



Multiple Sclerosis

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LEARNING OBJECTIVES

1. Classify the variabilities in patient presentation and multiple sclerosis (MS) disease course.
2. Analyze MS characteristics to distinguish the spectrum of MS and diagnostic subtypes.
3. Evaluate disease-modifying therapies for MS.
4. Apply a knowledge of the MS subtypes and available MS treatments to select appropriate therapy.
5. Assess treatment considerations of MS in pediatric patients and during family planning and pregnancy.

ABBREVIATIONS IN THIS CHAPTER

CIS	Clinically isolated syndrome
DIS	Dissemination in space
DIT	Dissemination in time
DMT	Disease-modifying therapy
IFN β	Interferon-beta
MS	Multiple sclerosis
OCB	Oligoclonal band
PML	Progressive multifocal leukoencephalopathy
POMS	Pediatric onset MS
PPMS	Primary progressive MS
RRMS	Relapsing-remitting MS
S1P	Sphingosine-1-phosphate
SPMS	Secondary progressive MS

[Table of other common abbreviations.](#)

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory disorder of the CNS, characterized by demyelination and neurodegeneration of the brain, spinal cord, and optic nerve, often leading to both physical and cognitive disability (Compston 2008). Although the exact cause of MS is unknown, it is thought to be an immune-mediated response to one or more environmental triggers in a genetically susceptible individual. The known risk factors for MS can be categorized into two major groups: genetic and environmental (Box 1). The immune-mediated response leads to inflammatory damage of the neuronal myelin, or demyelination, causing the formation of plaques (often called lesions), which may result in an MS exacerbation called a relapse. Of importance, not all lesions result in a symptomatic relapse – these lesions are often called subclinical MS activity. A patient with MS may have only one clinical relapse for every 10–20 subclinical brain lesions, whereas spinal cord lesions more often result in clinical relapses (Joy 2001). These asymptomatic changes can be identified with routine MRI. Over time, the accumulation of demyelination, together with the lack of remyelination, as well as ongoing immunologic changes often lead to axonal injury and loss, resulting in neurodegeneration and progression of symptoms and disability.

Multiple sclerosis affects about 2.8 million people worldwide, with around 10,000–20,000 new cases diagnosed each year (Walton 2020). In the United States alone, almost 1 million people are living with MS, with a higher prevalence in the northern part of the country (Wallin 2019). Although the onset of MS can occur during childhood or late adulthood, the diagnosis is most often made in those 20–50 years of age, with a peak at around 30 years, and women are given the diagnosis about 3 times as often as men (Compston 2008). These diagnostic trends are significant, because the age of diagnosis is commonly amid the productive, middle-aged years of life as well as during the childbearing years.

Box 1. Risk Factors for Multiple Sclerosis

Genetic Risk Factors

- Female sex
- White, northern European
- Family history, especially first-degree relative
- *HLA-DRB1*15:01* haplotype

Environmental Risk Factors

- Infectious: Epstein-Barr virus infection
- Noninfectious:
 - Cigarette smoking
 - Low vitamin D concentrations
 - Obesity, especially childhood and young adulthood
 - Geographic latitude/distance from equator

Information from: Ascherio A. Environmental factors in multiple sclerosis. *Expert Rev Neurother* 2013;13:3-9; Sawcer S, Franklin RJ, Ban M. Multiple sclerosis genetics. *Lancet Neurol* 2014;13:700-9.

Heterogeneity of MS

Multiple sclerosis is heterogeneous in presentation and clinical course, making diagnosis and treatment challenging. Some patients may have infrequent relapses and remain stable for many years, whereas others may have frequent relapses or substantial lesion burden and develop early onset of disability within a few years after diagnosis (Tremlett 2010). In addition, response to disease-modifying therapy (DMT) varies among patients, further complicating the therapy selection process both at the time of diagnosis and when a change in therapy is indicated. As experts in pharmacotherapy, clinical pharmacists can play a vital role in partnering with MS clinicians to develop individualized, patient-centric treatment plans.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the immunology related to the pathophysiology of MS
- Knowledge of CYP metabolism and drug knowledge of inhibitors and inducers of the CYP enzymes

[Table of common laboratory reference values](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Sospedra M, Martin R. [Immunology of multiple sclerosis](#). *Semin Neurol* 2016;36:115-27.
- FDA. [Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers](#)

