

# Maintaining Symptom Control and Quality of Life for Outpatients with Multiple Sclerosis: Treatment Update

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**Upon successful completion of this article, the pharmacist should be able to:**

1. Discuss the neurologic and inflammatory processes of relapsing-remitting and progressive multiple sclerosis as they relate to signs and symptoms of disease exacerbations.
2. Describe the place in therapy of systemic corticosteroids and established and emerging disease-modifying therapies according to 2010 expert consensus guidelines.
3. Identify the most common adverse effects of disease-modifying therapies, and outline a plan to reduce these effects while maintaining treatment goals.
4. Evaluate treatment options for patients who wish to delay medication to control relapses (such as women with multiple sclerosis who are pregnant, nursing, or trying to conceive).
5. Design alternative, behavioral, and other non-drug interventions that can improve the quality of life in patients with relapsing-remitting multiple sclerosis.

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## INTRODUCTION

Multiple sclerosis (MS) is the most common cause of neurologic disability in young adults in the United States today, and is the second-most common cause of disability in young adults. This neurodegenerative disorder involves immune and inflammatory components that contribute to progressive and chronic impairment of motor function and cognition. Despite the more than dozen medications approved for the most common form of MS, there remains no cure and insufficient efficacy in available treatment plans. Because MS does not increase mortality and only minimally lowers projected longevity, patients diagnosed with the disease often face multiple decades of chronic care, with inconsistent expectations about symptoms, progression, and treatment options. Current treatment goals are to reduce symptom impacts and maximize quality of life through well-rounded interventions and lifestyle adaptations. Pharmacists can become more active members of the health care team that cares for patients with MS by providing proactive medication counseling services, identifying appropriate assistance devices and behavioral improvements, and incorporating non-medication therapies into their patient interaction services.

## CONTRIBUTING FACTORS AND EPIDEMIOLOGY CAUSES AND RISKS

Like many autoimmune conditions, MS remains a chronic disease with no identifiable cause. However, multiple contributors to MS development have been identified. Genetics plays an important role, with two genes identified in 2007 by the International MS Genetic Consortium as indicators of likely MS onset. Approximately 15 percent of people with a first-degree relative who has MS are likely to receive a diagnosis; this is 20 percent greater than the likelihood in the general population. Genes alone are not enough to induce the onset of MS symptoms, however. Identical twins, for example, share only a 33 percent risk of both developing MS.

Along with family history, multiple environmental factors and behavioral choices contribute to MS development. Higher rates of MS are associated with latitudes further away from the equator, and people living in equatorial areas experience lower risk of onset. The geographic risk remains significant through puberty (15 years of age). That is, people who move to a latitude with lower MS risks before the age of 15 years will assume the new geographic risk. However, geographic clusters—in which a higher-than-expected prevalence of MS is observed in a single region—have been observed, which reflects the complicated overlapping causes and risks of the disease. These diagnostic clusters are monitored by the federal Agency for Toxic Substances and Disease Registry; cases of possible clusters can be referred to them at [atsdric@cdc.gov](mailto:atsdric@cdc.gov) or 888-422-8737.

Vitamin D plays an important disease-related role because it is associated with greater absorption of sunlight in equatorial regions, and as a stand-alone behavioral factor through supplemental vitamin intake, has recently been better clarified. Vitamin D is synthesized inside the body with sun exposure, and high vitamin D levels have been associated with less severe MS disability. In January 2014, a study of patients with MS quantified this association by correlating high blood vitamin D ( $\geq 50$  nmol/L) with better five-year outcomes than in patients with vitamin D levels  $< 50$  nmol/L. High vitamin D levels appear protective for patients early in an MS diagnosis, and early treatment with vitamin D appears to delay progression of symptoms. Its use was associated with less CNS activity, slower progression of lesions, and development of lesion volumes, and less disability. A corollary, that low vitamin D could increase the risk of developing MS, is still unclear.

Smoking is one of the most significant behavioral effects on MS development and progression. Smoking appears to contribute to the onset of CNS damage in MS, and patients with diagnosed MS who smoke experience more MS attacks, faster rates of progression, and increased severity of attacks. Conversely, patients already diagnosed with MS experience slowed disease progression if they quit smoking at any time.

Infectious assault also might increase the risk of MS development. Epstein-Barr virus (EBV), the infection that causes mononucleosis, has been suggested as a link to MS onset, especially in patients who are infected by EBV and develop their immune responses to the virus in teen or adult ages. The connection with EBV does not appear direct but instead suggests that an immune response to the viral infection may trigger the immune system attack that develops into MS in susceptible people.

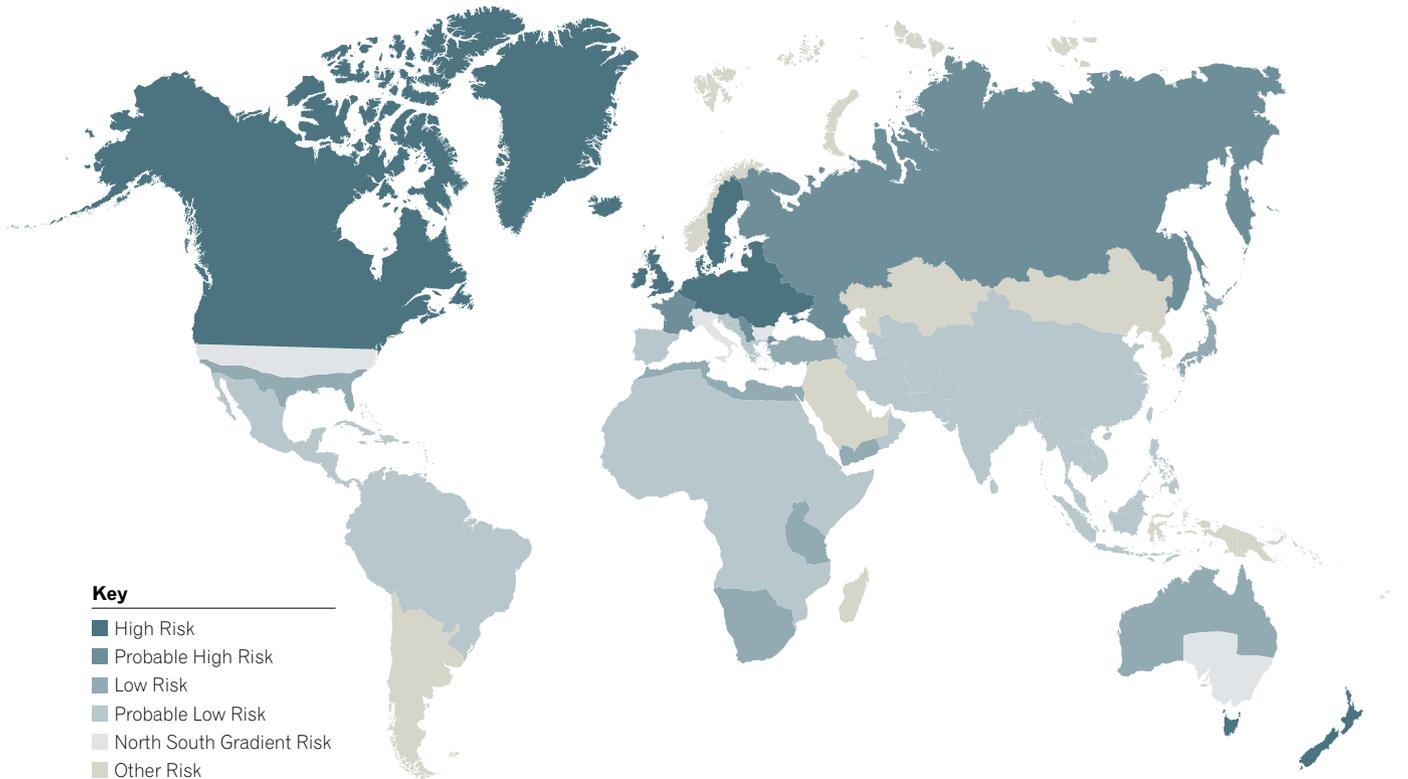
Numerous potential causes have been ruled out, including aspartame use, the presence of household pets, environmental allergies, exposure to heavy metals, and physical trauma. Connections among the existing risk factors remain poorly delineated, so identification of a single at-risk population is not possible for this challenging disease.

