Current and emerging therapies in the management of multiple sclerosis
American Pharmacists Association

Overview of multiple sclerosis
Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS). MS causes a variety of symptoms that can affect functional ability and quality of life considerably. Affecting approximately 400,000 people in the United States, with 200 new cases diagnosed weekly, MS is the leading cause of nontraumatic neurologic disability in young adults. MS typically presents between age 20 and 50 years, is two to three times more common in women than men, and is nearly two times more common in whites than blacks.

Pathogenesis
MS is characterized by destruction of the myelin on neurons (demyelination) and subsequent damage to the underlying axon (Figure 1). Activated T-cells and other immune cells cross the blood–brain barrier into the CNS and attack the myelin sheath on the axons. Resulting inflammation deteriorates the myelin, which slows or interrupts the conduction of nerve impulses along the axons. When acute inflammation decreases, symptoms abate partially or completely. However, demyelination can leave the underlying axon exposed and susceptible to damage. Axon loss is believed to be the major cause of permanent disability in MS.

Etiology
The exact cause of MS is unknown, although its proposed etiologies may include a combination of several factors such as genetic predisposition (i.e., upregulated immune system) and environmental factors (e.g., previous viral infections). Behavioral factors that also may increase susceptibility to MS include smoking and excess body weight. More research is needed to better understand the importance of these factors in development and progression of MS.

Learning objectives
At the conclusion of this knowledge-based activity, the pharmacist will be able to:
- Describe advances in the understanding of the pathophysiology, etiology, diagnosis, clinical presentation, and disease course of multiple sclerosis (MS).
- Review the current clinical management of MS including long-term efficacy and safety of disease-modifying therapies.
- Discuss new and emerging therapies for MS.
- Describe opportunities for the pharmacist to advance patient care of MS through adherence, managing adverse events, collaborating with health care providers in therapeutic selection, and assisting patients with medication administration.

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Pretest

1. Conduction of nerve impulses is impaired in multiple sclerosis (MS) as a result of:
   a. Destruction of myelin and the underlying axon.
   b. Depletion of dopamine and serotonin.
   c. Damage to sodium/potassium pumps.
   d. Dysfunctional receptors on dendrites.

2. After long-term (>15 years) treatment of relapsing-remitting MS with glatiramer acetate:
   a. Efficacy generally wears off.
   b. A majority of patients progress to secondary-progressive MS.
   c. More than 80% continue to walk without assistive devices.
   d. More than three-quarters of patients show progression on the expanded disability severity scale.

3. A recommended strategy to ameliorate the flulike symptoms of interferon (IFN) is to:
   a. Stop IFN for 3 months (“drug holiday”).
   b. Take analgesics at the time of injection or within an hour.
   c. Administer IFN cold, right from the refrigerator.
   d. Permanently cut the IFN dose by one-half.

Clinical subtypes of MS

MS may be categorized into the following four subtypes:

- **Relapsing-remitting MS (RRMS):** RRMS is the most common initial phase, occurring in approximately 85% of patients at diagnosis. It is characterized by acute episodes of neurologic decline, called “attacks,” followed by full or partial recovery with little or no disease progression. This phase can last for years or decades.

- **Secondary-progressive MS (SPMS):** Many patients with RRMS transition to SPMS, which is characterized by slow and steady irreversible neurologic dysfunction that occurs with or without attacks.

- **Primary-progressive MS (PPMS):** Approximately 10% of patients are initially diagnosed with PPMS, which is characterized by continuous neurologic decline from disease onset without distinct attacks.

- **Progressive-relapsing MS (PRMS):** PRMS is rare, occurring in 5% of patients. PRMS is similar to PPMS in that neurologic decline is steady from disease onset; however, occasional distinct attacks may occur.

In addition, it is widely recognized that some MS patients have a mild disease course with little to no accumulation of disability over time (“benign MS”); however, little consensus exists regarding how to identify such patients in the early years after diagnosis.

Initial presentation of MS

The first symptomatic attack consistent with MS is known as clinically isolated syndrome (CIS). CIS can present as a single symptom, such as optic neuritis (inflammation of the optic nerve), or multiple symptoms depending on the number and location of CNS lesions. Approximately 60% to 80% of patients with CIS who have demyelinating lesions on magnetic resonance imaging (MRI) are ultimately diagnosed with clinically definite MS (CDMS). Of important note, 20% of patients with CIS who have normal MRI scans also develop CDMS. Diagnosis of CIS is important so that treatment can be started to delay progression to CDMS.
Assess your knowledge
Take a moment to assess your current knowledge by reviewing the case study and answering the following questions. The case study is continued below, and answers to case study questions appear later in the article.

T.G., a 17-year-old white girl who lives in Boston, presents with blurred vision in her right eye. MRI is normal. Family history is noteworthy for an aunt who has MS. After further evaluation, T.G. is diagnosed with optic neuritis and CIS.

1. Why was she given a diagnosis of CIS rather than MS?
2. Should this patient receive a disease-modifying therapy at this time, and if so, which one would you recommend?