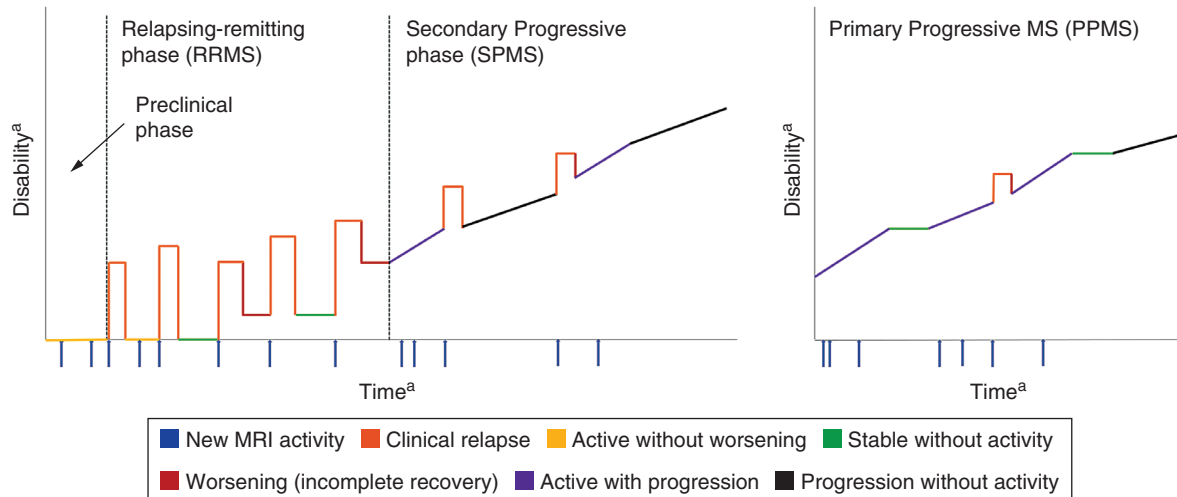
CLINICAL PRESENTATION AND MS SUBTYPES

Multiple sclerosis has several different subtypes, or phenotypes. About 85% of patients are initially given a diagnosis of relapsing-remitting MS (RRMS), wherein they have an acute clinical exacerbation of new or worsening symptoms that fully or partly resolve over several days to weeks. The location of the acute demyelinating lesion dictates the corresponding clinical relapse, which can be optic neuritis, a brain stem syndrome, or a spinal cord relapse such as transverse myelitis. By definition, a relapse is an episode of neurologic dysfunction that lasts 24 hours or more in the absence of fever, infection, or other causes of a pseudo-relapse (McDonald 2001). Although a pseudo-relapse may mimic symptoms of a true MS relapse, it is not caused by new or acute demyelination; rather, it is caused by the recurrence of symptoms from a previous lesion. An MS relapse often develops over hours to days and peaks within 2–3 weeks after onset, though it may persist for several months before improvement or resolution (Brownlee 2014). Any new or recurring symptoms within 30 days of onset of a previous event are considered one episode.

Ultimately, the disease of most patients with RRMS will evolve to a secondary progressive MS (SPMS) phenotype, in which gradual neurologic worsening is persistent and independent of a relapse. If untreated, this progression will occur in about one-half of patients with RRMS within 10 years and more than three-fourths of patients with RRMS within 25 years (Maroney 2014). The transition from RRMS to SPMS is gradual, without a finite transition time point.

Around 10%–15% of patients with MS present with a progressive disease course from onset, with few (if any) notable clinical relapses. This phenotype is called primary progressive MS (PPMS). Patients with SPMS and PPMS may also have disease activity (i.e., development of new or enlarged lesions with or without a clinical relapse), though this is less common than in patients with RRMS.

In 2013, the terms used to describe the MS phenotypes were updated and more specifically defined by the International Advisory Committee on Clinical Trials in Multiple Sclerosis. Two modifying terms (*activity* and *progression*) were highlighted to characterize the state of disease at any time point and the committee recommends that these disease modifiers should be evaluated annually. The terms *relapsing* and *active* have been used interchangeably, though active MS is now defined to include clinical relapses or radiologic evidence of MS (Lublin 2014) (Figure 1). In the context of FDA-approved indications and use, relapsing MS includes clinically isolated syndrome (CIS), RRMS, and active SPMS, which insinuates that active MS includes only the clinical features of relapse and does not include MRI activity in the absence of the clinical sequelae. Most MS experts agree that standardized verbiage to include the full definition of MS activity



Term	Definition
Active Disease	Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery, in the absence of fever or infection Radiologic/Imaging: Gd+ enhancing lesions, or new or enlarging lesions
Worsening disease	Any increase in impairment or disability; Worsening may be 1. residual deficits as a result of a relapse or 2. due to progressive disability during the progressive phase
Progressive disease	Accrual of disability, independent of a relapse or radiologic MS activity, sustained for at least 6 to 12 months; Occurs during the progressive phases of MS (SPMS or PPMS)

Figure 1. Multiple sclerosis phenotypes and definitions.

^aNot to scale.

Gd+ = gadolinium enhancing.

Information from: Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;83:278-86; Lublin FD, Coetzee T, Cohen JA, et al; International Advisory Committee on Clinical Trials in Multiple Sclerosis. The 2013 clinical course descriptors for multiple sclerosis: a clarification. *Neurology* 2020;94:1088-92; Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162-73.

(clinical or MRI) should be used routinely and consistently to improve accuracy and reduce confusion (Lublin 2020).

Diagnosis: McDonald Criteria

Since 2001, the International Panel on Diagnosis of Multiple Sclerosis, often called the McDonald criteria, has provided guidance for diagnosing MS. These criteria are based on the fulfillment of dissemination in space (DIS) and dissemination in time (DIT), using both clinical characteristics and radiologic evidence of current and prior disease activity (McDonald 2001). Dissemination in space is evidence of discrete MS lesions in more than one location within the CNS, whereas DIT supports that this activity occurred at different points in time. Recognizing that early treatment is correlated with improved outcomes, the most recent update in 2017 simplifies the diagnostic process, allowing the use of paraclinical features, such as the presence of oligoclonal bands (OCBs) specific to the

CSF, to support an early diagnosis of clinically definitive MS (Thompson 2018) (Table 1). Oligoclonal bands are proteins released because of damage to CNS myelin, and the presence of CSF-specific OCBs indicates CNS inflammation.

Clinically isolated syndrome is the first clinical event, commonly optic neuritis or partial myelitis, with no MRI evidence of DIS or DIT. Patients with CIS often develop relapsing MS, particularly if their MRI reveals brain lesions typical of MS at the time of their first clinical event. Typical MS lesions are located in the spinal cord or the periventricular, cortical, juxtacortical, or infratentorial regions of the brain and appear hyperintense on T2-weighted MRI. Gadolinium-enhancing MS lesions indicate acute demyelination and current MS activity. Lesions typical of MS may be incidentally identified before the clinical manifestation of a relapse or symptoms. This phenomenon is called radiologically isolated syndrome. When considering a diagnosis of MS, as well as CIS and radiologically isolated

Table 1. Summary of the 2017 McDonald Criteria

Clinical Presentation in a Person with Typical MS Activity/CIS at Onset		Additional Findings Needed for Diagnosis of Relapsing MS
≥ 2 clinical events	Plus, objective clinical evidence of ≥ 2 lesions OR Objective clinical evidence of 1 lesion with historical evidence of a prior event involving a different location	No additional findings required; however, MRI is often obtained to stage the disease severity and exclude other diagnosis
≥ 2 clinical events	Plus, objective clinical evidence of 1 lesion	DIS must be demonstrated by: ≥ 1 MRI lesions ^a typical of MS in ≥ 2 areas of the CNS ^b OR Additional clinical event implicating a different CNS site
1 clinical event	Plus, objective clinical evidence of ≥ 2 lesions	DIT must be demonstrated by: Simultaneous enhancing and non-enhancing MRI lesions ^a typical of MS ^b OR New T2 or enhancing lesion compared with baseline OR Additional clinical event OR CSF-specific OCBs
1 clinical event	Plus, objective clinical evidence of 1 lesion	Both DIS and DIT must be demonstrated AND One of the DIS criteria listed earlier One of the DIT criteria listed earlier
Clinical Presentation in a Person with Typical MS Activity/CIS at Onset		Additional Findings Needed for Diagnosis of Relapsing MS
1 yr of disability progression (retrospectively or prospectively determined) independent of clinical relapse		Plus two of the following: • ≥ 1 MRI lesions ^a typical of MS in the following brain regions: Periventricular, cortical, juxtacortical, or infratentorial • ≥ 2 MRI lesions ^a typical of MS in the spinal cord • Presence of CSF-specific OCBs

^aSymptomatic or asymptomatic T2-hyperintense lesions that are characteristic of MS.