## EPIDEMIOLOGY

Multiple sclerosis affects at least 300,000 Americans and more than 2 million individuals worldwide. Women are disproportionately affected; the most common form of MS occurs twice as often than in men. Disease onset occurs most often, in 70 percent of diagnoses, between the ages of 21 and 40 years, but anyone as young as 10 years and as old as 60 years can be diagnosed with the disease.

MS affects individuals of all ethnic backgrounds; however, MS is diagnosed more often in white populations, particularly those with Northern European ancestry, than in other ethnicities, regardless of other risk factors. Native

## Multiple Sclerosis Risk



**Source:** Map adapted from National Spinal Cord Injury Association. Accessed Oct. 16, 2014 at [www.spinalcord.org/multiple-sclerosis-on-the-map-whos-at-risk](http://www.spinalcord.org/multiple-sclerosis-on-the-map-whos-at-risk)

American and Asian populations across the globe have lower risks of MS, and diagnosis is quite rare in these groups. African Americans, though also at lower risk for development of MS, experience a more aggressive disease course when they are afflicted.

Geographic risks of MS are reflected in the epidemiologic patterns across the country. In the United States, there is a greater prevalence of multiple sclerosis in Northern states—such as Minnesota, Vermont, and Washington—than in Southern latitudes, such as Florida and Texas. This trend is also evident on a global scale: The rates of MS observed in countries such as Spain, Germany, and the United Kingdom significantly outnumber those seen in Kenya, Venezuela, or other nations with closer proximities to the equator. However, some areas of the globe appear unaffected by MS: Scandinavian and Alaskan Inuit populations experience extremely low rates of MS despite their Northern locations.

### MS DEVELOPMENT

#### Disease pathway

Although the disease is variable both in diagnosis and progression, the mechanism of MS symptom onset is quite clear.

The central nervous system, comprised of the brain, spinal cord, and optic nerve, is the only area of attack in MS development. Neural pathways within the central nervous system (CNS) are conducted within a myelin sheath, or protective covering around nerve cells, or axons. The fatty nature of the myelin sheath is responsible for the white matter's appearance. These sheaths are essential for rapid neural transmissions that allow the CNS to control all parts of our body. Without them, the nerve signals slow or stop. The widespread damage caused by MS results initially and almost entirely from the destruction of this myelin.

The earliest myelin damage in MS is thought to result from autoimmune attack in the CNS. Typically, immune cells cannot cross the blood-brain barrier but instead patrol the peripheral nervous and other organ systems throughout the body. When they are able to enter the brain they are thought to inappropriately attack the white matter there. The resulting inflammatory response at the immune cell site then damages myelin and axons.

Adding insult to injury, as the neurons lose their myelin sheath, scar tissue builds in the damaged white matter. These plaques, or lesions, can be as small as a pin or

as large as a golf ball. With continued demyelination, axons are destroyed and lose their ability to transmit information (called CNS gliosis because of the resulting scar tissue) and the cerebral cortex atrophies, causing irreversible physical and cognitive damage on top of the already-impaired functions from lesion damage.

Until recently, MS lesions were believed to occur only in the white matter myelin pathways, which could be directly linked to physical changes. Now, researchers believe that demyelination of grey matter also occurs and contributes to chronic impairments, particularly irreversible cognitive impairments of MS.

The location of an identified lesion in the white matter usually correlates well with physical changes of the disease, but the development of lesions throughout the CNS does not follow a predictable pattern of progression in individual patients or across the larger population. After diagnosis, symptoms can steadily worsen slowly or rapidly, or they can remain intermittent. Even intermittent attacks can range from mild to very debilitating.

### **MS SUBTYPES**

MS can be divided into particular subtypes according to the CNS lesion, and corresponding physical symptom, patterns. Each subtype presents with its own symptom commonalities, progression and prognosis rates, and areas of greatest impairment.

### **RELAPSING**

Most patients diagnosed with MS experience intermittent symptoms and periods of apparent health. This MS subtype, called relapsing-remitting MS, is the primary focus for research, treatment, and prevention of worsened disease. RRMS is the most common form of MS, documented in 85 percent of all diagnoses. Patients with RRMS experience the classical attack of symptoms that last days to weeks during acute inflammation in the CNS; after the attack, varying lengths of remission occur, as demyelinated lesions become inactive.

Identifying and treating patients with RRMS can be challenging because of the unpredictable symptom course. Recent research has shown, though, that CNS lesions develop in patients with RRMS even when they are in a period of so-called remission, without outward symptoms. Magnetic resonance imaging (MRI) of patients who appear to be in remission displays definite signs of inflammatory activity in the CNS. Symptoms may be not be present because the lesions are in areas of the brain that are not linked to physical movements or because the inflammation is low enough that patients do not perceive any change. In fact, clinicians estimate that only 10 percent of the active lesions in the CNS are perceived by the patients as "exacerbations," or periods of relapse.

### **PROGRESSIVE**

Patients with RRMS, without treatment, will eventually develop continually symptomatic disease, called secondary progressive MS (SPMS). Approximately 70 percent of all patients with RRMS eventually accumulate moderate disability and no longer experience times of remission; at this time, their disease is characterized as SPMS, and steady progression of disability occurs in place of acute relapses. Ongoing ambulatory impairment is especially common in SPMS and most often occurs after 10 to 30 years of living with the RRMS form.

In a small subset (15 percent) of patients with MS, progressive disease is present at diagnosis. Patients with this subtype, called primary progressive MS, or PPMS, are more likely to be diagnosed after the age of 40 years; incidence is similar in men and women. Patients with PPMS do not experience remission periods but have a slow and steady decline in function, as the CNS assault and clinical symptoms last for more than a year at a time. These patients more quickly develop chronic disability through impairment of motor functions and activities of daily living. PPMS is harder to identify on CNS imaging, because the inflammatory component appears to play a smaller role. Currently, almost no treatments exist to reduce or halt damage in patients with progressive MS.

### **CLINICALLY ISOLATED SYNDROME**

In unusual instances, a single symptom, associated with a single inflammatory event in the CNS, may mimic MS, but without a second clinical or laboratory finding to confirm diagnosis of relapsing or progressive disease. When the symptom lasts for at least 24 hours and demyelination is documented, patients may be diagnosed with clinically isolated syndrome, or CIS. Patients with CIS should be monitored closely, because they are more likely to go on later to receive a diagnosis of MS, usually in its relapsing-remitting form.

### **MS SYMPTOMS AND NATURAL COURSE**

MS symptoms are particularly challenging for patients, because they are often invisible to others. Patients can appear completely healthy while struggling with mobility, vision, and other aspects of daily tasks. Lingering effects between RRMS attacks are inconsistent and sometimes subtle.

Symptom presentation usually relates clearly to the location of the active, or developing, plaque in the CNS. In RRMS, symptoms begin over a few days and can last for only days or for as long as weeks to months. Although attacks are highly individualized, the types of symptoms that occur in early disease do follow a broad pattern of presentation that can aid diagnosis.

### **EARLY SYMPTOMS**

Initial symptoms of MS are often overlooked, because they disappear during remission. This pattern presents chal-

allenges to practitioners for diagnosis but also to patients who do not understand the ranges of symptoms that characterize MS onset.

Early symptoms that should prompt a pharmacist to encourage a patient to see a doctor are ocular symptoms and swallowing problems. Double vision, blurred vision, or pain behind the eyes can be the initial symptom that brings patients to an optometrist, ophthalmologist or primary care physician. Vision color disturbance and temporary blindness have been associated with initial MS lesions. Diagnosis may follow an ocular exam, MRI, and possibly a visual evoked potential examination. Bladder urgency and constipation may be early symptoms in young patients.

Persistent dizziness, limb or facial tingling, and muscle weakness in the hands or legs may develop. Stiffness in limb muscles can be extreme enough to affect walking or ability to stand. Half of patients with RRMS, during the natural progression of the disease, will experience ataxia. Balance and coordination are almost always impaired at some point in most patients, and clumsiness and fatigue are commonly reported symptoms.