Because first symptoms of MS (Table 1) are often mild and self-limiting, many patients may not understand why treatment is necessary. Pharmacists can play an active role in educating patients about the importance of early initiation of treatment with disease-modifying therapies (DMTs).

Diagnosis of MS
The McDonald criteria, the standard for diagnosing MS, requires dissemination of lesions in both space and time, demonstrated through the use of clinical and MRI findings. Dissemination in space can be established with at least two T2 lesions in separate areas of the CNS on MRI, and dissemination in time can be demonstrated with a new T2 or gadolinium-enhancing lesion on follow-up MRI at any time after baseline MRI. However, if MRI at the time of a first attack shows asymptomatic gadolinium-enhancing and nonenhancing lesions simultaneously, dissemination in time can be based on this finding alone, without a follow-up MRI.

Current agents for management of MS
Seven DMTs are approved by FDA for treatment of RRMS: subcutaneous and intramuscular interferon (IFN)β-1a, subcutaneous IFNβ-1b (available in two brands of the same formulation), glatiramer acetate, fingolimod, and natalizumab. IFNβ and glatiramer acetate have long been used as first-line DMTs. Fingolimod, the first oral MS DMT, may be considered first or second line for relapsing patients, taking into consideration its concerns.

IFNβ
IFNβ has antiviral, antiproliferative, and immunomodulatory activity. Available IFNβ formulations include IFNβ-1a 30 µg i.m. once weekly, IFNβ-1a 22 or 44 µg s.c. three times weekly, and IFNβ-1b 250 µg s.c. every other day. All IFNβ agents are indicated for treatment of RRMS to reduce the frequency of relapse and, with the exception of subcutaneous IFNβ-1a, also are approved for treatment of CIS.

Pivotal trials of all IFNβ DMTs in RRMS have demonstrated clinical efficacy in lowering relapse rates, reducing number of lesions, and reducing disease burden on MRI. In addition, these drugs delay the progression of physical disability, which is measured by the Krutzke expanded disability severity scale (EDSS). The EDSS scoring system is used primarily in clinical trials to assess extent of physical disability on a scale from 0 (normal neurologic examination) to 10 (death caused by MS). Table 2 summarizes important data from these trials.

Long-term efficacy of IFNβ DMTs. The 2-year PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis; described in Table 2) continued for another 4 years, with placebo patients randomized to active treatment. Continuing clinical and MRI benefits were noted in both ongoing treatment groups, and the crossover group experienced reductions in relapse count, MRI activity, and lesion burden accumulation compared with their previous placebo period (P < 0.001 for both doses). These benefits of subcutaneous IFNβ-1a have been sustained for 8 years of follow-up, with the original 44-µg-three-times-weekly treatment group showing lower relapse rates, disease progression, and accumulated disease burden than the crossover group.

Reinforcing these long-term findings, a recent post hoc evaluation noted that patients with the highest cumulative dose and the longest cumulative time on treatment (i.e., high exposure) had better clinical outcomes compared with patients who had lower cumulative dose and time on treatment (i.e., low exposure). Long-term (15-year) follow-up of intramuscular IFNβ-1a also showed durable benefits with regard to slowed progression of disability, overall health, and independence. At 16-year follow-up of the IFNβ-1b study participants, mortality was decreased in the treatment group versus placebo; however, data were missing for a sizable proportion of the original participants.

Comparative trials of IFNβ DMTs. Several studies have demonstrated that subcutaneous IFNβ-1a and IFNβ-1b are more effective than intramuscular IFNβ-1a but may have more adverse effects. A randomized investigator-blinded trial compared two IFNβ-1a formulations: IFNβ-1a 44 µg s.c. three times weekly and IFNβ-1a 30 µg i.m. once weekly. At
24 weeks, more patients were relapse free with IFNβ-1a 44 µg s.c. (75% vs. 63%) and fewer active lesions were observed on MRI with the subcutaneous regimen (P < 0.001 at 24 and 48 weeks). However, the subcutaneous IFNβ-1a regimen was associated with a higher incidence of injection site reactions (83% vs. 28%), neutralizing antibodies (25% vs. 2%), liver enzyme abnormalities (18% vs. 9%), and modified leukocyte counts (11% vs. 5%).26

Efficacy of IFNβ-1b compared with low-dose intramuscular IFNβ-1a was demonstrated in a randomized, open-label, prospective study comparing IFNβ-1b 250 µg s.c. every 48 hours with IFNβ-1a 30 µg i.m. once weekly in 188 patients with RRMS.27 At 2 years, more patients in the IFNβ-1b group were relapse free (51% vs. 36%, P = 0.03) and had no new T2 lesions on MRI (55% vs. 26%, P < 0.0003). Neutralizing antibodies and injection site reactions were more frequent in the IFNβ-1b group.27

In a double-blind dose-comparison study, 802 patients with RRMS were randomized to IFNβ-1a 30 µg i.m. (n = 402) or IFNβ-1a 60 µg i.m. (n = 400) weekly for 36 months or more.28 No differences were found in clinical or MRI outcomes or rate of EDSS disability progression between the two groups. No dose effects on relapse rates, number of new or enlarging lesions, or immunogenicity were observed. Incidences of neutralizing antibodies, flulike symptoms, and muscle weakness were slightly higher in the 60-µg group.28

Together, these studies suggest that efficacy is greater with IFNβ DMTs that are administered more frequently.