^bAreas of the CNS include the brain (periventricular, cortical or juxtacortical, or infratentorial regions) or spinal cord.

CIS = clinically isolated syndrome; DIS = dissemination in space; DIT = dissemination in time; MS = multiple sclerosis; OCB = oligoclonal band; PPMS = primary progressive MS.

Information from: Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162-73.

syndrome, the clinician must exclude other MS mimics, such as neuromyelitis optica spectrum disorder, neurosarcoidosis, infectious diseases, malignancy, and nutritional deficiencies, especially for populations in which MS is less common.

Highly Active MS and Poor Prognostic Risk Factors

Multiple sclerosis is a highly variable disease. It is difficult to predict which patients will have a rather mild disease course and which will have frequent relapses or rapid onset of disability. Several prognostic factors are associated with highly active MS and can be used to predict which patients may be

predisposed to unfavorable clinical outcomes (Box 2). These patients benefit from early diagnosis and identification of poor prognostic signs, as well as an “induction-style” treatment approach in which a high-efficacy DMT is used as the initial MS treatment to increase the probability of achieving minimal evidence of disease activity earlier in the disease course and therefore improve long-term outcomes (Díaz 2019; Rae-Grant 2018).

TREATMENT GOALS IN MS

Managing MS requires a multipronged approach, which includes treating acute relapses, modifying the disease

Box 2. Highly Active MS and Risk Factors for Poor Prognosis

Highly Active MS

- ≥ 2 relapses in previous 12 mo
- Incomplete recovery from a relapse
- Severe relapse resulting in significant increase in disability (e.g., change in EDSS ≥ 1)
- EDSS ≥ 3 within 5 yr of onset with superimposed relapses
- Change in EDSS ≥ 2 points in previous 12 mo
- ≥ 2 Gd+ lesions ≥ 3 mm
- ≥ 3 T2 lesions on two consecutive MRIs 6–12 mo apart
- Early brain atrophy

Poor Prognostic Signs

- Age ≥ 40 yr at onset
- Male sex
- African American
- Motor, sphincter, cerebellar, spinal cord symptoms
- Brain stem or spinal cord lesions at onset
- ≥ 2 events in first 2 yr of onset

EDSS = expanded disability status scale; Gd+ = gadolinium enhancing; MS = multiple sclerosis.

Information from: Rush CA, MacLean HJ, Freedman MS. Aggressive multiple sclerosis: proposed definition and treatment algorithm. *Nat Rev Neurol* 2015;11:379-89; Ford CC, Morrow SA. CMSC Practical Guidelines for the Selection of Disease-Modifying Therapies in Multiple Sclerosis: CMSC DMT Guideline Writing Group. February 2019.

course to reduce MS activity and slow disability progression, minimizing symptoms to improve quality of life, and encouraging a healthy lifestyle to address modifiable risk factors. Clinical pharmacists are an important member of the interdisciplinary care team and can positively affect patient care and outcomes by helping with therapy selection, mitigating adverse effects, and promoting adherence.

Treating MS Activity—Role of High-Dose Steroids

To accelerate recovery and minimize residual neurologic deficits, high-dose corticosteroids can be used for acute relapses, particularly when the symptoms affect quality of life or activities of daily living. Of importance, infection or other causes of a pseudo-relapse should be ruled out before steroid administration. A common treatment dose is 1000 mg of intravenous methylprednisolone given once daily for 3–5 days, with or without an oral steroid taper. Because intravenous administration of steroids can be logistically challenging and cost-prohibitive, an orally administered corticosteroid at a therapeutically equivalent dose is an appropriate alternative (Le Page 2015). Use of oral steroids has increased significantly in the past several years, and many MS specialists prefer this option for its convenience and cost savings (Liu 2017). For patients with a suboptimal response to a corticosteroid, or those with contraindications to corticosteroid use,

alternative treatment with an adrenocorticotropic hormone or plasma exchange may be warranted.

Modifying the Disease Course—Role of DMTs

Although DMTs are not curative, they have significantly improved the long-term outcomes—specifically reduced disease activity and prolonged time to disability—in patients with MS. Historically, the therapeutic effect of most DMTs was targeted at minimizing the inflammatory demyelination of MS. These DMTs are therefore most effective and consequently approved for use during the relapsing or active phase of MS. Several newer agents have shown more promising benefits for patients with progressive forms of MS.

Injectable Platform Therapies

Two classes of injectable therapies, often called platform therapies, have been used for decades as first-line agents in MS treatment. Although the efficacy of these injectable therapies is inferior to that of many of the newer agents, their favorable safety profile has contributed to their continued use in treating CIS and relapsing forms of MS, mainly in patients with milder disease and those who are risk-averse to the higher-efficacy therapies.

Interferon-beta

Many interferon-beta (IFN β) therapies are available on the U.S. market. In individual randomized, placebo-controlled trials, each IFN β product reduced annual relapse rates by around 30%–35% and improved MRI and disability outcomes. Common adverse effects include injection site reactions, flu-like symptoms, and elevated liver enzymes. The IFN β therapies differ in their dose and route of administration, and therapy selection largely depends on patient preference and insurance formulary criteria (Table 2).

Glatiramer Acetate

Glatiramer acetate, now offered in several generic preparations, is the only non-IFN β injectable platform therapy. Both approved dosing regimens reduced relapse rates by 29%–34% compared with placebo in randomized trials. Injections with glatiramer acetate may cause injection site reactions, an immediate post-injection reaction, and lipoatrophy (see Table 2).

Oral Therapies

Since 2010, with the approval of the first oral DMT, MS treatment has expanded to include eight oral therapies, with several more on the horizon. Although head-to-head data are limited, the oral DMTs have shown efficacy outcomes versus placebo that are more favorable than the platform therapies. In general, the benefit of increased efficacy is often counterbalanced with a more significant adverse effect profile, making it imperative to assess risk-benefit for each patient during the treatment selection process (Table 3).