Heat intolerance is one classic symptom of MS at any stage. Overheating also is associated with worsening of other symptoms, including vision and balance. For patients who experience heat intolerance frequently, pharmacists can recommend cooling wraps or vests for immediate relief. Pharmacists can help patients identify clothing constructed from materials that wick sweat and help the body cool itself.

## **LATER SYMPTOMS**

As relapses continue, damage accumulates and worsens the patient's overall disability even during remissions. Bowel and bladder control issues become more frequent. Neurologic effects such as dizziness, balance disruption, hearing loss, problems with speech, chewing, and swallowing are common later in the disease course. Vision changes may continue as damage to the optic nerve progresses. Uhthoff's syndrome is a sign of optic nerve demyelination in which vision begins to blur or dim when patients overheat due to weather or exercise.

Muscle weakness, tremor, and spasm may affect small or large portions of the body. Patients may report tingling and numbness in the limbs to facial pain and twitching. These contribute to problems with mobility, coordination and control of limb activity. These walking difficulties often require assistive devices and care by a physical therapist.

Fatigue remains a common and bothersome symptom during later relapsing and progressive disease forms. This subjective symptom may worsen in late afternoons and may be present regardless of other symptoms or attacks. It may worsen especially with heat or exertion. Some patients

will experience constant low-level fatigue. Sleep disturbances, particularly insomnia and restless legs syndrome also become common as the disease progresses.

Cognitive impairments are more likely in later disease and are easily missed in physical evaluations. At least half of patients experience cognitive changes that include poor concentration and memory, lack of focus, and impaired judgment. Related cognitive symptoms include poor attention, reasoning, planning, and problem solving. These effects may be minor and infrequent at first and gradually become more noticeable to the patient others. Mood changes, especially depression, are quite common and are, associated with coping difficulties or as a symptom of MS itself. Depression, whether it existed before or after MS diagnosis and diagnosed alone or with anxiety, is itself associated with increased cognitive symptoms of MS. In addition, the overall MS population carries a higher risk of suicide, such that routine screening for suicidal ideation is suggested. When patients come to the pharmacy for MS medications, informal clues about their mental status can be an important observation between follow-up with their primary care physician and neurology specialists. Details about grooming, hygiene, ease of eye contact and conversation, and appropriate dress for the weather are indicators of larger mental status concerns.

A formal mental status evaluation, however, must only be conducted with permission of the patient—or it will be considered assault. A practical option for pharmacists who note disturbed mental affect during consultation is to refer the patient tactfully to a clinician for formal evaluation. For example, a member of the pharmacy staff may remark that a patient who has long worn a close-cropped haircut and been clean-shaven seems to be growing a beard and long hair. The pharmacist might ask about the patient's change in appearance and listen for clues that he is indifferent to his appearance or has a physical barrier to usual grooming. These could be signs of depression, disease relapse or disease progression.

Patients with primary or secondary progressive disease who experience chronic mobility issues and movement disorders are most likely to require assistive devices that the pharmacy can provide. Patients can improve mobility and safety by being fitted for walkers or canes, and they can maintain independence by using a reacher, an elevated toilet seat, installing shower handles and using bath stools.

## **TRIGGERS**

Despite the variety of symptoms and pathways, all types of MS share some triggers. Many patients report increased symptoms following exposure to heat or physical activity. Fever, hot baths, and sun exposure can initiate a relapse, and patients with MS may report heat intolerance as well.

Although exercise and movement play important roles in maintaining function in patients with MS, unstructured activity and overexertion can lead to increased symptoms in some patients. Infections, with or without fever, also may increase the immune and inflammatory responses that worsen CNS damage.

The symptoms of MS do not increase mortality or reduce longevity, but they do have sometimes severe impacts on patient quality of life. The focus in identifying and caring for patients with this chronic disease must involve prevention of disability and reduction of lesions to minimize symptoms. The ability to identify triggers is an important contributor to reducing relapse, with or without medication therapy, and patient-reported outcomes are a large part of disease evaluation. Patients can more easily identify their personal triggers by keeping a log or journal that associates symptoms of relapse with recorded activities, locations, and food intake on the attack days. Personalized electronic diaries can be especially useful; these tools can track symptoms and triggers as well as medication adherence and adverse effects. Specialized electronic tools are being studied in ongoing clinical trials, but mobile applications (“apps”) are also available to patients on a variety of web-enabled devices. A summary of apps for MS clinicians and patients is available on the Healthline.com website (<http://www.healthline.com/health-slideshow/top-iphone-android-multiple-sclerosis-apps>).

## **DIAGNOSIS AND EVALUATION**

### **CLINICAL EVALUATION AND TOOLS**

Diagnosing MS as early as possible is critical to establishing care—including medication therapy—that slows disease progression. However, no single tool, test, or clinical feature is yet able to definitively diagnose the condition. Even though sclerosis that is now MS was first described in the early 1800s, diagnosis today relies almost entirely on clinical evaluation, which takes into account patient history, a thorough physical evaluation, and neurologic testing. The irregularity of attack durations and frequencies, as well as the wide range of presenting symptoms, contributes to patient confusion and diagnostic delays. For example, disabilities like gait problems or poor bladder control develop during an acute relapse but can resolve almost entirely during periods of remission, making evaluation of these disappearing symptoms at a medical appointment more difficult. Often, when symptoms are recognized as a larger problem, diagnosis occurs only after elimination of overlapping conditions, including neoplasms, myelitis, small-vessel ischemia, and other challenging diseases.

When MS is suspected on the basis of persistent symptoms without a known cause, physicians have several evaluation methods available to confirm a suspected MS diagnosis. MRI with contrast is the scan of choice to visual-

ize CNS lesions; active and past areas of inflammation appear as bright white and dark shadow areas, respectively. Contrast MRI is a safe, dye-free, and noninvasive method of visualizing MS lesions. The technique was first used in 1981 to identify plaques and, by 1988, confirmed the presence of active lesions in patients who did not exhibit symptoms. A baseline MRI at diagnosis also can be a useful comparator with later MRIs to document patient progression.

Additional tools to confirm a suspected diagnosis of MS include evoked potential and lumbar puncture testing. Evoked potentials measure the electrical response of nerves and physical movements to visual stimulation. Visual, auditory, and sensory (limb) tests are available, but only visual evoked potential (VEP) testing is considered for diagnosis because of its accuracy. In VEP testing, electrodes attached to the scalp record how fast a patient's brain responds to visual checkerboard stimuli. Demyelination of MS slows conduction and increases reaction time to those stimuli. Evoked potentials are most often used when diagnosis is suspected but symptoms—especially early visual symptoms—are too subtle to be reported by the patient.

Lumbar puncture, or spinal tap, obtains cerebrospinal fluid (CSF) that can be analyzed for indicators of inflammation, such as abnormally high levels of immunoglobulins. These spinal taps can rule out infections or other immune disorders, but they are painful and invasive. Because they lack specificity for MS also, CSF measurements are infrequently used to confirm or evaluate an MS diagnosis.

### **STANDARDIZED DIAGNOSTIC CRITERIA**

Diagnosis of MS requires dissemination of symptoms or lesions in time and space: at least two separate symptom flares (each persisting for at least 24 hours and separated by at least 30 days) and at least two different types of symptoms (reflecting different areas of CNS damage) must occur. Older criteria required at least two separate symptom flares and evidence of two separate CNS areas of attack (observed by different symptom patterns). In 2001 and 2005, the McDonald criteria incorporated MRI findings into the dissemination requires but complicated guidance. To simplify the diagnostic approach, the National MS Society Task Force in 2010 supported a revision of the McDonald criteria.

This most current guidance again requires two separate areas of damage in the CNS with symptoms separated by at least one month, but allows evidence of additional lesions on a single contrast MRI to contribute to diagnosis after the first attack. The revisions are intended to shorten the time to diagnosis and avoid treatment delays; for example, a patient with one attack but two lesions can be diagnosed with MS if an MRI shows that the lesions are disparate in space (brain location) or time (past versus active).