Adverse effects of IFNβ DMTs. Common adverse effects of IFNβ products are flulike symptoms (e.g., low-grade fever, chills, myalgias) and injection site reactions (e.g., redness, irritation, rarely necrosis).3 Injection site reactions improve in most patients in 3 to 6 months.3 Prophylaxis with acetaminophen or a nonsteroidal anti-inflammatory drug can manage flulike symptoms. Slow initiation of the drug, starting with 25% to 50% of the dose and working up weekly to the full dose, also may reduce flulike symptoms.3

Glatiramer acetate
Several different mechanisms have been proposed for the therapeutic effect of glatiramer acetate in MS, including activation of regulatory T-cells that suppress other immune cells

### Table 2. Pivotal trials of IFNβ DMTs

<table>
<thead>
<tr>
<th>Trial, duration</th>
<th>IFNβ product (vs. placebo)</th>
<th>Study population</th>
<th>Primary endpoints</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ Multiple Sclerosis Study Group, 2 years</td>
<td>IFNβ-1b 50 or 250 µg s.c. every other day</td>
<td>372 RRMS patients</td>
<td>Differences in RR, proportion of relapse-free patients</td>
<td>Reduced RR with 50 µg (1.17, ( P = 0.0101 )) and 250 µg (0.84, ( P = 0.0001 )) vs. placebo (1.27); more patients relapse-free with 250 µg (36 vs. 18, ( P = 0.007 )). Follow-up MRI analysis showed fewer active and new lesions (median 80% reduction in disease activity vs. placebo, ( P = 0.0082 )); burden of disease reduced vs. placebo (( P = 0.001 )).</td>
</tr>
<tr>
<td>PRISMS, 2 years</td>
<td>IFNβ-1a 22 or 44 µg s.c. t.i.w.</td>
<td>560 RRMS patients</td>
<td>Differences in RR</td>
<td>Reduced RR with 22 µg (1.82) and 44 µg (1.73) vs. placebo (2.56; ( P = 0.005 )); decreased accumulation of physical disability, number of active lesions on MRI.</td>
</tr>
<tr>
<td>MSCRG study, 2 years</td>
<td>IFNβ-1a 30 µg i.m. once weekly</td>
<td>301 RRMS patients</td>
<td>Time to sustained disability progression of ( \geq 1.0 ) point on EDSS</td>
<td>Significant reductions in primary end point vs. placebo (( P = 0.02 )); 34.9% of control patients and 21.9% of IFNβ-1a group progressed. IFNβ-1a also reduced relapses (( P = 0.03 )) and number/volume of gadolinium-enhancing lesions on MRI (( P = 0.02–0.05 )).</td>
</tr>
</tbody>
</table>

Abbreviations used: IFN, interferon; MRI, magnetic resonance imaging; MSCRG, Multiple Sclerosis Collaborative Research Group; PRISMS, Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis; RR, relapse rate; RRMS, relapsing-remitting multiple sclerosis.

Source: References 17–20.
involved in demyelination and depletion of T-cells that damage myelin. Glatiramer acetate is indicated for patients with RRMS to reduce the frequency of relapses and for patients with CIS. It is administered once daily as a 20-mg subcutaneous injection.

Glatiramer acetate has demonstrated short- and long-term efficacy in a prospective study of RRMS. After 2 years of treatment, the annualized relapse rate was reduced by 29% in patients receiving glatiramer acetate (n = 125) compared with placebo (n = 126, \( P = 0.007 \)). Disability progression was reduced in significantly more patients receiving glatiramer acetate (24.8%) than placebo (15.2%, \( P = 0.037 \)), as measured by EDSS change since baseline. Treatment was well tolerated.

A recent follow-up report after 15 years of treatment noted that in two-thirds of patients with a mean disease duration of 22 years who have continued taking glatiramer acetate (n = 100), 65% had not progressed to SPMS, 57% experienced stabilized or improved EDSS scores, and 82% retained their ambulatory independence without assistive devices. The study is planned to continue for 20 years of follow-up.

Recent randomized comparative studies have not found differences in efficacy between glatiramer acetate and higher-dose subcutaneous IFNβ formulations. In two trials comparing glatiramer acetate with subcutaneous IFNβ-1b for 2 to 3.5 years, no differences were seen between groups in primary outcomes of lesion volume and relapse risk. Both studies also noted no differences between groups in secondary outcomes, including EDSS progression and cognition. Similarly, a 2-year comparative trial of glatiramer acetate with subcutaneous IFNβ-1a found no significant differences between groups in time to first relapse, relapse rate, and number or volume of active lesions.