Table 2. Injectable Platform Disease-Modifying Therapies

Medication	Dose	Adverse Effects	Monitoring	Special Consideration
IFN β 1b	0.25 mg SC every other day	Injection site reactions	CBC, LFT, TSH	Each agent differs in titration, dose, frequency, route of administration, storage, and stability
IFN β 1a	22 mcg or 44 mcg SC three times weekly	Flu-like symptoms	None	
	<i>Or</i> 30 mcg IM every 7 days	Liver enzyme elevation Leukopenia Thyroid disorder Depression		
Pegylated IFN β 1a	125 mcg SC or IM every 14 days			
Glatiramer acetate	20 mg SC every day	Injection site reactions		None
	<i>Or</i> 40 mg SC three times weekly	IPIR Lipoatrophy		

IM = intramuscular(ly); IPIR = immediate post-injection reaction; LFT = liver function test; SC = subcutaneous(ly); TSH = thyroid-stimulating hormone.

Information from: Filipi M, Jack S. Interferons in the treatment of multiple sclerosis: a clinical efficacy, safety, and tolerability update. *Int J MS Care* 2020;22:165-72; Khan O, Rieckmann P, Boyko A, et al.; GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol* 2013;73:705-13.

Sphingosine-1-Phosphate Modulators

Currently, three sphingosine-1-phosphate (S1P) receptor modulators have been approved for the treatment of relapsing forms of MS: CIS, RRMS, and active SPMS. Inhibition of S1P receptors on lymphocytes leads to their sequestration within the lymph nodes and therefore reduces peripheral circulation and migration into the CNS. Each agent has varying levels of affinity to several S1P receptor subtypes; siponimod and ozanimod are more selective than their predecessor fingolimod (Table 4). This selectivity results in lower rates of adverse events such as bradyarrhythmia, which, together with a dose titration, allows many patients to start therapy without having to take the first dose under medical supervision, which is always required of fingolimod. Other notable adverse effects of S1P modulators include headache, lymphopenias, infections including progressive multifocal leukoencephalopathy (PML), liver enzyme elevation, and macular edema. Thorough medication reconciliation is important when considering an S1P modulator because of the many interacting medications.

In separate clinical trials, both fingolimod and siponimod reduced relapse rates by about 55% compared with placebo in patients with relapsing MS and active SPMS, respectively (Kappos 2018, 2010). Siponimod also significantly reduced disability progression in patients with SPMS. Ozanimod has a relapse rate reduction of 48% in patients with relapsing MS compared with an active comparator, IFN β intramuscularly weekly (Cohen 2019; Comi 2019). All three S1P modulators have favorable MRI outcomes (Cohan 2020).

Fumaric Acids

Dimethyl fumarate and diroximel fumarate are both prodrugs that rapidly convert to their active metabolite, monomethyl fumarate. All three fumaric acids are FDA approved for

relapsing forms of MS, to include CIS, RRMS, and active SPMS. Their mechanism of action in MS is thought to be a result of anti-inflammatory effects from activation of the Nrf2 pathway. Compared with placebo in patients with RRMS, dimethyl fumarate reduced the annualized relapse rate by 44%–53% and had favorable MRI outcomes (Fox 2012; Gold 2012). The efficacy of both diroximel fumarate and monomethyl fumarate is based on pharmacokinetic studies that support their bioequivalence to dimethyl fumarate, though they may cause fewer GI adverse effects, which are common when initiating dimethyl fumarate (Wynn 2020; Naismith 2019). However, dimethyl fumarate–induced stomach upset can often be mitigated by taking each dose with food. Other notable adverse effects of the fumaric acids are flushing, lymphopenia, and infections, including PML.

Teriflunomide

Teriflunomide, the active metabolite of leflunomide, reduces activated lymphocytes in the CNS through the inhibition of dihydroorotate dehydrogenase and pyrimidine synthesis. Teriflunomide is also approved for relapsing forms of MS, to include CIS, RRMS, and active SPMS. In patients with RRMS, teriflunomide has efficacy outcomes similar to interferons, with a relapse rate reduction of 32% and favorable MRI outcomes compared with placebo (O'Connor 2011). The common adverse effects of headache, stomach upset, hair thinning, peripheral neuropathy, increased liver enzymes, and neutropenia are usually mild and transient. Teriflunomide is teratogenic and should be avoided unless reliable contraception is used in both women and men of reproductive potential. Although the half-life of teriflunomide is 18 days, an accelerated elimination procedure with cholestyramine or activated charcoal can be used to reach undetectable concentrations within 2 weeks.

Table 3. Oral Disease-Modifying Therapies

Medication	Dose	Serious ADEs	Monitoring	Special Considerations
S1P Modulators				
Fingolimod	0.5 mg once daily (pediatric patients ≤ 40 kg: 0.25 mg once daily)	Bradycardia, prolonged QTc Macular edema Lymphopenia	ECG, fundus examination of eyes, CBC, ALC, LFT, blood pressure	Avoid if recent cardiac event, such as myocardial infarction or stroke, or class III or IV heart failure, or type II second- or third-degree heart block
Siponimod	1 or 2 mg once daily	Infections	Screen for VZV antibodies	Washout for certain interacting medications
Ozanimod	0.92 mg once daily	Liver enzyme elevation Altered pulmonary function Hypertension Skin cancer	PFT and skin examination recommended for susceptible individuals	Avoid live virus vaccines Rebound MS activity after discontinuation Fetal risk PML risk
Fumaric Acids				
Dimethyl fumarate	240 mg twice daily	Lymphopenia Infections	CBC, ALC, LFT	Dose titration to reduce GI upset and flushing
Diroximel fumarate	462 mg twice daily	Liver enzyme elevation		PML risk (cases reported with DMF)
Monomethyl fumarate	190 mg twice daily			
Pyrimidine Synthesis Inhibitor				
Teriflunomide	7 or 14 mg once daily	Hepatotoxicity ^a Teratogenicity ^a Neutropenia, lymphopenia Hypertension	LFT, CBC, blood pressure Screen for tuberculosis and pregnancy	Monthly LFT for first 6 mo Fetal risk Accelerated elimination, if necessary, because of long half-life
DNA Synthesis Inhibitor				
Cladribine	10 mg tablets ^b as directed (weight-based, cyclic dose) Cumulative dosage of 3.5 mg/kg orally, divided into two courses (or years) Each treatment course is divided into two cycles (or months)	Malignancy ^a Teratogenicity ^a Lymphopenia Infection Liver enzyme elevation GVHD	Before each course: CBC, ALC, LFT, MRI Screen for VZV antibodies, tuberculosis, hepatitis B, hepatitis C, HIV, pregnancy Follow standard cancer screening guidelines	Fetal risk Drug interactions include hemotoxic agents, antiviral and antiretroviral agents, BCRP inhibitor/inducers, hormonal contraceptives Separate from oral medications by 3 hr Avoid live virus vaccines Cytotoxic agent requires careful handling procedures PML risk

^aBoxed warning.