## DISABILITY EVALUATION

After diagnosis, symptom impact can be measured with different assessment scales, including the clinically validated Kurtzke Expanded Disability Status Scale (EDSS). The EDSS quantitatively categorizes from 0 to 10 the degree of disability experienced by MS patients. A score of 0 indicates a normal neurological exam and corresponding normal functional capabilities; a score of 10 indicates death associated with MS impairments. The EDSS reflects progression over the natural or treated course of the disease and allows health care providers to establish a symptom timeline. This scale is especially useful in quantifying the residual effects of MS damage, through evaluation during periods of remission.

## MS TREATMENT OPTIONS

### Corticosteroids

Until the 1990s, no treatments existed to stop the course of MS by slowing or preventing the occurrence of relapses. Instead, treatment was aimed exclusively at symptom control during an attack, to minimize symptoms only as they occurred. This approach primarily involved anti-inflammatory drugs, and corticosteroids were the mainstay selection for patients with RRMS flares. Corticosteroids can reduce inflammation quickly and can increase the speed of recovery time from an attack in RRMS. In patients who experience severe disease flares, though, the American Academy of Neurology recommends plasmapheresis, which quickly removes the immune cells causing the inflammatory assault, instead of traditional corticosteroid administration.

Intravenous methylprednisolone at a high bolus dose of 1,000 mg has been administered monthly for patients with primary or secondary progressive disease; however, corticosteroids generally have little effect in patients with progressive forms of MS because of the smaller inflammatory role in this disease subtype. The same bolus dose can be administered for 3-5 days at the first indication of a flare in RRMS to control symptoms before they worsen. The IV medication can be followed by an oral corticosteroid taper to avoid common adverse effects of high-dose steroid administration.

Methylprednisolone does not contribute to long-term disease control, but only briefly reduces the inflammatory response. In addition to this lack of long-term disease control, challenges of corticosteroid use include difficulty of administration and concerns about short- and long-term adverse effects. Immediate adverse effects associated with corticosteroid injections include bleeding and injection-site reactions; long-term risks of corticosteroid use included increased susceptibility to infection and higher rates of osteoporosis.

Today, methylprednisolone is less often used by physicians as monotherapy and is instead more common as adjunctive therapy in patients who experience relapse

symptoms while receiving a first-line disease-modifying therapy (DMT). This combination treatment approach may shorten the relapse duration or reduce the symptom severity. Some clinical studies have demonstrated greater efficacy of additive bolus methylprednisolone at minimizing symptoms than the maintenance regimen alone, but the true benefits remain unclear.

### Standard Disease-Modulating Therapies

In 1993, treatment for MS changed drastically, with the approval of the first agent to reduce or prevent relapse in RRMS, known as a disease-modulating or -modifying therapy (DMT). Approval of interferon (IFN) beta-1b (Betaseron) was followed closely by that of IFN beta-1a (Avonex, Rebif). IFN betas as a class minimize relapse duration, frequency, and severity by tempering the number of pro-inflammatory agents produced by the body; however, these DMTs do not cure or reverse MS.

Two of three IFN beta formulations are available as single-dose pre-filled syringes or autoinjectors for patient administration. The third is supplied as a syringe prefilled with diluent for a single-dose vial. Although they have similar names, the doses, schedules, and injection sites vary (Table 1). The standard formulations available for outpatient self-injection include IFN beta-1a 30  $\mu\text{g}$  weekly as an intramuscular injection (Avonex); IFN beta-1a 22  $\mu\text{g}$  or 44  $\mu\text{g}$  as a subcutaneous injection (Rebif); and IFN beta-1b 0.25 mg (1 mL) as a subcutaneous injection administered every other day (Betaseron). Titration options are available for all three products. Although Avonex is most often initiated at the 30- $\mu\text{g}$  weekly maintenance dose, it may also be tapered upward in 7.5- $\mu\text{g}$  increments with the AVOSTARTGRIP titration kit. Similarly, maintenance Rebif doses of 22  $\mu\text{g}$  or 44  $\mu\text{g}$  may be initiated immediately or achieved after titration; the Rebif Rebidose titration kit provides a baseline dose of 8.8  $\mu\text{g}$ , or 20 percent of the maintenance goal, for a four-week upward titration. Betaseron may be administered in increments of 0.0625 mg (0.25 mL) as a subcutaneous injection every other day, with increases every two weeks, until the target goal of 1 mL is achieved.

Unless there is evidence of leukopenia or abnormal liver function tests, dosages of IFNs do not require adjustment for hepatic or renal impairment. IFNs are in FDA pregnancy category C meaning that patients who are of reproductive age are advised to consult their physicians and together weigh the risks and benefits of using these medications. Unless pregnancy is impossible, even women who are not planning a pregnancy should have this conversation.

All three available IFN DMTs provide similar efficacy for relapse reduction compared with placebo in clinical studies, making them solid first-line options for treating RRMS. However, their injection-site administration method,

**Table 1: Standard DMTs: IFN Formulations and Glatiramer Acetate**

	<b>Interferon beta-1a (Avonex)</b>	<b>Interferon beta-1a (Rebif)</b>	<b>Interferon beta-1b (Betaseron)</b>	<b>Glatiramer Acetate (Copaxone)</b>
<b>Doses available</b>	30 µg maintenance and 7.5-µg tapers	22 µg or 44 µg maintenance and 8.8-µg tapers	250 µg maintenance and quarter-dose tapers	20 mg and 40 mg maintenance options; NOT interchangeable
<b>Administration</b>	Intramuscular injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
<b>Dosing schedules</b>	Once weekly	Three times a week, at least 48 hours apart	Three times a week, at least 48 hours apart (estimated as every other day)	Daily (20 mg) or three times a week (40 mg) according to patient preference
<b>Formulations for patient use</b>	Prefilled syringe and auto-titration prefilled kit	Prefilled syringe; Autoinjector	Single-use vial with prefilled diluent syringe	Prefilled syringes: white plunger (20 mg) and blue plunger (40 mg); must remain away from direct light and should remain refrigerated until 20 minutes before administration
<b>Common adverse effects or safety requirements</b>	Injection-site reactions, flu-like symptoms, Med Guide must be dispensed describing potential serious side effects of these medications including but not limited to: depression or suicidal ideation (particularly with Avonex); increased hepatic injury; risk to pregnancy, allergic reaction, seizure, blood problems (RBC, WBC, platelet) and exacerbated cardiovascular disease Monitor LFTs, CBC, and cardiac function at initiation and periodically during treatment (ie, at 1, 3, 6, 9, and 12 months, and every 6 months thereafter)			Injection-site reactions, urticaria and difficulty breathing, flushing and chest pain

varying dosage frequencies, and sometimes bothersome adverse effects contribute to poor adherence.

Common adverse effects of IFN therapy include myalgia, headache, and flu-like symptoms. Allergic reactions, including shock, hives, and dyspnea, are possible with IFN use. Some patients receiving Avonex experience heightened depression and suicidal ideation. Patients who receive IFN therapy, including Avonex, must receive a copy of the product's medication guide with each prescription and refill. The guide explains the best methods for administering the medication as well as the possible adverse effects that can occur with IFN use.

Avonex also has been associated with increased rates of hepatic injury and with exacerbations of cardiac symptoms in cardiovascular disease. When either INF beta-1a or beta-1b is prescribed, patients should undergo baseline and periodic (at one, three, six, nine, and 12 months) liver function tests, complete blood cell counts, and cardiac evaluations. After one year of treatment, period laboratory monitoring may be performed every six months.

Injection-site reactions account for more than 75 per-

cent of patient-reported adverse events with IFNs. Patient training for appropriate injection technique is essential before an IFN product is dispensed. Sites of injection should vary each week, and areas of the skin that are red or bruised should not be selected as injection sites. Pain, bleeding, and edema have occurred at injection sites when patients inject subcutaneous formulations into the muscle or intramuscular formulations into the fatty layers of skin. Skin tissue necrosis may occur, though rarely, with subcutaneous injections. Patients must be able to distinguish between subcutaneous and intramuscular injection sites and must rotate injection sites to minimize local adverse effects and achieve appropriate drug dosages.