Adverse effects of glatiramer acetate. The most common adverse effect of glatiramer acetate is an injection site reaction that can include redness, swelling, and hives or welts. For many patients, this reaction occurs with every injection, especially during the first 3 to 6 months. A rare self-limited (15–20 minutes) postinjection reaction has been associated with glatiramer acetate use, consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria. Patients should be advised that this reaction is temporary and should resolve quickly. They should remain calm, sit with the head upright, and breathe slowly. If symptoms do not abate within a few minutes or if they experience swelling in the face, tongue, or eyes or cannot swallow easily, they should call 911. When the reaction does resolve, patients should contact their health care provider and discontinue medication until advised by their health care provider. Lipoatrophy at the injection site also is rare but noteworthy because it has no known treatment and is believed to be permanent. Proper injection technique and daily rotation of injection sites may minimize its occurrence.

Fingolimod. Fingolimod, the first oral DMT for RRMS, reduces the number of lymphocytes in the circulatory system by preventing their exit from secondary lymph organs and, consequently, their entry into the CNS. Fingolimod is approved for treatment of RRMS to reduce frequency of relapses and delay physical disability. The recommended dose is 0.5 mg orally once daily, to be taken with or without food.

In a double-blind, placebo-controlled, Phase III study, 1,272 patients with RRMS were randomized to fingolimod 0.5 or 1.25 mg/day or placebo for 2 years. Compared with placebo, fingolimod 0.5 and 1.25 mg significantly reduced the annualized relapse rate by 54% and 60%, respectively (\( P < 0.001 \)). Risk of disability progression was reduced in both active treatment groups, as were the number of new or enlarged lesions and loss of brain volume compared with placebo (\( P < 0.001 \)). A similar placebo-controlled randomized study of fingolimod in RRMS is ongoing.

A double-blind, double-dummy, Phase III trial compared fingolimod 0.5 and 1.25 mg/day with IFNβ-1a 30 µg i.m. once weekly for 1 year in 1,292 patients with RRMS. The annualized relapse rate was lower with both doses of fingolimod than with IFNβ-1a (0.16 and 0.20 vs. 0.33, respectively; \( P < 0.001 \)), and more patients taking fingolimod remained relapse free (83% and 80% vs. 69%, respectively; \( P < 0.001 \)). Lesion activity and loss of brain volume also were more effectively reduced with both fingolimod doses compared with IFNβ-1a. Disability progression was similar but small among all treatment groups.

Adverse effects of fingolimod. Common adverse effects of fingolimod include headache, influenza, diarrhea, back pain, liver enzyme elevations, and cough. Potentially serious adverse effects of fingolimod are malignancies, bradycardia/atrioventricular block (at the first dose only), increased risk of infections, macular edema, and shortness of breath.

A risk evaluation and mitigation strategy (REMS) was developed to ensure that health care providers and patients are appropriately advised about the safe use and serious risks of fingolimod. As described in the REMS, patients starting fingolimod should be monitored for bradycardia for at least 6 hours after taking the first dose. Patients may have mild to moderate symptoms of dizziness or fatigue or be aware of a slow or irregular heartbeat that should resolve within 24 hours. Bradycardia typically resolves within 1 month of treatment initiation. Patients should be instructed to contact their health care provider if they experience dizziness, tiredness, or slow or irregular heartbeat at any time during treatment. If treatment is interrupted for 2 weeks or more, monitoring for at least 6 hours is again required after the next dose.

Natalizumab. Natalizumab is a monoclonal antibody that targets the cellular adhesion molecule alpha-4 integrin, thereby preventing the adhesion of endothelial cells with immune cells, which effectively stops immune cells from entering the CNS. Despite the efficacy of natalizumab, safety concerns have relegated its use to second-line therapy to reduce relapse frequency and delay physical disability in patients with RRMS who have had inadequate response to or cannot tolerate first-line DMTs. It is administered as a 300-mg intravenous infusion once every 4 weeks.

Two Phase III trials have demonstrated the efficacy of natalizumab in RRMS. In a double-blind placebo-controlled trial,
627 patients randomized to natalizumab experienced reduced rate of relapse (68%), decreased risk of sustained disability progression (42%), fewer new or enlarging T2 lesions (83%), and fewer gadolinium-enhancing lesions (92%), all of which were significant ($P<0.001$) compared with patients on placebo ($n=315$).45

In a randomized, double-blind, Phase III trial, 1,171 patients taking intramuscular IFNβ-1a who had continued to experience disease activity were randomized to intramuscular IFNβ-1a plus placebo ($n=582$) or intramuscular IFNβ-1a plus natalizumab ($n=589$) for 2 years.46 Combination therapy resulted in a lower annualized relapse rate (0.34 vs. 0.75, $P<0.001$), lower probability of disability progression (42% vs. 50%, $P<0.001$) compared with patients on placebo ($n=315$).45