^bDose for each treatment course is rounded to the next 10-mg increment.

ADE = adverse drug effect; ALC = absolute lymphocyte count; BCRP = breast cancer receptor protein; DMF = dimethyl fumarate; GVHD = graft-vs.-host disease; PFT = pulmonary function test; PML = progressive multifocal leukoencephalopathy; VZV = varicella zoster virus.

Information from: Pawate S, Bagnato F. Newer agents in the treatment of multiple sclerosis. *Neurologist* 2015;19:104-17; Naismith RT, Wolinsky JS, Wundes A, et al. Diroximel fumarate (DRF) in patients with relapsing-remitting multiple sclerosis: interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study [published online ahead of print, 2019 Nov 4]. *Mult Scler* 2019; Wynn D, Lategan TW, Sprague TN, et al. Monomethyl fumarate has better gastrointestinal tolerability profile compared with dimethyl fumarate [published online ahead of print, 2020 Jun 25]. *Mult Scler Relat Disord* 2020;45:102335; Mavenclad [prescribing information]. Rockland, MA: EMD Serono, 2019.

Table 4. Unique Differences Among S1P Modulators

Medication	Receptor Subtypes	Drug Interactions	Special Considerations
Fingolimod	S1P ₁ ; S1P ₃ ; S1P ₄ ; S1P ₅	<p>Contraindicated with class Ia and III antiarrhythmics</p> <p>Use caution with other antiarrhythmics, QTc-prolonging agents (e.g., citalopram, ciprofloxacin), heart rate-lowering agents (e.g., β-blockers, verapamil, digoxin), strong inhibitors/inducers of CYP3A4 (e.g., carbamazepine, ketoconazole), immunosuppressants</p>	<p>FDO required before initiation of therapy and repeated if ≥ 14-day lapse in therapy</p> <p>Pediatric approval for age ≥ 10 yr</p> <p>PML has been reported</p>
Siponimod	S1P ₁ ; S1P ₅	<p>Avoid with antiarrhythmics (especially class Ia and III), QTc-prolonging agents, strong dual inhibitors/inducers of CYP2C9 and CYP3A4 (e.g., fluconazole, carbamazepine, rifampin)</p> <p>Avoid after alemtuzumab</p> <p>Use caution with heart rate-lowering agents, immunosuppressants, moderate dual inhibitors/inducers of CYP2C9 and CYP3A4 (e.g., modafinil, efavirenz)</p>	<p>CYP2C9 genotype needed to determine dose</p> <p>FDO required if certain cardiac history</p> <p>Dose titration required (with or without FDO) and should be repeated if ≥ 4-day lapse in therapy</p> <p>Refrigeration required before opening</p>
Ozanimod	S1P ₁ ; S1P ₅	<p>Contraindicated with monoamine oxidase (MAO) inhibitors (e.g., selegiline, linezolid)</p> <p>Avoid with strong CYP2C8 inhibitors/inducers (gemfibrozil, rifampin) and BCRP inhibitors (e.g., cyclosporine)</p> <p>Use caution with antiarrhythmics (especially class Ia and III), QTc-prolonging agents, immunosuppressants</p> <p>Coadministration with MAO inhibitors, adrenergic/serotonergic drugs (SSRIs, SNRIs, TCAs), and tyramine-rich foods may increase the risk of hypertensive crisis</p>	<p>Dose titration required</p> <p>Monitor for hypertensive crisis</p>

BCRP = breast cancer receptor protein; FDO = first dose observation; PML = progressive multifocal leukoencephalopathy; SNRI = serotonin norepinephrine reuptake inhibitor; S1P = sphingosine-1-phosphate; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Information from: Manufacturers' package inserts; Cree BAC, Mares J, Hartung HP. Current therapeutic landscape in multiple sclerosis: an evolving treatment paradigm. *Curr Opin Neurol* 2019;32:365-77.

Cladribine

Cladribine is a DNA synthesis inhibitor causing cytotoxic depletion of B and T lymphocytes. Cladribine has a unique weight-based dosing regimen consisting of two dosing courses, each divided into two dosing cycles, which totals 16–20 doses over a 2-year period. Patient care scenario 1 describes a practical example of calculating the dose for each course. Although cladribine is approved for relapsing forms of MS, to include RRMS and active SPMS, cladribine is not recommended for CIS because of its safety profile and the recommendation to reserve its use for patients with an inadequate response to, or who cannot tolerate, an alternative DMT. These more serious potential adverse drug effects include malignancy, lymphocytopenia, serious infection, and teratogenicity. Like teriflunomide, cladribine is contraindicated in women and men of reproductive potential who do not reliably use contraception.

Of interest, cladribine may reduce the effectiveness of hormonal contraceptives, and additional barrier contraception should be recommended, when appropriate. In addition, several other medications may interact with cladribine; hence, a thorough medication reconciliation is required. The more common adverse effects with cladribine include headache, nausea, and respiratory tract infections. Cladribine efficacy in RRMS is similar to that of the S1P modulators, with a 57% reduction in relapse rates and significantly improved MRI outcomes compared with placebo (Giovannoni 2018).

Parenteral Monoclonal Antibodies

Four humanized monoclonal antibodies are currently available for MS treatment. Each of these parenteral agents (natalizumab, alemtuzumab, ocrelizumab, ofatumumab) is considered highly efficacious for relapsing forms of MS. Like

Patient Care Scenario

A woman (weight 75.5 kg) with treatment-refractory relapsing MS has been referred to you, the clinical pharmacist,

for assistance with cladribine initiation. Calculate the patient's dose for cycles 1 and 2 of treatment course 1.

