</td>
<td>PPMS affects about 10% of patients at diagnosis. It is characterized by continuous neurologic decline from the time of disease onset. Distinct attacks do not occur.</td>
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<tr>
<td>Progressive-relapsing multiple sclerosis (PRMS)</td>
<td>PRMS affects about 5% of patients. It is characterized by continuous neurologic decline from the time of diagnosis, accompanied by distinct attacks.</td>
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</table>

Source: References 6 and 34.
Fingolimod also is associated with an increased risk of serious infections. Suspension of fingolimod should be considered if patients develop a serious infection. Before initiating fingolimod, patients without a history of chickenpox or vaccination against varicella zoster virus should be tested for antibodies to varicella. Vaccination of antibody-negative patients should be considered before starting fingolimod treatment. The use of live attenuated vaccines should be avoided during and for 2 months after stopping fingolimod.

Macular edema can occur, with or without visual symptoms. An ophthalmologic evaluation should be performed before starting fingolimod and 3 to 4 months after initiation.

Fingolimod may cause fatal heart failure. Women of childbearing potential should use effective contraception during and for 2 months after stopping fingolimod. A registry for women who become pregnant during fingolimod treatment is available.

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose.

Natalizumab. The most common adverse reactions in patients with MS who took natalizumab were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash.

Progressive multifocal leukoencephalopathy (PML)—an opportunistic viral infection of the brain that usually leads to death or severe disability—has occurred in patients who received natalizumab. Patients who have significantly compromised immune system function generally should not be treated with natalizumab. Treatment duration, previous immunosuppressant use, and presence of anti–John Cunninghamham virus antibodies are associated with increased risk of PML in natalizumab-treated patients.20 Ongoing monitoring is crucial, and natalizumab should be discontinued at the first signs of PML.

Natalizumab also may increase the risk for certain other infections. Patients should be monitored for development of these infections as well.21

Teriflunomide. Teriflunomide was approved for the treatment of MS in September 2012. It is the active metabolite of leflunomide (which is used in the treatment of rheumatoid arthritis and psoriatic arthritis). The most common adverse events associated with teriflunomide are increased alanine aminotransferase (ALT) levels, alopecia, diarrhea, influenza, nausea, and paresthesia.22

Severe hepatotoxicity including fatal liver failure has been reported in patients treated with leflunomide, and a similar risk is expected for teriflunomide. Transaminase and bilirubin levels should be obtained within 6 months before initiating teriflunomide, and ALT levels should be monitored at least monthly for at least 6 months after initiating treatment. If hepatotoxicity is suspected, treatment should be discontinued and an accelerated elimination procedure involving cholestyramine or activated charcoal for 11 days should be used. Teriflunomide is contraindicated in patients with severe hepatic impairment.22

Teriflunomide may cause major birth defects and is labeled Pregnancy Category X. It is contraindicated in those who are pregnant or women of childbearing potential who are not using reliable contraception.22

In addition, teriflunomide may decrease white blood cell counts; a complete blood cell count should be taken before starting therapy. Patients should be monitored for signs and symptoms of infection, and the accelerated elimination procedure should be used if a serious infection occurs. Likewise, the accelerated elimination procedure should be used if patients develop severe skin reactions and considered in those developing peripheral neuropathy.22

Mitoxantrone. Mitoxantrone is an oncologic medication that also is used in select patients with worsening MS. It is rarely used because it is associated with risks of acute myelogenous leukemia and cardiotoxicity, including reduced left ventricular ejection fraction and potentially fatal heart failure.23,24 The risk of cardiotoxicity increases with cumulative doses; treatment should not exceed 2 to 3 years. Patients with MS who reach a cumulative dose of 100 mg/m² should be monitored for evidence of cardiac toxicity before each subsequent dose. Patients with MS should not receive a cumulative dose greater than 140 mg/m².25