Along with physical injection-site reactions, anxiety associated with self-injection is commonplace. Injection anxiety is a real barrier to patient adherence, and the National MS Society offers a patient injection anxiety tool for clinicians (along with numerous other useful tools to assist practitioners with meeting patient needs) at <http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Resources-for-You-and-Your-Practice/Re->

sources-and-Tools. The Injection Anxiety tool includes a workbook for patients and a manual for clinicians that guides the team along a six-session program to overcome this barrier to important treatments. Pharmacists may access the free tool components at the above web site or by email request at [healthprof\\_info@nmss.org](mailto:healthprof_info@nmss.org).

By 1996, the synthetic drug glatiramer acetate (GA; Copaxone) was approved to treat RRMS as an alternative to IFN therapy. Although its mechanism of action is not definitively understood, glatiramer acetate appears to minimize MS relapses through an immunomodulatory function that increases the number of suppressor T cells in the peripheral nervous system. Even though multiple sclerosis damage occurs in the central nervous system, eradication of peripheral T cells prevents T cell entry across the blood brain barrier, thus minimizing CNS debilitation. The efficacy of glatiramer acetate is considered approximately equivalent to that of IFN formulations in clinical studies, making the drug another first-line treatment option. Glatiramer acetate also may be used as a second-line therapy after an IFN, but the two types of DMTs should not be used together to treat RRMS.

Like the IFNs, glatiramer acetate is delivered only by injection, as a subcutaneous injection of either 20 mg/mL or 40 mg/mL from prefilled, single-dose syringes. The 20-mg/mL dosage has a white plunger and is injected daily; the 40-mg/mL formulation has a blue plunger and is injected three times per week. The syringe formulations cannot be interchanged and should be stored under refrigeration, between 36 degrees Fahrenheit and 46 degrees F (2 degrees Celsius and 8 degrees C), both in the pharmacy and at home; all formulations should be kept away from direct light. The syringes should reach room temperature before being injected by patients; to achieve the best temperature for injection, pharmacists should counsel patients to remove the syringe from refrigeration 20 minutes before administration. If refrigeration is not accessible, the syringes may be stored at room temperature, between 59 degrees F and 86 degrees F (15 degrees C and 30 degrees C), for a maximum of 30 days.

The maintenance doses (20 mg daily or 40 mg three times weekly) may be started immediately, or patients can gradually transition from glatiramer acetate 20 mg daily to 40 mg three times weekly. The transition option may be preferable when patients want to manage symptoms and minimize side effects on a lower strength before moving to a more convenient dosing schedule. It is important to note again that the 20-mg and 40-mg doses are not interchangeable, and that 20-mg syringes should not be used on the three-times-a-week schedule. Dosing adjustments for patients with renal or hepatic function impairments are not required, and pregnancy and nursing are not contraindications for use (FDA category B). However, it is unclear

whether glatiramer acetate crosses the placenta or is excreted in breast milk. For this reason, it is best for pregnant or lactating patients to weigh the risks and benefits of use with the help of their physicians.

Like the IFNs, glatiramer acetate requires patient instruction for injectable use and is associated with injection-related adverse effects and anxiety. Rotation of injection sites at least once weekly reduces the risk of developing pain, redness, and swelling. Irreversible lipatrophy and skin necrosis are rare but potential adverse injection-site reactions.

Some common adverse effects of glatiramer acetate are chest pain and flushing; urticaria and difficulty breathing also may occur. These symptoms can begin at any time during treatment but are most likely to occur at least one month after starting the medication. These symptoms typically resolve within 15 minutes, and they warrant professional medical attention if they persist for several weeks.

The decision to initiate therapy with an IFN versus with glatiramer acetate is individualized and involves an assessment of patient preferences about dosing frequencies, adverse effect risks, hepatic function, and concomitant drug therapies.

## **NEW TREATMENT OPTIONS MONOCLONAL ANTIBODIES**

Only in the 2000s did new drug approvals on MS treatments expand into monoclonal antibodies and other disease-modulating approaches. New additions to the MS arsenal include Tysabri, Gilenya, Aubagio, and more.

Monoclonal antibodies act against MS by modulating, or changing the actions, of the immune system. The first approved agent, natalizumab (Tysabri), works by minimizing immune cell movement across the blood brain barrier, thus blocking cell entry into the CNS. It is administered by IV injection monthly. Its efficacy is very high: the annualized relapse rate over 1-2 years is 68 percent, and natalizumab carries a significantly reduced risk of progression compared with IFN beta-1a at two years. It also reduces enhanced lesions on MRI by 92 percent, and it significantly increases quality of life as measured by the SF-36 survey, which evaluates health outcomes from a patient quality-of-life perspective. Natalizumab is indicated for patients who do not respond to IFN or glatiramer acetate. It remains second-line because of its risk for progressive multifocal leukoencephalopathy (PML), a sometimes fatal viral infection in the CNS. Symptoms of PML are similar to those of MS but do not remit; patients who receive natalizumab for more than two years are at greatest risk, as are those who have had prior immunosuppressive therapy. Other adverse effects are mild and infrequent; hypersensitivity is possible.

Recently, natalizumab has been considered as a stronger treatment option in patients with severe MS or with

refractory disease, particularly when the patient is negative for the JC virus antibody. Patients may be tested for JC virus before the drug is considered; patients with antibodies against JC virus have been infected with the virus in the past and therefore are at greater risk of developing PML with treatment.

Newer monoclonal antibodies in clinical trials for the treatment of MS are daclizumab (Zenapax) and alemtuzumab (Lemtrada). Alemtuzumab targets CD52 on B and T cells, and it was approved in 2013 in the EU and Canada but did not receive FDA approval for use in the United States. In some studies, alemtuzumab led to significantly lower numbers of lesions, whether new or enlarged, compared with IFN beta-1a and had less brain volume reduction after two years. Accumulated disability also was significantly reduced, and alemtuzumab appeared more effective than IFN beta-1a at reducing relapse rates in some clinical trials.

However, alemtuzumab is associated with serious infections, occurring in two-thirds of all treated patients, and with a high rate of infusion-related reactions, in which 90 percent of treated patients experience headache, rash, nausea, and fever; and additional serious adverse events. Immune thrombocytopenia occurred in 3 percent of patients, thyroid changes occur in nearly one-third of patients in studies, and possible delayed secondary autoimmune events have been noted.

Daclizumab is an anti-CD25 antibody that blocks CD25 expression on T cells to reduce inflammation. In clinical studies, daclizumab reduces relapse rate, MRI disease activity, and disability compared with placebo or with IFN beta treatment. In trials, daclizumab is being administered by subcutaneous injection once every four weeks. In patients who are refractory to IFN treatments, daclizumab has displayed improvements in EDSS scores and >75 percent reduction in the number of lesions. Monthly doses also are being studied in patients with secondary progressive disease, though results remain unclear. Daclizumab and other investigational monoclonal antibody agents, such as ocrelizumab, are promising future treatments for MS, but their approval and patient population base could be limited by their adverse effect profiles. For example, studies of ocrelizumab in patients with lupus or rheumatoid arthritis have been discontinued because of the severe adverse effect profile noted with its use, particularly the opportunistic infection rates.

## **ORAL DISEASE-MODIFYING THERAPY**

In 2010, oral DMTs were introduced; these agents may increase adherence to and ease of chronic medication dosing in patients with RRMS.

Fingolimod (Gilenya), approved in 2010, is the first oral treatment for RRMS. It is a sphingosine-1-p receptor modula-

tor that blocks autoimmune activity by inhibiting white blood cells from leaving the lymph, entering the circulation, and crossing the blood brain barrier. Fingolimod has been dosed at 0.5 mg, or 1.25 mg daily by mouth in phase 3 studies. At these doses, fingolimod reduces the annualized relapse rate approximately 60 percent versus placebo and improves MRI results, and it significantly reduces the annualized relapse rate at one year compared with IFN beta-1a treatment. Only the 0.5-mg dosage is approved in the United States.