Table 3. Early treatment of CIS reduces risk of CDMS

<table>
<thead>
<tr>
<th>Trial, duration</th>
<th>DMT (vs. placebo)</th>
<th>DMT dose</th>
<th>Reduced CDMS risk with DMT</th>
<th>Time to conversion (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreCISE, 3 years$^a$</td>
<td>Glatiramer acetate</td>
<td>20 mg/day s.c.</td>
<td>45% ($P&lt;0.001$)</td>
<td>722 vs. 336</td>
</tr>
<tr>
<td>CHAMPS, 3 years$^a$</td>
<td>IFNβ-1a</td>
<td>30 µg/week i.m.</td>
<td>44% ($P=0.002$)</td>
<td>NR</td>
</tr>
<tr>
<td>ETOMS, 2 years</td>
<td>IFNβ-1a</td>
<td>22 µg/week s.c.</td>
<td>39% ($P=0.047$)</td>
<td>569 vs. 252</td>
</tr>
<tr>
<td>REFLEX, 2 years$^b$</td>
<td>IFNβ-1a$^c$</td>
<td>44 µg s.c. i.w.</td>
<td>51% ($P&lt;0.00001$)</td>
<td>NR</td>
</tr>
<tr>
<td>BENEFIT, 2 years$^d$</td>
<td>IFNβ-1b</td>
<td>250 µg q.a.d.</td>
<td>50% ($P&lt;0.001$)</td>
<td>618 vs. 255</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extension trials</th>
<th>DMT</th>
<th>DMT dose</th>
<th>Reduced CDMS risk with early vs. delayed DMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMPIONS, +2 years</td>
<td>IFNβ-1a</td>
<td>30 µg/week i.m.</td>
<td>43% ($P=0.030$)</td>
</tr>
<tr>
<td>BENEFIT, +3 years</td>
<td>IFNβ-1b</td>
<td>250 µg s.c. q.a.d.</td>
<td>37% ($P=0.003$)</td>
</tr>
</tbody>
</table>

Abbreviations used: BENEFIT, Betaseron (IFNβ-1b) in Newly Emerging MS for Initial Treatment; CDMS, clinically definite multiple sclerosis; CHAMPIONS, Controlled High-risk subjects (IFNβ-1a) Avonex Multiple sclerosis Prevention Study in Ongoing Neurologic Surveillance; CHAMPS, Controlled High-risk subjects (IFNβ-1a) Avonex Multiple sclerosis Prevention Study; DMT, disease-modifying therapy; ETOMS, Early Treatment Of MS study (Rebif); NR, not recorded; PreCISE, Study to Evaluate the Effect of Early Glatiramer Acetate (Copaxone) Treatment in Delaying the Conversion to CDMS of Subjects Presenting with a CIS; REFLEX, Rebif FLEXible dosing in early multiple sclerosis.

$^a$Placebo arms stopped early to offer all patients open-label treatment with active drug.

$^b$Extension trial (REFLEXION) currently ongoing to provide long-term (up to 5 years) follow-up data.

$^c$A serum-free formulation of IFNβ-1b was used in this study and is currently not available in the United States.

$^d$Acetate (Copaxone) Treatment in Delaying the Conversion to CDMS of Subjects Presenting with a CIS; REFLEX, Rebif FLEXible dosing in early multiple sclerosis.

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Because of the risk of PML, use of natalizumab in the United States is monitored by the Tysabri Outreach: Unified Commitment to Health system, known as the TOUCH Prescribing Program. This restricted distribution program serves to educate health care providers and patients about use and risks of natalizumab and mandates that[10,49]:

- Natalizumab is used only as monotherapy in patients with RRMS who have not responded adequately to or who cannot tolerate first-line DMTs.
- Natalizumab is administered only through infusion centers registered with TOUCH.
- Before initiating therapy, patients must receive MRI scans.
- Patients must be evaluated at 3 and 6 months after the first infusion and every 6 months thereafter.

Switching therapies

Patients who do not respond well to one DMT may need to switch to another first- or second-line DMT. Possible markers of nonresponse to treatment include continued, frequent relapses or MRI findings that show high gadolinium-enhancing activity or considerable new lesion formation not associated with relapse.26 Switching therapies also may be necessary for patients experiencing intolerable adverse events; however, switching within 6 months of treatment is discouraged because many adverse events lessen over time.27 Switching from one IFNβ to another also is not advised because IFNβ products have the same mechanism of action and similar adverse event profiles.29

Mitoxantrone

Mitoxantrone is indicated for reducing neurologic disability and frequency of relapses in SPMS, PRMS, and worsening RRMS.11 It may be considered for selected patients with worsening disease[51] but is used infrequently because of associated risks of acute myelogenous leukemia and cardiotoxicity, including decreased left ventricular ejection fraction (LVEF).11,52 The recommended dosage is 12 mg/m² i.v. every 3 months.11 Maximum cumulative exposure to mitoxantrone should not exceed 140 mg/m² (i.e., 2–3 years at the recommended dose).11
Early treatment of CIS delays disease progression

In several randomized, placebo-controlled, Phase III trials using glatiramer acetate or IFNβ formulations, early treatment in patients with CIS demonstrated significant reductions in the risk of developing CDMS (Table 3).53–59

Emerging therapies for MS

A number of other DMTs are being studied for use in MS (Table 4).50–67 Four additional oral therapies recently completed Phase III trials, and data are beginning to emerge.