ANSWER

The first step is to calculate the total cumulative dose. The cumulative dose is 3.5 mg/kg multiplied by her weight of 75.5 kg for a total of 264 mg. This cumulative dose is divided into two treatment courses, which are taken 1 year apart. The calculated dose for each course is 132 mg ($264 \div 2$). Cladribine is available in tablets of

10 mg each; hence, the dose for each treatment course is rounded to the next 10 mg increment. Her dose for course 1 is therefore 140 mg. Each course is then divided into two treatment cycles, which are taken at months 1 and 2 of each year. This patient's dose for treatment course 1 divides evenly to 70 mg ($140 \div 2$) for cycles 1 and 2.

1. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. *Mult Scler* 2018;24:1594-604.

2. Mavenclad manufacturer's package insert.

with the oral agents, the benefit of these highly effective therapies must be weighed against the risk of more serious side effects and adverse drug effects (Table 5). In addition, ocrelizumab is the first DMT approved for PPMS. Mitoxantrone is omitted from this discussion because it is rarely used, given its significant cardiotoxicity and adverse hematologic effects.

Natalizumab

Natalizumab is an antibody that binds leukocyte α 4-integrins, thus blocking receptor adhesion and preventing migration of inflammatory leukocytes into the CNS. In a pivotal clinical study of patients with RRMS, natalizumab dosed every 4 weeks reduced relapse rates by 68% and new brain lesions by 83% compared with placebo (Polman 2006). The most common adverse effects with natalizumab include headache, fatigue, arthralgias, nausea, and respiratory tract infections. The most significant adverse drug effect of natalizumab is a serious brain infection, PML, and the agent's label includes a boxed warning for this. The three identified risk factors for the development of this rare, but potentially life-threatening ADE are: presence of anti-JCV (John Cunningham Virus) antibodies, duration of natalizumab therapy, and prior immunosuppressant therapy. Of importance, the presence of detectable anti-JCV antibodies is not a contraindication for natalizumab use, and MS clinicians may recommend this agent, depending on a patient's specific risk. The risk of PML in an individual patient receiving natalizumab can be estimated using the incidence data in Table 6 (Plavina 2014). A recent retrospective study suggests that extending natalizumab dosing to 6- or 8-week intervals reduces the risk of PML. Although it is unclear whether this extended-interval dosing will significantly affect efficacy outcomes, one recent prospective study shows positive results (van Kempen 2020). Many MS experts consider this a reasonable risk mitigation strategy, particularly for patients with a high anti-JCV antibody index (Ryerson 2019). Because of its high efficacy and overall favorable

safety profile, natalizumab remains a first-line agent, particularly for patients with highly active MS or risk factors for a poor prognosis who have a negative or low positive anti-JCV antibody index.

Although PML has been reported in patients with MS receiving other DMTs (including fingolimod, dimethyl fumarate, alemtuzumab, and ocrelizumab), the usefulness of JCV antibody testing has not been validated as a predictive PML risk factor for any therapy other than natalizumab. In addition, although no cases have been reported in patients with MS as a result of other DMTs, their potential risk of causing PML should still be considered according to each agent's mechanism of action. These therapies include cladribine, S1P modulators (siponimod, ozanimod), fumaric acids, and ofatumumab.

Alemtuzumab

Alemtuzumab is an antibody against CD52, a surface protein on various immunologic cells, including T and B lymphocytes. The mechanism of alemtuzumab in MS is through T- and B-cell lysis and depletion, therefore causing significant immunologic and hematologic effects such as lymphocytopenia, neutropenia, and anemia. Alemtuzumab, dosed cyclically for 2 years, has several boxed warnings for infusion reactions, autoimmune conditions, malignancy, and stroke, as well as a stringent Risk Evaluation and Mitigation Strategies (REMS) program, which requires frequent laboratory monitoring. In addition, premedication is necessary before each infusion to mitigate serious infusion reactions, and antiviral prophylaxis is recommended for at-risk patients. In a clinical trial against an active comparator, IFN β subcutaneously three times weekly, alemtuzumab reduced relapse rates by 55% and significantly improved MRI outcomes in patients with RRMS (Cohen 2012). Alemtuzumab is approved for relapsing forms of MS; however, because of its safety profile, it should be reserved for patients with an inadequate response to two or more DMTs.

Table 5. Parenteral Monoclonal Antibody Disease-Modifying Therapies

Medication	Dose	Serious ADEs	Monitoring	Special Considerations
Natalizumab	300 mg IV every 4 wk	PML ^a Hepatotoxicity Infusion-related reaction	Anti-JCV antibodies MRI LFT	REMS for PML risk
Alemtuzumab	Year 1: 12 mg IV daily × 5 days Year 2: 12 mg IV daily × 3 days	Infusion-related reaction ^a Autoimmune disorders ^a : ITP, nephropathies, thyroid, cytopenia, hepatitis Stroke ^a Malignancy ^a : Thyroid, melanoma, lymphoproliferative disorders Lymphopenia Infection	CBC, ALC, LFT, TSH, SCr, urinalysis Screen for VZV antibodies, tuberculosis, HIV, HPV, skin cancer	REMS program requires baseline and ongoing laboratory monitoring (at monthly, quarterly, and annual intervals) for at least 48 mo after the last dose Premedicate before infusion Herpes prophylaxis if CD4 ⁺ count < 200 cells/mm ³ Avoid live virus vaccines PML risk Fetal risk
Ocrelizumab	300 mg IV on days 0 and 15; then 600 mg IV every 6 mo	Infusion-related reaction Hepatitis B reactivation Reduction in immunoglobulins Infection Breast cancer	Baseline serum immunoglobulins Screen for hepatitis B Follow standard breast cancer screening guidelines	Premedicate before infusion Avoid live virus vaccines PML risk Fetal risk
Ofatumumab	20 mg SC on weeks 0, 1, and 2; then once monthly starting on week 4	Injection-related reaction Hepatitis B reactivation Reduction in immunoglobulins Infection	Baseline serum immunoglobulins Screen for hepatitis B	Consider premedications before first dose Avoid live virus vaccines PML risk Fetal risk

^aBoxed warning.

HPV = human papillomavirus; IV = intravenous(ly); JCV = John Cunningham virus; LFT = liver function test; PML = progressive multifocal leukoencephalopathy.