Although most adverse effects of fingolimod are well tolerated, some screening and observation are required with administration. Mild side effects include headache, flu, dyspnea, nausea, and diarrhea. Lowered heart rate is possible within one hour after a dose; this effect is dose proportional and can result in clinical bradycardia or AV block. Patients should be observed at the infusion site for six hours after dosing. In addition, risk of infection is higher with fingolimod use because of its reductive effect on white blood cell entry into the circulation. In studies, two fatal cases of herpes infections (herpes zoster and herpes simplex encephalitis) occurred. In one death, the patient had a history of varicella zoster virus, resulting in a recommendation that patients should be screened for prior varicella zoster virus infection and receive a varicella zoster vaccination before first using fingolimod. Fingolimod might be linked to tumor activity, possible PML, and partial exacerbation of MS symptoms after use ends.

Additionally, the drug is pregnancy category C because animal studies show risk to fetus though there is no documented harm to human fetus. Patients who are considering fingolimod must stop taking the drug before any conception occurs. A large subpopulation of patients with MS is contraindicated for fingolimod use as well: patients with recent (six months) MI, TIA, angina, stroke, or heart failure, those on antiarrhythmia drugs, and possibly patients with T2DM all should not receive Gilenya therapy. Because of these serious adverse effect restrictions and contraindications, Gilenya should be reserved for a last-line treatment option. Patients who do receive fingolimod must undergo a baseline ECG, LFTs, CBC, eye exam, skin exam, and vaccination history.

Teriflunomide (Aubagio), approved in 2012 for RRMS at doses of 7-14 mg, inhibits peripheral B and T cells that lead to inflammation and reduces the movement of those cells into the CNS. Teriflunomide is administered by mouth once daily. It significantly reduces the annualized relapse rate and delays disability and improves MRI scans in patients compared with placebo at either dose, and it works well in patients who have received prior DMTs or who are treatment naïve. Teriflunomide also provides significant benefits as an add-on therapy compared with standard DMT monotherapy. Adverse effects include nausea, diarrhea, increased ALTs, and hair thinning. There

is a boxed warning describing hepatotoxicity and teratogenicity. Patients should undergo a baseline and monthly (for six months) LFT evaluation. Teriflunomide is in pregnancy category X and also appears in semen. Teriflunomide may last in a woman's serum for two years after the last dose; pregnancy should not be considered until serum levels in men or women reach  $<0.02$  mg/L. An accelerated elimination regimen, which involves cholestyramine and activated charcoal therapies, is provided by the manufacturer of Aubagio for patients who wish to conceive safely. Details on the elimination regimen are available for download at <http://www.aubagio.com>.

Laquinimod, a highly bioavailable oral DMT being studied in clinical trials for RRMS, offers possible neuroprotective effects and modulates proinflammatory immune responses. Despite its favorable pharmacokinetic profile, its efficacy remains modest at doses of 0.1, 0.3, or 0.6 mg/d. In clinical studies, only 0.6 mg/d was effective at reducing lesions and the annualized relapse rate. In addition, its adverse effects are challenging and include headache, respiratory infections, increased LFTs, asthenia, dizziness, cough, musculoskeletal pain, and nausea/vomiting, and diarrhea.

Additional agents with varying places in the course of treatment include dimethyl fumarate (DMF, also known as BG-12), mitoxantrone, pegylated INF beta-1a, and dalfampridine.

DMF has been explored for decades worldwide as a treatment for another autoimmune condition, psoriasis. In MS, DMF possibly acts by blocking inflammatory cell movement into the CNS by blocking white blood cells at receptor sites. DMF (Tecfidera) was approved by FDA in 2013 for the treatment of RRMS. DMF capsules taken twice daily are considered a first-line therapy alternative. Its efficacy is comparable to other DMTs, and DMF is especially effective at improving motor functioning. DMF also significantly increases quality of life and well being, as measured by the SF-36 survey. Overall, efficacy was significantly better than placebo at two years in clinical trials. Significant MRI improvement versus placebo have been observed with high doses, but relapse rate improvements were not always significant. Differences in benefits were not significant compared with glatiramer acetate.

DMF dosage recommendation is an initiation with seven days of 120 mg twice daily, then increased to 240 mg twice daily after seven days. Adverse effects associated with DMF are generally mild, such as flushing, pruritus, proteinuria, and gastrointestinal discomfort. Flushing may be reduced by taking each dose with food. White blood cell counts can decrease during DMF use, so CBC should be measured at baseline and every six months to one year, or as needed more often. PML has been observed in a patient taking DMF for psoriasis; patients with MS should be observed closely during DMF treatment, especially if lymphopenia occurs.

Dalfampridine (Ampyra), approved in 2010, is an aminopyridine that fills a useful role in patients with advanced RRMS or progressive disease: it is approved specifically to improve walking function and physical mobility in MS. Dalfampridine improves conduction of nerve signals in patients who experience ataxia. In clinical trials, after receiving dalfampridine, patients experienced significantly increased walking speed and leg strength compared with patients who received placebo. Dalfampridine oral tablets are taken twice daily approximately 12 hours apart. Tablets should be swallowed whole and patients should not double up or take extra doses if a dose is missed. Dalfampridine should be avoided in patients who have a history of seizure activity or who have impaired kidney function defined as creatinine clearance of less than 50 mL/min

### **OTHER PARENTERAL DRUGS**

Mitoxantrone (Novantrone) is used for patients with RRMS. It is also the only agent also indicated for patients with progressive disease. Mitoxantrone is administered by intravenous infusion over 5-15 minutes over three months. It is considered a last resort that is used for patients with rapid loss of function from the disease, because of its limited benefits and its black-box cardiotoxicity profile; it should not be used first line, even for patients with progressive or severe disease. Patients who are most likely to respond are those younger than 50 years old and without longstanding disability. Cardiac evaluation (such as left ventricular ejection fraction [LVEF] measurement) is recommended before administration and periodically if symptoms of congestive heart failure develop. Patients with LVEFs  $<50$  percent or who reach a lifetime dose of 140 mg/m<sup>2</sup> should not receive mitoxantrone.

The newest addition to the MS treatment arsenal, approved in Europe and in the United States in August 2014, is Plegridy, or peginterferon beta-1a. Pegylation of this IFN agent results in a longer half-life and less frequent injections. This formulation is administered subcutaneously in a 0.5-mL autoinjector pen and is dosed every two weeks. Its safety is well established, and its efficacy versus placebo at reducing relapse rate and EDSS disability is likewise well documented in clinical trial data.

Pharmacists may be approached by patients with MS about off-label or investigational treatment options, or about nondrug therapies. For example, drugs in the statin anti-hypercholesterolemia drug class have been considered off label for nerve protection in MS. Statins carry immunomodulating properties but also may be pro-inflammatory. When statins have been studied in MS, most evaluations showed no prevention of myelin sheath degeneration or plaque development and only minimal effects on brain shrinkage. Any consideration of these treatments should be discouraged. Likewise, no compelling efficacy

evidence from symptom measures or MRI scans supports the use of IVIG to treat any type of MS.

### SELECTING TREATMENT REGIMENS

Today's DMT options are numerous and include the IFNs, GA, fingolimod, DMF, teriflunomide, and mitoxantrone; these are supplemented by the monoclonal antibodies and emerging therapies. DMTs have been a treatment mainstay for more than 20 years, because they reduce inflammation and regulate immune cells. After all of this time, though, there still are no consensus guidelines for starting or revising treatments, or for selecting the optimal starting course in a given patient.

DMTs are most effective in early RRMS. Traditionally, patients with MS who had little to no symptoms could logically opt to delay treatment. Because more recent research into brain lesions shows that CNS damage occurs even without outward symptoms, the argument exists to support early treatment in all diagnosed patients. The need to start treatment early must be individually balanced with the considerations of adverse effects, adherence rates associated with longer time on medications, and durability of an effective response. DMTs work best before disease progresses even to moderate disability, which can be irreversible if it remains untreated. Even patients with mild disease, when untreated, become disabled within 10 to 20 years. Today's approach is to evaluate patients after a first attack and then search the CNS for lesions on a contrast MRI. Treatment should be considered even if the first attack was potentially representative of clinically isolated syndrome. Patients should be re-evaluated at least every 6-12 months.