Oral cladribine selectively depletes T-cells and some types of B-cells and reduces inflammation.60 In a completed placebo-controlled Phase III trial, cladribine significantly reduced relapse rates, lesions on MRI, and progression of disability.60 Cladribine was associated with an increased risk of lymphocytopenias, severe infections/infestations, and malignancies.60 In March 2011, FDA denied approval of cladribine a second time, calling for more safety data and analysis of risk-to-benefit ratio but said that the existing data are sufficient to support efficacy in reducing exacerbations and progression.60

Results of Phase III trials for two other oral therapies, laquinimod and teriflunomide, were presented at the 2011 American Academy of Neurology (AAN) annual meeting. Both therapies significantly reduced annualized relapse rates and various MRI measures of disease compared with placebo.61,62 Laquinimod 0.6 mg/day and teriflunomide 14 mg/day (but not 7 mg/day) also significantly reduced progression of disability.61,62 Both therapies were well tolerated, with no increase in serious adverse events compared with placebo.61,62 Laquinimod was associated with reversible increases in liver enzyme levels without clinical evidence of liver dysfunction.61 No alanine aminotransferase elevations occurred in the Phase III study of teriflunomide,62 but these were observed in an earlier Phase II study.60 Neither of these studies has been published in a peer-reviewed journal, and FDA has not reviewed these therapies. A Phase III trial also has been completed for dimethyl fumarate; results will be reported at a future medical conference.63

Managing MS relapse

Patients should be encouraged to report all relapses to their health care provider because relapse frequency is factored into deciding whether to continue or change the patient’s DMT.70 Corticosteroids are the most commonly used treatment for MS relapse and can be given safely with MS DMTs.71 Steroids speed clinical recovery but do not necessarily improve the extent of recovery.70 (Recovery following a relapse may be complete or incomplete, regardless of treatment.) The most common corticosteroid regimen used consists of 3 to 5 days of methylprednisolone 500 to 1,000 mg/day i.v., sometimes followed by a 1- to 3-week oral prednisone taper.70,71 Comparable doses of oral steroids are sometimes given instead of intravenous therapy; efficacy and safety are thought to be similar.72 Benefits of corticosteroid treatment must be weighed against known risks, including mood changes, elevations in blood pressure and serum glucose levels, and gastrointestinal adverse effects.70

Table 4. Investigational therapies for multiple sclerosis

<table>
<thead>
<tr>
<th>Multiple sclerosis therapy</th>
<th>Status as of April 2011</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cladribine</td>
<td>One Phase III published; additional data requested by FDA</td>
<td>Oral</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Phase III reported</td>
<td>Oral</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Phase III reported</td>
<td>Oral</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Phase III recently completed; data have not been reported</td>
<td>Oral</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Phase III ongoing</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Phase III ongoing</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Phase II reported</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>

Source: References 60–67.

Relative contraindications—or conditions that at least require close monitoring—include diabetes, hypertension, pregnancy, poorly controlled psychiatric disorders, peptic ulcer, history of steroid intolerance, or concomitant use of warfarin sodium.70,71 Steroids should not be used long term to treat MS.71

A recent guideline from AAN concludes that plasmapheresis may be effective for steroid-refractory relapses but is not effective in SPMS or PPMS.72 This procedure, also called plasma exchange, involves removing red blood cells and other components from the patient’s blood, exchanging the plasma with donor plasma or albumin solution, and then restoring the patient’s other blood components.73

Improving mobility in MS

The only pharmacologic therapy approved by FDA specifically and exclusively for walking is dalfampridine. Indicated to improve walking in patients with MS, dalfampridine is a potassium channel blocker and may restore conduction in demyelinated nerve fibers.74 Dalfampridine was evaluated in two randomized, placebo-controlled, Phase III trials, with 301 patients given active treatment for 14 weeks and 239 patients treated for 9 weeks, respectively.75,76 The primary outcome measure was walking speed. In both studies, dalfampridine significantly increased the proportion of patients who showed response on the Timed 25-Foot Walk test: 35% vs. 8%, respectively (P < 0.0001), in the first trial75 and 43% vs. 9%, respectively (P < 0.0001), in the second trial.76 Adverse effects included urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, and a potential increased risk of seizure, particularly at higher-than-recommended doses.74

Dalfampridine is available as a 10-mg extended-release tablet for oral administration. The maximum dose is 10 mg twice daily.74 Patients should be told to take the doses 12 hours apart and not to take a double dose if they miss a dose.74 Dalfampridine tablets should be swallowed whole—not broken, crushed, or chewed—either with or without food.74 Dal-
Fampridine is contraindicated for patients who have a history of seizures, have moderate to severe renal impairment, or are already taking compounded 4-aminopyridine (the active ingredient in dalfampridine). Dalfampridine and 4-aminopyridine are not bioequivalent and cannot be substituted.

Tell me more!
The National MS Society website (www.nationalmssociety.org/index.aspx) has a wealth of information for patients and clinicians about MS, including strategies for managing the disease and its many symptoms.

Assess your knowledge (continued)
T.G.’s health care provider prescribes IFNβ-1b 250 µg s.c. administered every other day. During a pharmacy consultation, the pharmacist reviews the injection training for the product and discusses the importance of adherence. During the next year, T.G. is largely adherent to treatment. During a follow-up medication therapy management visit, she tells the pharmacist that a recent MRI showed no new lesions and that she has had no new neurologic symptoms. She says she has minor flulike symptoms after each injection. Because she has been doing well and finds the adverse effects bothersome, she questions whether she should continue on medication at all and, if she does, whether she can switch to the new oral MS medication she heard about so she does not have to self-inject.