**REMS programs**

Some of the products used in the treatment of MS have REMS programs, which are required by FDA in certain cas-
es to manage known risks (Table 2). For medications that have REMS programs, pharmacists are responsible for administering certain elements to assure safe use. For example, fingolimod has a REMS program that requires the use of a medication guide to educate patients about risks associated with the medication, a letter and safety information guide for health care providers, and a 5-year postmarketing safety study. Natalizumab has a restricted distribution program for health care providers, and a 5-year postmarketing safety medication guide to educate patients about risks associated with the medication. If patients present with new symptoms of cognitive dysfunction, the entire medication regimen should be reviewed to determine whether recent changes could be contributing to symptoms. However, none of these medications has been specifically designed to manage risk of PML. A medication guide is required to be distributed with dalfampridine (which is used for symptom management). Teriflunomide should be dispensed with a medication guide but does not have a REMS program.

### Injection training

Learning to inject medications can be a challenge for patients, and a subset of patients will continue to experience injection anxiety after an initial period of adjustment. Patients with MS can be provided with several tips for making injections easier. Pharmacists can improve adherence to injectable medications by training patients to use appropriate injection techniques, building trust, promoting injection self-efficacy, and educating about strategies to prevent injection site reactions. Important education points for injection training are listed in Table 3.6

Patients may wish to use autoinjectors, which often are available from manufacturers free of charge. Autoinjectors are easier to administer than regular needles and can be helpful for patients with dexterity issues and those who do not like to look at needles. Autoinjectors can be programmed to inject to the correct depth for each patient, which helps to eliminate some administration errors. Injections will be less painful if they are brought to room temperature before injecting. Patients also can ice the injection site before and after injection, as well as massage the area.32

Some patients receiving glatiramer acetate experience an acute postinjection reaction. Health professionals can provide tips to avoid this reaction and counseling that can help patients manage this adverse effect.33

### Managing common symptoms of MS

DMTs only reduce the progression rate of MS; they do not stop it. As MS progresses, the symptoms tend to increase. In addition to medications specifically approved for treating MS, many other medications are used in MS patients to assist in managing symptoms of MS or in managing the adverse effects of other medications. Pharmacists can plan an important role in educating patients about the use of these therapies, as well as nonpharmacologic management strategies. Several common conditions and their management strategies are discussed here.

#### Cognition

Approximately one-half of all MS patients develop cognitive dysfunction, which affects their ability to think, reason, concentrate, or remember. Cognitive changes can occur at any time throughout the disease process but generally correlate with the extent of lesions seen on MRI. Loss of cognitive function generally progresses slowly but is unlikely to improve dramatically after it occurs. About 5% to 10% of patients develop severe cognitive dysfunction.

Several medications have been studied for their effects on cognitive dysfunction, including donepezil (Aricept—Eisai), ginkgo biloba, memantine (Namenda—Forest Laboratories), and rivastigmine (Exelon—Novartis). To date, evidence supporting pharmacologic treatment of cognitive dysfunction with these agents is lacking, but additional studies are ongoing.

Patients can be educated to use coping strategies to manage cognitive dysfunction, such as keeping lists, developing structured organizational systems, or using handheld organizational tools such as smart phones, to compensate for memory problems and other changes. Patients with cognitive dysfunction may require adherence tools such as pill boxes to promote medication adherence. Efforts to simplify medication regimens also may be helpful.

Cognitive dysfunction may be an adverse event associated with the use of other medications, especially anticholinergics. If patients present with new symptoms of cognitive dysfunction, the entire medication regimen should be reviewed to determine whether recent changes could be contributing to symptoms.

### Table 3. Education points for injection training

<table>
<thead>
<tr>
<th>General tips</th>
<th>Tips specific to glatiramer acetate</th>
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<tbody>
<tr>
<td>■ Product preparation, dosing schedule, and recommended injection technique vary by product; follow protocols in labeling and medication guide</td>
<td>■ Do not rub or massage injection area on the same day as injection</td>
</tr>
<tr>
<td>■ Wash and dry hands, then clean injection site with an alcohol wipe; let it dry before injecting</td>
<td>■ Warm the area with a heat pack</td>
</tr>
<tr>
<td>■ Rotate injection sites according to product labeling and medication guide</td>
<td>■ Do not inject into red, bruised, or irritated sites</td>
</tr>
<tr>
<td>■ Consider use of autoinjectors, which may be available for free: ensure adequate needle penetration into tissues, never reuse a syringe and properly dispose of all syringes, and ice the area before/after injection</td>
<td>■</td>
</tr>
</tbody>
</table>