Treatment should be selected on the basis of the adverse effect profile, the administration route, and patient antibody profiles. Avonex or Copaxone are still considered the best first-line options in 2014 summary recomTable 2: Initial Doses for First Line Disease-Modifying Therapies access- through UptoDate (<http://www.uptodate.com/contents/treatment-of-relapsing-remitting-multiple-sclerosis-in-adults#H35>). Initial therapy should be continued until the adverse effects become intolerable to the patient or until the disease fails to respond to therapy. Treatment adjustment for nonresponsive disease then can involve adjunct methylprednisolone or treatment switch to natalizumab or another second-line agent. Early and sustained treatment slows the disease course and maintains higher quality of life. However, clear reasons to delay or interrupt treatment do exist, and nondrug treatment options are available in addition to medications.

### SPECIAL CONSIDERATIONS

In a condition that persistently impairs physical and cognitive function without shortening life expectancy,

**Table 2: Initial Doses for First Line Disease-Modifying Therapies**

- IFN beta-1a 30 mcg IM weekly
- IFN beta-1a 22 mcg or 44 mcg SQ three times weekly
- IFN beta-1b 0.25 mg/1 mL SQ every other day
- GA 20 mg SQ daily
- DMF 120 mg twice daily delayed release capsule for 1 week, then 240 mg twice daily by mouth
- Teriflunomide 7 mg or 14 mg tablet once daily by mouth

maintaining a high quality of life is especially important to the patient. When prescription treatments cause undue adverse effects, are not adhered to during remission periods of apparent health, or must be avoided when risks outweigh benefits, pharmacists can guide patients through multiple nondrug options and behavioral modifications that minimize the impact of MS on daily living. Likewise, adding these quality-of-life efforts can improve patient functioning even while they receive prescription therapy.

Many clinical or personal situations may warrant treatment delay or interruption, either because risks for severe side effects outweigh potential benefits or because of patient preference or adherence concerns. For example, patients who wish to conceive, patients with early-stage MS who experience relapses infrequently and have few apparent symptoms, patients wary of any risk for side effects, and patients who are not willing to administer self-injections may present cases where treatment delay or interruption should be discussed with the patient.

Patients being treated for neuropsychiatric conditions might elect to avoid treatment with corticosteroids, because these drugs can aggravate mood, energy, and sleep levels. However, mitoxantrone, glatiramer acetate, and the IFNs have not been associated with altered affect or sleep disturbances, though the IFN products have medication guides that describe the specific risks for suicidal ideation.

Women with MS who are asymptomatic in early disease and are of childbearing age may consider delaying therapy. DMTs in general are not approved for use in pregnancy and are not recommended during nursing. Similarly, women with MS who are stable on a first-line drug may elect to interrupt treatment for a pregnancy. The natural progression of MS during pregnancy may factor into this decision: relapses are less frequent during trimesters 2 and 3, possibly because of increased maternal levels of immunosuppressants and corticosteroid levels. Pharmacists can counsel women that fertility is not altered by MS, that anesthesia during delivery is considered safe, and that rebound increases in relapse are possible after delivery, when natural corticosteroid production decreases. During pregnancy, pharmacists can reinforce safety in women with MS, who may experience aggravation of bladder problems and fatigue and who may require assistive devices to

maintain mobility when balance and gait are affected by changing centers of gravity. Women who do experience acute relapses during pregnancy or nursing may safely receive methylprednisolone/prednisone treatment. Registries are available for physicians to report use of off-label DMTs and any associated fetal outcomes. Open registries include hotlines for Aubagio (1-800-745-4447, option 2), Gilenya (1-877-598-7237), and Tecfidera (1-800-456-2255).

Pharmacists should encourage patients without clinical reasons to avoid treatment to begin a first-line agent without delay after diagnosis, in most instances, because research shows that lesions are developing even when symptoms are not apparent. The importance of adherence to the injection schedule even during periods of remission should be emphasized as early as possible in these treatment decisions.

### COPING SKILLS

Many patient advocacy organizations exist for MS to encourage primary research into disease mechanisms and treatments as well as to provide patients with answers about how to live well with the disease. The MS Association of America (<http://www.mymsaa.org/>) offers videos, brochures, and even children's books that explain MS to patients and family. Their blog, MS Conversations, makes the history of and new research into MS accessible and understandable for patients and supporters.

In 1946, the National MS Society was established as a reputable source of information about coping with the disease. In addition to supporting standardized diagnostic criteria, the Society encourages the use of health journals and the involvement of a team of caregivers, including friends, family, and health care providers, to help the patient maintain independence and functionality. Nondrug

therapy incorporates a range of health providers: speech therapists, occupational and physical therapists, ophthalmologists, and more.

The National MS Society also offers a navigator for patients, with a toll-free hotline, to connect people with a new MS diagnosis with a range of local practitioners to develop well-rounded, multifactorial treatment planning. Unfortunately, pharmacists are not listed in their collection of providers; however, pharmacists who are approached by patients with MS at the counseling window should actively involve themselves in the entirety of patient care and recommend the navigator when patients are in need of non-pharmaceutical care. Pharmacists can contribute beyond medication management by providing assistive devices, such as walkers, canes, and bath bars, to fit patient needs. They also can encourage routine and manageable exercise levels and avoidance of triggers as well as recommend adaptations at home that can reduce falls and encourage support groups for their patients.

Stress relief is particularly important to well being and avoidance of relapse that patients attempt many different approaches to relieve anxiety. Acupuncture, exercise, and specialty diets are just a few examples of these efforts. Acupuncture was evaluated in 1997 by the NIH for many symptoms commonly experienced by patients with MS (such as urinary control, depression, dizziness, pain, headache, and anxiety)—but not for MS itself. It is unclear whether acupuncture has an effect on the immune system contribution to MS disease progression.

Moderate levels of exercise have recognized physical and psychological benefits in MS. However, over-exertion can trigger symptom attacks, so patients should consult a physical or exercise therapist to determine their most appropriate exercise levels and durations.

Dietary changes are not recommended for patients

**Table 3: Pregnancy Risk Category of Drugs Indicated for Multiple Sclerosis**

Pregnancy Category A	Pregnancy Category B	Pregnancy Category C	Pregnancy Category D	Pregnancy Category X
	Glatiramer acetate (Copaxone)	Dimethyl Fumarate (Tecfidera) Interferon beta-1b (Betaseron) Interferon beta-1a (Avonex) Interferon beta-1a (Rebif) peginterferon beta-1a (Plegridy) natalizumab (Tysabri) dalfampridine (Ampyra) alemtuzumab (Campath) Fingolimod (Gilenya)	Mitoxantrone (Novantrone)	Teriflunomide (Aubagio)

with MS without oversight by a nutritionist or other health care provider. A well-balanced diet is essential for overall health and provides enough nutrients for patients with MS. Many people with the disease try to delay relapse by changing their diets or adding nutritional supplements. The Swank diet comprises lower daily saturated fat levels and higher polyunsaturated fat levels than typical diets; supplements like vitamin B12 and magnesium are used by some patients to reduce muscular symptoms of MS.

### COMPLEMENTARY MEDICINE

Like diet and nutritional supplements, complementary medicine products aim to minimize disease effects without prescription therapy. Patients with any disorder may turn to complementary and alternative medicine (CAM) because they believe these treatments are more natural or safer than prescription therapies. Many CAM options are effective, but many others use impure products or carry unsafe side effects. Pharmacists must relate to patients the balance of safety and usefulness of CAM, especially in a condition that is as chronic and progressive as MS.

In 2013, American Academy of Neurology assessed the efficacy of many CAM products for MS symptoms, including ginkgo biloba, omega-3 fatty acid supplementation to a low-fat diet, lofepramine with phenylalanine and vitamin B12 (also known as the Cari Loder regimen), bee venom therapy, and cannabinoids.

Ginkgo biloba 120 mg taken twice a day was considered possibly effective for the reduction of fatigue but not effective for improving cognition. It did not cause excessive bleeding or any other significant adverse effects in patients with MS.