Information from: Blinkenberg M, Soelberg Sørensen P. Monoclonal antibodies for relapsing multiple sclerosis: a review of recently marketed and late-stage agents. *CNS Drugs* 2017;31:357-71; and manufacturer's package information.

Table 6. Estimated Risk^a of Natalizumab-Associated PML

Anti-JCV Antibody Index	Natalizumab Treatment Duration		
	1–24 mo	25–48 mo	49–72 mo
≤ 0.9	0.1 (0.0–0.15)	0.3 (0.0–1.28)	0.4 (0.0–1.25)
≤ 1.1	0.1 (0.0–0.23)	0.7 (0.0–1.85)	0.7 (0.0–1.98)
≤ 1.3	0.1 (0.0–0.28)	1.0 (0.0–2.38)	1.2 (0.0–2.56)
≤ 1.5	0.1 (0.0–0.30)	1.2 (0.20–2.61)	1.3 (0.24–2.78)
> 1.5	1.0 (0.84–0.88)	8.1 (7.06–8.98)	8.5 (7.41–9.46)

^aCumulative risk estimates (99% CI).

PML = progressive multifocal leukoencephalopathy.

Information from: Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014;76:802-12.

Ocrelizumab

Ocrelizumab is an anti-CD20 antibody that depletes circulating B cells, similarly to rituximab, which is used off-label for treatment-resistant and progressive MS (Pawate 2015). As a humanized antibody, ocrelizumab may have fewer significant infusion-related reactions than rituximab, though premedication is still recommended. Other common adverse effects are respiratory and dermatologic infections. Patients and providers considering ocrelizumab should also consider the warning for hepatitis B reactivation and breast cancer. After a split first dose, ocrelizumab is infused every 6 months. In a clinical trial against an active comparator, IFN β subcutaneously three times weekly, ocrelizumab reduced relapse rates by 47% and significantly improved MRI outcomes in patients with relapsing MS (Hauser 2017). In addition to its indication for relapsing forms of MS, ocrelizumab is the first DMT approved for PPMS, according to the results of a randomized, placebo-controlled trial showing a 25% reduction in confirmed disability progression and a significant reduction in new lesions in patients with PPMS (Montalban 2017). The greatest benefit was in patients with PPMS younger than 55 with radiologically active MS before enrollment.

Ofatumumab

Ofatumumab is the first subcutaneously self-injected anti-CD20 antibody approved for relapsing forms of MS, including CIS, RRMS, and active SPMS. Compared with teriflunomide in two phase III studies, ofatumumab reduced the annualized relapse rate by 50% and 58% and reduced new or enlarging T2 lesions by 82% and 84% (Hauser 2020). The most common adverse effects include local injection site reactions (erythema, urticaria, pain), systemic injection-related reactions (fever, chills, headache, myalgia, fatigue), and upper respiratory tract infections. Systemic injection-related reactions usually occur within 24 hours after the first injection and can be mitigated by premedicating with a combination of antihistamines, acetaminophen, and corticosteroids. However, a subgroup analysis shows that use of an antihistamine and acetaminophen results in fewer reported adverse effects than when a corticosteroid is added to the premedication regimen. Ofatumumab is contraindicated in patients with an active hepatitis B infection.

Therapy Selection

Treatment with a DMT should be considered soon after diagnosis because early treatment improves long-term outcomes. With DMTs rapidly expanding, the therapy selection process can be challenging because of the many factors that collectively determine the most appropriate therapy for a patient (Box 3). The American Academy of Neurology (AAN) and the Consortium of Multiple Sclerosis Centers (CMSC) recently published practice guidelines to help clinicians navigate the complexities of selecting therapy for treatment-naive patients and those who may require a DMT change because of a suboptimal response or intolerable adverse effects. A

Box 3. Considerations for Therapy Selection

Patient-specific

- Diagnosis and subtype
- DMT history
- Comorbidities
- Concurrent medications
- Patient preference
- Risk tolerance
- Pregnancy potential

Therapy-specific

- Adverse effect profile
- Administration
- Financial burden
- Potential ADEs

ADE = adverse drug effect; DMT = disease-modifying therapy.

Information from: Ford CC, Morrow SA. CMSC Practical Guidelines for the Selection of Disease-Modifying Therapies in Multiple Sclerosis: CMSC DMT Guideline Writing Group. February 2019; Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:777-88.

suboptimal treatment response includes clinical or MRI activity that occurs while the patient has adhered to the correct dose and administration of a DMT for a sufficient time, generally at least 6 months (Ford 2019).

2018 AAN Practice Guidelines

The 2018 AAN practice guidelines emphasize several strategies for DMT use in adult patients with MS. These guidelines also emphasize the importance of a patient-centric, shared decision-making approach. Moreover, the guidelines highlight key considerations when initiating a new DMT, which include evaluating patient readiness to start therapy and adhere to ongoing safety monitoring, setting realistic expectations, and dedicating a follow-up interaction for DMT education for patients with newly diagnosed disease. Depression can be a primary or tertiary symptom of MS, is associated with poor outcomes, and should be addressed before DMT initiation, when possible. The AAN also provides guidance for assessing ongoing disease activity and evaluating adherence to the prescribed DMT to determine when it may be appropriate to change to another therapy or discontinue treatment altogether (Rae-Grant 2018).

2019 CMSC Practical Guidelines

Although echoing many of the AAN recommendations, the CMSC published in 2019 detailed practical guidelines for DMT selection in relapsing MS, highly active MS, and progressive MS (Figure 2). The most appropriate DMTs are those with the most favorable risk-benefit profile, considering all the previously mentioned patient- and therapy-specific factors. An

escalation approach (i.e., initially starting with a platform or other moderate-efficacy DMT) may be appropriate for many patients with relapsing MS, especially if they are risk-averse to the significant adverse drug effects associated with the more effective therapies. However, for those who present

with highly active disease or risk factors for such, an induction-style approach with a higher-efficacy first therapy is strongly encouraged. Although the monoclonal antibodies are considered the most effective agents for relapsing MS, most MS experts consider fingolimod and cladribine more