Source: Reference 6.
Fatigue
Fatigue that is severe enough to interfere with patient function is one of the most common symptoms of MS, affecting approximately 80% of patients, and is a primary reason that patients give for leaving the workforce.34 Fatigue can have many causes. A type of fatigue called “lassitude” or “MS fatigue” is specific to patients with MS and has the following features34: generally occurs on a daily basis; may occur early in the morning, even after a restful night’s sleep; tends to worsen as the day progresses; tends to be aggravated by heat and humidity; comes on easily and suddenly; is generally more severe than normal fatigue; and is more likely to interfere with daily responsibilities.

In addition, a number of other factors can contribute to feelings of fatigue in patients with MS, such as poor sleep resulting from frequently awakening for overactive bladder, muscle spasms, or depression and the additional effort required to complete tasks because of physical impairments.

Amantadine hydrochloride (Symmetrel—Endo) and modafinil (Provigil—Teva) are the most commonly prescribed medications to treat fatigue in patients with MS but do not have an indication for this purpose. Other options that may have some beneficial effects include stimulants (e.g., methylphenidate [Ritalin—Novartis], dextroamphetamine [Dexedrine—CorePharma]), fluoxetine (Prozac—Eli Lilly; particularly for patients with comorbid depression), or dalfampridine.10,36

Depression and other emotional changes
Depression also occurs in about one-half of patients with MS and ranges in severity from mild to severe.

Depression could be situational—a psychological reaction to a chronic disabling condition. However, depression is more common in patients with MS than in patients with other severe disabling conditions. Therefore, depression is believed to be related to the neuropathology of MS and/or associated with MS fatigue. Depression also may appear as an adverse effect of other medications, such as corticosteroids used for treating MS attacks, and/or interferon.34

Selective serotonin reuptake inhibitors (SSRIs) are generally used as first-line treatment. Tricyclic antidepressants are second-line options and may be helpful for patients with insomnia, bladder spasticity, and/or chronic pain.10 Bupropion could be a good choice for patients with sexual dysfunction. Selective norepinephrine reuptake inhibitors (e.g., venlafaxine [Effexor—Wyeth], duloxetine [Cymbalta—Lilly]), desvenlafaxine [Pristiq—Wyeth]) may be preferred for patients with fatigue. Patients using pharmacologic treatments for depression should be informed that the benefits may take several weeks to appear.

Bladder dysfunction
Another symptom of MS that affects approximately 80% of patients with MS is bladder dysfunction, which occurs when MS lesions affect nerves involved with controlling the bladder. Bladder dysfunction can include failure to empty (hypermotor bladder), failure to store (hyperreflexive bladder), or nocturia. Sphincter dyssynergy is the failure to store along with failure to empty. It is caused by dyscoordination of the detrusor muscles of the bladder and the external urethral sphincter muscles. Instead of relaxing completely during voiding, the urethral sphincter muscle contracts and interrupts the flow of urine.10,34

Hyperreflexive bladder is the most common problem. It manifests as urinary urgency and frequency and voiding only small amounts of urine. Over time, urgency worsens and can lead to incontinence. It can be treated with anticholinergic medications (e.g., oxybutynin [Ditropan—Janssen] or tolterodine [Detrol—Pharmacia and Upjohn] with our without low-dose imipramine (Tofranil—Mallinckrodt). However, it is particularly important to consider the adverse effect profile when selecting an agent and consider issues such as the impact on balance and cognitive impairment, as well as other common issues such as dry mouth, constipation, dizziness, and vision changes. In August 2011, FDA approved the use of onabotulinumtoxinA (Botox—Allergan) to treat urinary incontinence resulting from detrusor overactivity in patients with MS.37

Sphincter dyssynergia can be treated with alpha-blocking drugs, such as terazosin (Hytrin—Abbott), tamsulosin (Flomax—Boehringer Ingelheim), alfuzosin (Uroxatral—Sanofi Aventis), sand ilodosin (Rapaflo—Watson), which relax the internal sphincter. Adverse events include decreased blood pressure, which can cause severe dizziness, particularly after the first dose.