Omega-3 fatty acids found in fish oil or olive oil, when added to a low-fat diet, did not reduce symptoms, and the safety of this therapy was not reported. Similar conclusions were reached for lofepramine, an oral tricyclic antidepressant available throughout Europe and the United Kingdom, combined with phenylalanine and vitamin B12 as well as for bee venom therapy. If patients ask about bee venom therapy, pharmacists should counsel on the possibility of dangerous anaphylactic reactions associated with unknown (or known) allergy to bees.

The efficacy and safety of cannabinoids were reviewed by the academy on the basis of 11 studies. The safety and efficacy of smoked cannabinoids could not be established. However, oral formulations, such as cannabinoid extract and synthetic THC, were effective at reducing spasticity and pain for up to one year. An oromucosal spray formulation was classified as probably effective for reducing spasticity for up to six weeks and discomfort for up to 10 weeks. Regarding safety, the academy noted that cannabinoids can cause neurological problems, including disorientation; and gastrointestinal upset, such as nausea and vomiting.

Cardiovascular and hematological changes, though rare, may develop.

### CONCLUSION

Both relapsing-remitting and progressive MS challenge patients to maintain adherence to demanding, and sometimes ineffective, medications and to build ongoing self-care awareness for multiple decades while avoiding serious adverse effects and improving quality of life. Pharmacist guidance on drug interactions, emerging treatment options for all subtypes, and effective complementary and alternative medications substantially reduces symptoms and maintains independence for outpatients with this chronic condition. ■

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**Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at [chris.linville@ncpanet.org](mailto:chris.linville@ncpanet.org).**

## Continuing Education Quiz

Select the correct answer.

1. Pharmacists are already an integral part of the MS patient's health care provider team and MS Navigator resources.
  - a. True
  - b. False
  
2. Which of the following are already identified as possible causes of MS?
  - a. Puberty (age >15 years)
  - b. Alcohol use (>3 times weekly)
  - c. Genetic predisposition
  - d. History of *S. pneumoniae* infection
  
3. Smoking is associated with which of these MS endpoints?
  - a. Increased number of attacks
  - b. Increased severity of attacks
  - c. Faster rates of MS progression
  - d. Two of the above
  - e. All of the above
  
4. O.R.W., a 38-year-old African-American and a regular patient at your Georgia pharmacy, asks about risks of MS and places to live. He is moving to Maine and has a history of the disease on his maternal side. What facts can you share about his particular risks?
  - a. His risk will be increased because of the new northern latitude.
  - b. He should begin vitamin D immediately to reduce his risk.
  - c. He has a lower risk of developing MS than people with the same genetic history but Asian or Native American ethnic backgrounds.
  - d. His risk drops to almost nothing when he turns 41 years of age.
  
5. MS pathogenesis revolves around
  - a. Myelin damage by immune cells in the peripheral nervous system
  - b. Immune and inflammatory cell entry across a blood-brain barrier breach
  - c. Axon damage that is always temporary
  - d. plaques in the CNS that are at least 4.5 cm diameter, roughly the size of a golf ball
  
6. Key features of RRMS include
  - a. Flares, or attacks, that can last up to 24 hours
  - b. Symptoms that are clearly reversible after flares end
  - c. Active CNS inflammatory lesions during flares and past lesions associated with prior flares
  - d. Active lesions that are always perceived by the patient as physical symptoms
  
7. Your 25-year-old patient, G.M., was recently diagnosed with RRMS. She worries about her risk of progression and fears using a wheelchair for the rest of her life. What statistics about the disease can you share to better inform her about her prognosis?
  - a. Only 30 percent of patients with RRMS convert to progressive disease.
  - b. Disability is rarely in ambulatory form.
  - c. Conversion to progressive disease most often occurs after 10 to 30 years of living with RRMS.
  - d. Many treatments exist for progressive disease, so a wheelchair is unlikely in her future.
  
8. G.M. is reassured but wants to know more about what symptoms she will experience in early disease. She has opted to wait to start disease modifying therapy because her diagnosis was made on the basis of dizziness and correlating MRI results. She received reading material and a follow-up appointment date in eight weeks. What symptoms do you describe to G.M. to watch for until her next appointment?
  - a. Ocular symptoms, including blurring, double vision, pain, and color changes
  - b. Fatigue, which patients report as symptoms but clinicians do not consider serious enough to monitor
  - c. Heat sensitivity, which is more likely to develop after at least 10 years of living with MS
  - d. Cognitive symptoms similar to Alzheimer's disease, which can require full-time nursing assistance
  
9. Because symptoms are so variable, and because G.M. does not have another appointment soon, what are some behavioral techniques that you can suggest to improve her quality of life now?
  - a. Daily diary use to note triggers and extent of symptoms
  - b. Moderate exercise as often as possible without overdoing it
  - c. Share information about MS—especially invisible symptoms—with friends and family for support
  - d. All of the above

- 10.** You also warn G.M. to especially note triggers such as \_\_\_\_\_ because it may worsen CNS damage
- Tanning booth use
  - Snowy or icy weather
  - Using a personal trainer for >one hour/day
  - Viral infection with or without fever
- 11.** The latest diagnostic criteria
- Recommend a single, gold standard test to identify MS quickly
  - Were updated in 2014
  - Guide diagnosis according to symptom dissemination across time and space
  - Are called the revised Fowler criteria
- 12.** After four months, G.M. begins disease-modifying therapy. Which pair of DMT agent and instructions is accurate?
- Rebif 44  $\mu\text{g}$ ; inject subcutaneously using the needle provided in the autoinjector or prefilled syringe three times a week.
  - Copaxone 40 mg; remove prefilled syringe from refrigeration and immediately inject subcutaneously, once weekly.
  - Copaxone 20 mg; remove prefilled syringe from refrigeration and immediately inject subcutaneously, three times per week.
  - Betaseron 250  $\mu\text{g}$ ; reconstitute and inject 5 mL daily into the upper-outer arm.
- 13.** Glatiramer acetate has which of the following?
- Greater efficacy than interferon beta-1b on all MS evaluation measures
  - A long period of titration to avoid side effects
  - An oral alternative formulation
  - No liver function testing requirements
- 14.** Mitoxantrone offers which of the following?
- The only approved treatment option for progressive disease
  - The best option for patients older than 50 years of age
  - No cardiac risks
  - A first-line alternative when injection anxiety is high
- 15.** Oral options for G.M. to consider when her injectable disease-modifying therapy begins to lose efficacy or adverse effects become intolerable are
- Fingolimod 14 mg by mouth daily
  - Teriflunomide 14 mg by mouth daily
  - Dalfampridine 150 mg by mouth twice daily
  - Plegridy 125 mg by mouth daily
- 16.** Which of the following is FALSE regarding disease-modifying therapy with dimethyl fumarate?
- Starting dose is 120 mg twice daily, then maintenance dose 240 mg twice daily.
  - DMF is the only disease-modifying therapy in pregnancy class B.
  - DMF may lower white blood cell count.
  - Flushing caused by DMF is common and may decrease over time.
  - None of the above are false.
- 17.** Adverse effects associated with monoclonal antibody treatments include
- PML with natalizumab and possibly with DMF
  - PML with all monoclonal antibody formulations
  - PML regardless of JC virus antibody status
  - broad opportunistic infections
- 18.** A literature review of 11 studies on the use of cannabinoids shows that they
- Can cause disorientation and GI upset
  - Are commercially available as sublingual drop formulations
  - Are clearly effective for treating CNS damage caused by MS
  - Are clearly safe for use in patients with MS
- 19.** A repeat visitor to your pharmacy approaches you with a question about using ginkgo supplements to treat her relapsing-remitting MS (RRMS). What can you advise about ginkgo for her?
- Ginkgo biloba has been associated with excessive bleeding when studied in patients with MS.
  - Ginkgo supplements are considered very safe in patients with MS.
  - Ginkgo is effective at reducing fatigue and improving cognition in patients with RRMS.
  - Ginkgo biloba might reduce fatigue in some patients with MS at doses of 120 mg twice daily.
- 20.** Assistive devices offered by pharmacists to improve quality of life and safety in patients with MS include
- Heating vests
  - Compression stockings
  - Reading glasses
  - None of the above