Pharmacists can be a great resource for patients with injection anxieties who may require extra support and assistance. Pharmacists also can provide strategies for managing adverse effects, as discussed above. Finally, a key opportunity exists for pharmacists to improve MS outcomes by promoting adherence to DMT.

Promoting adherence
Between 17% and 41% of MS patients stop taking DMTs, usually within the first 2 years. In a longitudinal prospective study of 97 MS patients taking DMT, nearly three-quarters missed at least one dose during the study period (January 2002 to April 2005), more than one-half missed doses on at least two occasions, and 10% missed more than 10 doses in any 6-month period. Nearly 20% had stopped taking any treatment by the end of follow-up. Taking less than recommended doses can lead to more disease activity, both clinically and on MRI. Reasons for nonadherence include perceived lack of efficacy, adverse events, injection fears, laboratory abnormalities, depression, forgetting doses, denial of illness, treatment impact on lifestyle, cost, cognitive and physical barriers to performing injections, socioeconomic and cultural factors, and lack of support.

The pharmacist’s role
Pharmacists can play an important role in facilitating optimal use of MS medications. Pharmacists can collaborate with health care providers in making treatment recommendations and monitoring for treatment response and adverse events. Patients starting on a DMT require reinforcement of learning regarding proper dosing and administration (Table 5).

Table 5. Injection training

<table>
<thead>
<tr>
<th>Follow the protocol in the Medication Guide; product preparation, dosing schedule, and recommended injection technique vary by product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wash and dry your hands, then clean injection site with an alcohol wipe; let it dry before injecting</td>
</tr>
<tr>
<td>Rotate injection sites, per Medication Guide</td>
</tr>
<tr>
<td>Do not inject into red, bruised, infected, or irritated sites</td>
</tr>
<tr>
<td>Use autoinjector (available free of charge from manufacturer)</td>
</tr>
<tr>
<td>Inject medication at room temperature</td>
</tr>
<tr>
<td>Ensure adequate needle penetration into subcutaneous tissues (or intramuscular tissue for IFNβ-1a intramuscular injectable)</td>
</tr>
<tr>
<td>Do not rub or massage injection area on same day as glatiramer acetate injection</td>
</tr>
<tr>
<td>Properly dispose of all used syringes; never reuse a syringe</td>
</tr>
<tr>
<td>Ice the area before/after injection for IFN or warm the skin with a heat pack before injecting glatiramer acetate</td>
</tr>
<tr>
<td>Suggest the patient ask his/her health care provider about smaller length/gauge needles</td>
</tr>
</tbody>
</table>

Abbreviation used: IFN, interferon.
Source: References 29, 38, and 77–79.

Where can patients go for answers?
Direct patients to the Ask the Doctor forum at the MS Foundation website (www.msfocus.org/forums.aspx), where questions and concerns are addressed by a panel of health professionals.

Pharmacists can help improve adherence by establishing realistic patient expectations, providing education to the patient and family, and helping to manage adverse effects of therapy. Patients need education that DMTs are not a cure, are not likely to eliminate existing symptoms or disability, and mitigate but do not eliminate future disease activity. Although it may sound obvious, patients also should be reminded that these therapies work only if patients take them, preferably consistently. Over time, pharmacists should reinforce to the patient the need to continue treatment—even if no disease activity is apparent or if relapses have occurred, both of which are likely to lead patients to consider discontinuing. The pharmacist also should provide support by acknowledging the difficulty of adhering consistently to long-term medication use.

Medication therapy management (MTM) services should be offered to patients with MS, including review of medications, assessment of patient knowledge and concerns, and education on key MS topics. MTM has been shown to improve adherence and patients' perceptions of their ability to manage health, as well as reduce relapses in MS.

Summary
MS is a chronic inflammatory and neurodegenerative disease characterized by demyelination and axonal damage. The exact causes of MS are not fully understood but likely involve a combination of genetic and environmental factors. CIS is a single, symptomatic neurologic episode consistent with MS. Diagnosis of CDMS requires the presence of at least two lesions on MRI separated by time and space. Treatment of CIS and MS should
be initiated as early as possible with one of the injectable DMTs to reduce the frequency of relapse, disease activity evident on MRI, and progression of disability. Patients should be counseled about proper injection technique and the need for adherence. Patients with inadequate response to IFNβ and/or glatiramer acetate may be treated with natalizumab or fingolimod, which offer excellent efficacy but require closer monitoring for potential adverse events. Patients should be encouraged to report all relapses to help determine the need for more aggressive treatment. Acute relapses may be managed with corticosteroids to speed recovery. Dalfampridine is not a DMT but may help improve walking and mobility in patients with MS.

Assess your knowledge case study responses

1. CIS is a single episode that is consistent with MS, and she may be experiencing her first MS event. However, with one clinical event plus a normal MRI, she does not meet criteria for dissemination in space and time, so she cannot be given a full diagnosis of MS at this time.

2. Yes, patients with CIS should receive first-line MS DMTs, which may prevent or postpone conversion to CDMS. First-line therapy for a patient with CIS includes IFNβ-1a, IFNβ-1b, or glatiramer acetate.