Patients with hyperreflexive bladder can implement nonpharmacologic approaches, including the Crede maneuver (applying pressure right above the bladder to assist emptying), timed voiding, and self-catheterization. Patients are more prone to urinary tract infections and may require antibiotic prophylaxis; however, the risk for the development of resistant bacteria must be factored into the treatment decision.

Bowel dysfunction
Bowel dysfunction in MS most commonly manifests as constipation. (Diarrhea can occur but is generally not directly caused by MS.) Constipation may be caused by neurologic lesions that decrease intestinal motility as well as insufficient fluid intake and reduced physical activity. Neurologic lesions also can lead to loss of bowel control.

Patients with constipation should be educated to drink adequate liquids and include plenty of fiber in the diet (or add a supplement such as psyllium if needed). Stool softeners such as docusate sodium, or if needed, stimulant laxatives such as bisacodyl or senna, can also be helpful but should not be used continuously. If more than 2 or 3 days pass without a bowel movement, an enema or suppository should be recommended.34

Pain and sensory symptoms
Pain and sensory symptoms are common in patients with MS, with neuropathic pain due to neurologic lesions affecting approximately 50% of patients. Specific conditions may
include trigeminal neuralgia, burning, itching, L’Hermitte’s sign, or face twitching. Treatment includes carbamazepine (Tegretol—Novartis), tricyclic antidepressants, gabapentin (Neurontin—Pfizer), pregabalin (Lyrica—PF Prism), duloxetine, topiramate (Topamax—Janssen), tiagabine (Gabitril—Cephalon), or capsaicin cream.38

MS patients also may experience musculoskeletal pain resulting from poor posture, poor balance, or abnormal use of the muscles or joints due to spasticity. NSAIDs or other analgesics are indicated for pain of musculoskeletal origin.10

**Spasticity**

Spasticity (ranging from stiffness to painful uncontrollable muscle spasms) affects approximately 70% of patients with MS and is most common in the legs.39 Flexor spasticity involves the hamstrings and hip flexors, making the hips and knees bent and difficult to straighten. Extensor spasticity involves the quadriceps and adductors, making the hips and knees straight with the legs very close together or crossed at the ankles. Spasticity can be induced by a variety of stimuli, including urinary tract infections, constipation, pressure ulcers, and poorly fitting assistive devices. In addition, interferon beta products enhance nerve conduction in the spinal cord and can exacerbate spasticity.39

For some patients with lower-extremity weakness, some spasticity is beneficial because it aids walking. In this case, the goal of treatment is to balance the needs for comfort (reliief of spasticity) and function (walking). On the other hand, spasticity also may interfere with walking and lead to falls. Therefore, treatment goals must be individualized.

Without treatment, spasticity can result in serious complications, including contractures (painful and disabling frozen or immobilized joints, especially in the hips, knees, shoulders, ankles, and elbows) and pressure sores. Because these complications can also trigger spasticity, they can lead to a vicious cycle. Thus, treatment is crucial.34

Treatment of spasticity often involves several members of the health care team, including pharmacists, physicians, nurses, physical therapists, and occupational therapists, and may combine exercise, medication, and or modifications in daily activities, as well as the use of orthotics or braces.

First-line therapy usually is initiated with the muscle relaxant baclofen (Gablofen—CNS Therapeutics and Lioresal—Medtronic). Adverse effects include fatigue and weakness. It is critical that patients do not stop baclofen abruptly because that can lead to seizures, hallucinations, or even death. The muscle relaxant tizanidine (Zanaflex—Acorda Therapeutics) is a second option for patients; it is associated with adverse effects sedation or dry mouth and may lower blood pressure.

Other less commonly used drugs include benzodiazepines (e.g., diazepam [Valium—Roche], clonazepam—Klonopin). However, they are sedating and may be used at bedtime for patients who also have sleep disorders or have spasms that interfere with sleep. They should generally be avoided in patients with cognitive impairment.31 Gabapentin may be helpful in patients with both spasticity and neuropathic pain.

Dantrolene (Dantrol—JHP) generally is used only if other drugs have not been effective. It is associated with hepatotoxicity and blood abnormalities. Other potential treatments include the nerve block agent phenol or botulinum toxin injections, which have been shown to be effective in relieving spasticity in individual muscles.40

**Walking**

Gait disturbances are a common problem in patients with MS. In addition to spasticity, muscle weakness, balance issues, sensory deficits, and fatigue can contribute to gait problems. Nonpharmacologic approaches include exercise, physical therapy, gait training, and assistive devices.

Dalfampridine (Ampyra—Acorda Therapeutics; previously called fampridine) was approved in 2010 to improve ability to walk in MS patients. This product is a potassium channel blocker and may restore conduction in demyelinated nerve fibers.41 In clinical trials, dalfampridine improved walking speed by about 25%.42,43

Patients receiving dalfampridine should be educated to take the first dose first thing in the morning and the second dose approximately 12 hours later. Dalfampridine can be taken with or without food. Adverse events include urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, and a potential increased risk of seizure. Patients should not take dalfampridine if they have a history of seizures or moderate to severe renal impairment or if they are taking 4-aminopyridine (the active ingredient in dalfampridine).31 Dalfampridine and 4-aminopyridine are not bioequivalent and cannot be substituted for each other.

**Dizziness and vertigo**

Dizziness and vertigo may occur when lesions affect the complex pathways that coordinate visual, spatial, and other input to the brain. Dizziness (feeling off balance or light-headed) occurs more commonly, while vertigo (the sensation that surroundings are spinning) occurs less frequently. If they interfere with patient function, dizziness or vertigo can be treated with the motion sickness agents meclizine (e.g., Antivert—Pfizer) or scopolamine skin patches (Transderm Scop—Novartis) or the antinausea medication ondansetron (Zofran—GlaxoSmithKline). A short course of corticosteroids may be indicated for severe cases.34

**Vision problems**

Visual disturbances are common in patients with MS, but total blindness is not. Optic neuritis is common and occurs when lesions or inflammation occurs along the optic nerve or neural pathways that control eye movements or visual processing. The visual symptoms include blurring or graying of vision, a scotoma or dark spot in the center of the visual field, or blindness in one eye. Although distressing for patients, optic neuritis is almost always self-limiting and patients can expect a good recovery. A course of treatment with cortico-
steroids may be helpful. Other common visual disturbances include uncontrolled eye movements and diplopia (double vision).34

**Tremor**

Tremor (uncontrollable shaking) is common in MS and can occur in many areas of the body. Depending on the area affected, it can lead to other impairments, such as dysarthria (difficulty in speaking) or dysphagia (difficulty in swallowing). Tremor often is challenging to manage.34

Botulinum toxin injections have been found to have considerable positive improvements for patients experiencing tremor, with reductions in tremor severity and improvements in writing noted over 12 weeks of therapy. Weakness was more common in patients receiving botulinum toxin than placebo; it was mild (just detectable) to moderate (still able to use limb) and resolved within 2 weeks.44

Other agents that may have positive effects include the antituberculosis agent isoniazid (multiple generics), the antihistamine hydroxyzine (multiple generics), the beta-blocker propranolol (Inderal—Akrimax), the anticonvulsive medication primidone (Mysoline—Valeant), the diuretic acetazolamide (Diamox—Duramed), and the antianxiety drugs buspirone (Buspar—Bristol-Myers Squibb) and clonazepam.34

**Sexual dysfunction**

MS often interferes with sexual function in both men and women. Damage to nerve pathways associated with sexual arousal can directly affect arousal and orgasm. Also, symptoms such as fatigue and spasticity, psychological changes, certain medications (including certain antidepressants, beta blockers, and monoamine oxidase inhibitors), and pain can have an impact. In addition, bladder or bowel problems can lead to embarrassment that hinders sexuality.