3. She should continue on her current treatment regimen. Treatment should be continued indefinitely unless benefit is clearly lacking or adverse effects are intolerable or if better therapy becomes available; changes to another therapy should be made only if a medical reason exists. The oral treatment she referred to, fingolimod, is not FDA approved for patients with CIS. It might be considered later if she has additional relapses and signs of disease activity despite continued adherence to IFNβ.

References


CPE exam

Instructions: The assessment test for this activity must be taken online; please see “CPE information” below for further instructions. There is only one correct answer to each question. This CPE activity will be available online at www.pharmacist.com no later than June 30, 2011.

1. Conduction of nerve impulses is impaired in multiple sclerosis (MS) as a result of:
   a. Destruction of myelin and the underlying axon.
   b. Depletion of dopamine and serotonin.
   c. Damage to sodium/potassium pumps.
   d. Dysfunctional receptors on dendrites.

2. The most common initial presentation of MS is:
   a. Progressive-relapsing MS
   b. Primary-progressive MS
   c. Relapsing-remitting MS (RRMS)
   d. Secondary-progressive MS (SPMS)

3. According to the McDonald criteria, depending on magnetic resonance imaging (MRI) findings, the earliest possible point at which CDMS can be diagnosed is:
   a. At the first clinical episode.
   b. 30 days after a first clinical episode.
   c. 60 days after a first clinical episode.
   d. At the time of a second clinical episode.

4. Comparative trials suggest that which of the following interferon (IFN) therapies may have the least potent efficacy but a more mild safety profile?
   a. IFNβ-1b 250 µg s.c. every other day
   b. IFNβ-1a 22 µg s.c. every other day
   c. IFNβ-1a 44 µg s.c. every other day
   d. IFNβ-1a 30 µg i.m. every week

5. In a 15-year follow-up of RRMS patients taking glatiramer acetate:
   a. Efficacy generally wore off over time.
   b. More than one-half progressed to SPMS.
   c. More than 80% continued to walk without assistive devices.
   d. More than 75% showed progression on the expanded disability severity scale.

6. Which of the following MS therapies works by trapping lymphocytes in secondary lymph organs, preventing them from entering the circulation and the CNS?
   a. IFNβ
   b. Glatiramer acetate
   c. Fingolimod
   d. Cladribine

7. Which of these MS therapies requires enrollment into a special program for monitoring because of an increased risk of progressive multifocal leukoencephalopathy?
   a. Fingolimod
   b. Natalizumab
   c. Glatiramer acetate
   d. Mitoxantrone

8. A patient who was recently diagnosed with MS asks you which therapy you would recommend. You tell her that the most commonly used first-line agents with long-term safety records are:
   a. Mitoxantrone or one of the IFNβ formulations.
   b. Glatiramer acetate or fingolimod.
   c. Natalizumab or an IFNβ product.
   d. An IFNβ product or glatiramer acetate.

9. Which of the following is a rare but characteristic adverse effect of glatiramer acetate?
   a. Flu-like symptoms
   b. Depression
   c. Chest pain/palpitations
   d. Thrombocytopenia

CPE information

To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before June 15, 2014, can receive credit.

CPE instructions: Get your documentation of credit now! Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3.
1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APHA members enter your user name and password. Not an APHA member? Just click “Create one now” to open an account. No fee is required to register.
3. Successfully complete the CPE exam and evaluation form to gain immediate access to your documentation of credit.

Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APHA Member Services at 800-237-APHA (2742) or by e-mailing InfoCenter@pharmacist.com.
10. In the case study described in the main text, the pharmacist should tell the patient that she can ameliorate her flulike symptoms by:
   a. Stopping IFN for 3 months (i.e., “drug holiday”).
   b. Taking analgesics at the time of injection or within an hour.
   c. Administering IFN cold, right from the refrigerator.
   d. Permanently cutting the IFN dose by one-half.

11. Which of the following is the recommended first-line treatment for acute relapse?
   a. Intravenous methylprednisolone
   b. Glatiramer acetate
   c. IFNβ-1b or IFNβ-1a
   d. Plasmapheresis

12. To date, this medication, although proven effective, has been associated with an increased risk of lymphocytopenias, severe infections/infestations, and malignancies and therefore FDA approval has been rejected until more safety data become available.
   a. Laquinimod
   b. Teriflunomide
   c. Dimethyl fumarate
   d. Cladribine

13. Which of the following therapies is indicated to improve walking in patients with MS?
   a. Natalizumab
   b. Dalfampridine
   c. Glatiramer acetate
   d. Fingolimod

14. When explaining the need for adherence to MS disease-modifying therapy (DMT), the pharmacist should convey that long-term adherence will:
   a. Eventually cure MS.
   b. Reverse existing disability and symptoms.
   c. Reduce relapse frequency and rate of progression.
   d. Prevent the need for a wheelchair in the future.

15. MS DMTs should be injected:
   a. Into the thighs exclusively.
   b. Into the abdomen exclusively.
   c. Into the buttocks exclusively.
   d. Into rotating injection sites.