Treatment of erectile dysfunction in men can include a variety of strategies, including the phosphodiesterase-5 inhibitors sildenafil (Viagra—Pfizer), vardenafil (Levitra—Bayer), and tadalafil (Cialis—Lilly) and injectable medications that increase blood flow in the penis (e.g., alprostadil). Alprostadil also can be given either by injection or as a suppository. Other options include the MUSE (medicated urethral system for erections) system, which involves inserting a small suppository into the penis, inflatable devices, and implants. Fewer options are available for women. Who experience vaginal dryness may benefit from the use of a lubricant, many of which can be purchased OTC.34

**Patient case**

S.J. is a 37-year-old woman with MS who has been receiving treatment with interferon beta for several years. She is a mother of three school-aged children and has a part-time job. She presents complaining of progressive difficulty walking and occasionally losing her balance and bumping into things. Review of her difficulty walking shows little indication that spasticity is an issue currently. Rather, her difficulty appears to be stemming more from poor coordination.

Upon a thorough review of her current symptoms, she reports worsening fatigue, feelings of depression, bladder dysfunction, and sexual dysfunction. She also reports signs of possible cognitive issues: “My kids keep telling me I’m flaky because I get their after-school activity schedules mixed up.”

What interventions would you recommend for S.J. at this time?

**Patient case interventions.** Because S.J. reports occasionally losing her balance, you probe further and discover that she sometimes feels dizzy and lightheaded, and this, along with fatigue, contributes to her difficulty walking. It does not appear that spasticity, tremor, or weakness are the primary cause of S.J.’s difficulty walking. Therefore, S.J. appears to be an appropriate candidate for a trial of dalfampridine.

You also suggest treatment with an OTC formulation of meclizine.

Next, you address S.J.’s fatigue. Feelings of fatigue are common in working mothers of young children. S.J. further describes her symptoms and reports that they frequently worsen in heat and humidity and sometimes make her so exhausted that she does not have energy to care for her children. Because she also appears to have some issues with memory and focus, you suggest initial therapy with methylphenidate. In addition, you recommend the use of an online scheduling program such as Google calendars to assist her in organizing all of her family activities and responsibilities.

Finally, it is possible that S.J.’s depression is contributing to the fatigue and sexual dysfunction. You propose initial treatment with an SSRI, with the goal of monitoring therapy to assess the impact on feelings of depression and on sexual function and fatigue.

**Summary**

MS is a chronic neurologic disorder characterized by demyelination and axonal damage that result in neurologic dysfunction that produces numerous symptoms. Treatment of MS with a DMT can reduce the frequency of relapse and slow the progression of MS. However, available therapies are associated with important risks and adverse effects and must be managed carefully. Thorough patient education and ongoing support is essential to promote adherence and optimal outcomes.

Symptomatic management is another critical component of the care of patients with MS. Pharmacists can play an important role in working with patients to optimally manage the wide range of symptoms that may appear throughout the course of the disease.

**Resources**

- National Multiple Sclerosis Society: www.nationalmsociety.org
- Multiple Sclerosis Foundation: www.msfocus.org
- All About Multiple Sclerosis: www.muit-sclerosis.org
References

CPE assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following agents used in managing patients with multiple sclerosis (MS) is considered a disease-modifying therapy?
   a. Teriflunomide
   b. Dalfampridine
   c. Botulinum toxin
   d. Dantrolene

2. A primary goal of the use of disease-modifying therapies for MS is to:
   a. Repair axonal damage.
   b. Minimize symptoms associated with MS.
   c. Slow disease progression.
   d. Manage acute attacks.

3. Identification of reliable biomarkers for MS could potentially:
   a. Lead to elimination of the need for disease-modifying therapies.
   b. Eliminate the use of clinical endpoints in monitoring response to therapy.
   c. Identify which patients are at risk of accelerated disease progression.
   d. Minimize the need for symptom management.

4. In a study by Clerico et al., which of the following was the primary reason that patients with multiple sclerosis were nonadherent to treatment?
   a. Dislike of injections
   b. Adverse events associated with therapy
   c. Belief that the medication was not effective
   d. Cost associated with therapy

5. Which of the following strategies is recommended to minimize influenza-like symptoms in patients taking interferon?
   a. Administer injections at bedtime
   b. Take acetaminophen before injections
   c. Limit fluid intake
   d. Perform at least 20 minutes of vigorous exercise before injections

6. Patients should avoid rubbing the injection site on the same day they receive an injection of which of the following medications?
   a. Glatiramir acetate
   b. Interferon beta
   c. Natalizumab
   d. Alprostadil

7. Patients should receive the first administration and have 6 hours of monitoring in a medical facility when receiving which of the following medications?
   a. Interferon beta
   b. Glatiramer
   c. Natalizumab
   d. Fingolimod

8. Which of the following medications is associated with a risk of progressive multifocal leukoencephalopathy?
   a. Mitoxantrone
   b. Glatiramer
   c. Natalizumab
   d. Fingolimod

9. Which of the following statements best describes postinjection reactions in patients receiving glatiramer?
   a. Patients who experience a postinjection reaction should discontinue glatiramer.
   b. The reaction typically dissipates after about 15 minutes.
   c. The reaction is a medical emergency requiring immediate medical attention.
   d. Postinjection reactions are associated with improved efficacy.

10. Which disease-modifying therapy is used rarely due to risk for leukemia and cardiotoxicity?
    a. Glatiramer
    b. Natalizumab
    c. Fingolimod
    d. Mitoxantrone

11. Which of the following medications has a REMS (risk evaluation and mitigation strategy) program that requires documentation of safe use conditions?
    a. Dalfampridine
    b. Natalizumab
    c. Fingolimod
    d. Mitoxantrone

12. Which of the following medications has beneficial effects for treating both walking and fatigue?
    a. Dalfampridine
    b. Modafinil
    c. Tizanidine
    d. Meclizine
13. Which of the following interventions is most likely to benefit patients with MS who experience cognitive dysfunction?
   a. Ginkgo biloba
   b. Memantine
   c. Rivastigmine
   d. Coping strategies such as use of organizational tools

14. Which of the following medications are recommended as first-line therapy for depression in patients with MS?
   a. Selective serotonin reuptake inhibitors
   b. Tricyclic antidepressants
   c. Bupropion
   d. Amphetamines

15. For patients with bladder dysfunction, botulinum toxin is approved to treat:
   a. Hyporeflexive bladder.
   b. Sphincter dyssynergia.
   c. Detrusor overactivity.
   d. Stress urinary incontinence.

16. Patients are at risk for seizures, hallucinations, or death if which of the following medications used to treat spasticity is abruptly discontinued?
   a. Baclofen
   b. Dantrolene
   c. Tizanidine
   d. Gabapentin

17. When treating spasticity, which of the following medications should be avoided by patients with cognitive impairment?
   a. Baclofen
   b. Diazepam
   c. Gabapentin
   d. Botulinum toxin

18. Which of the following medication/medication classes for treating depression might be a better choice for S.J. (see case study in article) if her fatigue does not improve?
   a. Selective norepinephrine reuptake inhibitors
   b. Bupropion
   c. Tricyclic antidepressants
   d. Monoamine oxidase inhibitors

19. Which of the following is a correct statement about optic neuritis in patients with MS?
   a. Failure to initiate treatment with corticosteroids within 48 hours of symptom onset can result in permanent vision loss.
   b. It is a common presenting symptom of MS but is usually self-limiting.
   c. Approximately 80% of patients who experience optic neuritis develop complete vision loss in 10 years.
   d. It responds well to treatment with anticonvulsant agents such as gabapentin.

20. Which of the following treatment interventions may be helpful for women with MS who experience sexual dysfunction?
   a. Phosphodiesterase 5 inhibitors
   b. Alprostadil injections
   c. The MUSE (medicated urethral system for erections) system
   d. Lubricants