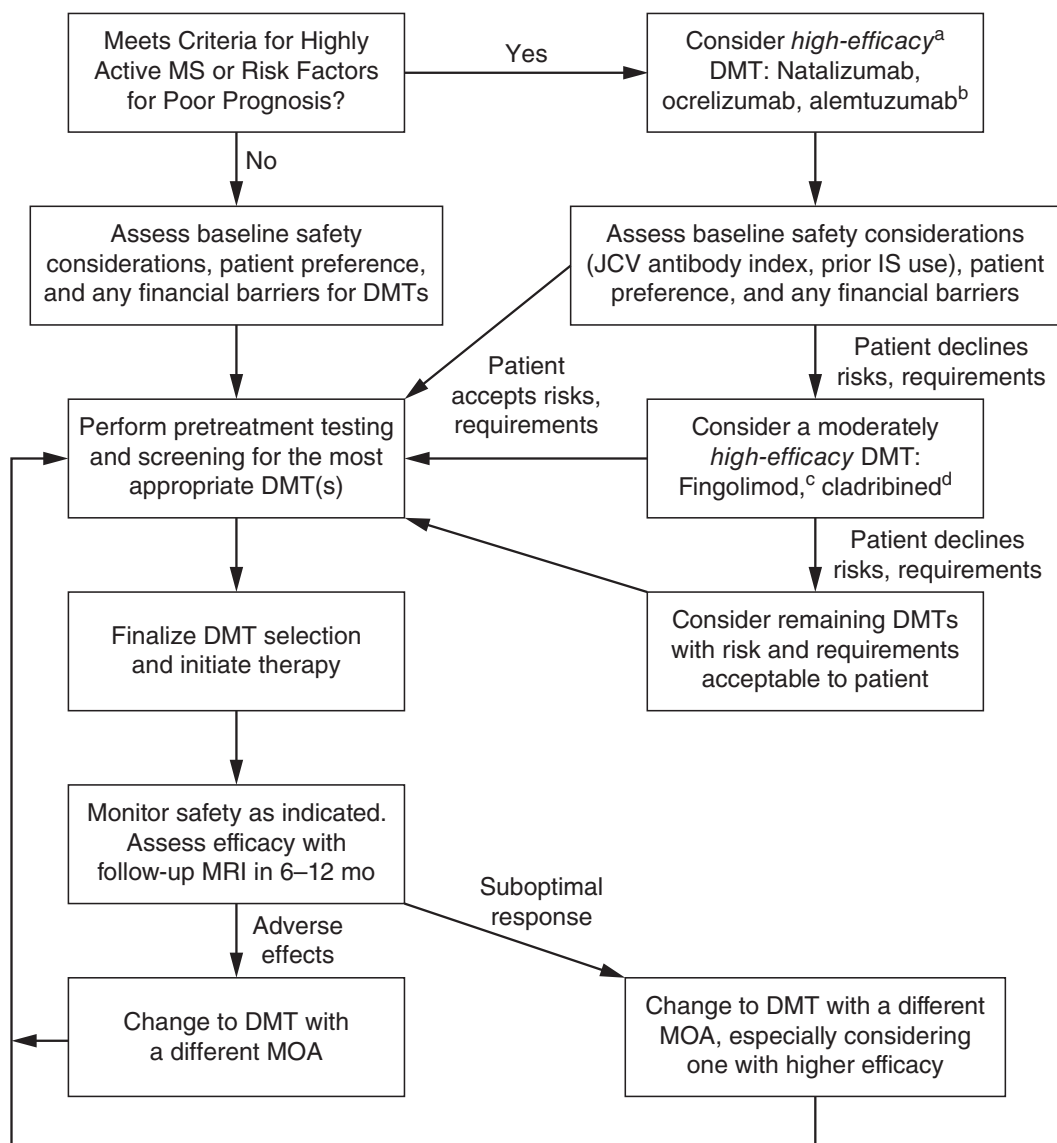


Figure 2. Treatment algorithm for relapsing forms of multiple sclerosis (assumes patient meets diagnostic criteria for relapsing or active MS, including CIS).

^aPublished before FDA approval of ofatumumab.

^bShould generally be reserved for patients who have had an inadequate response to ≥ 2 drugs indicated for the treatment of MS.

^cPublication before FDA approval of other S1P modulators.

^dShould generally be reserved for patients with an inadequate response to ≥ 1 drug indicated for the treatment of MS.

ADE = adverse drug effect; DMT = disease-modifying therapy; IS = immunosuppressant; JCV = John Cunningham virus; MOA = mechanism of action.

Information from: Ford CC, Morrow SA. CMSC Practical Guidelines for the Selection of Disease-Modifying Therapies in Multiple Sclerosis: CMSC DMT Guideline Writing Group. February 2019.

highly effective than the non-S1P oral therapies and the injectable platform agents. Ocrelizumab should be considered for all patients with PPMS. Any patient with progressive MS and evidence of inflammatory disease activity, clinically or radiologically, may benefit from DMT (Ford 2019).

When changing to a different DMT, often because of sub-optimal response, intolerable adverse effects, or patient preference, the MS clinician must again consider many factors to determine the most appropriate next therapy. In addition, clinicians must consider the timing of the transition from one DMT to another to balance the risk of any overlapping toxicities (e.g., lymphopenia) with the risk of MS activity from a prolonged lapse in therapy. Moreover, of concern is the potential risk of rebound MS activity and severely increased disability after discontinuing natalizumab and the S1P modulators. Therefore, it is recommended to transition with the shortest therapy gap possible after discontinuing any of these agents. Because of the potential for increased adverse effects and lack of enhanced benefit, combination therapy with more than one DMT is not recommended (Lublin 2013).

DMTs and Vaccines

Although vaccine safety for people with MS has been questioned, most scientific evidence supports no change in the risk of developing MS and no increased risk of MS activity after vaccination (Mailand 2017). The efficacy of vaccines in patients with untreated MS does not differ from that in healthy controls, and MS experts recommend that people with MS receive vaccinations according to the standard guidelines (Farez 2019). Because of their various immunomodulating and immunosuppressive effects, DMTs raise concern for decreasing vaccine efficacy and increasing vaccine-induced infection. Overall, non-live virus vaccines, including those against infections such as seasonal flu, pneumonia, shingles, and COVID-19 are considered safe for patients with untreated MS and those taking a DMT. Live virus vaccines should be avoided during treatment with several immunosuppressive therapies, including S1P modulators, cladribine, alemtuzumab, ocrelizumab, and ofatumumab. Any necessary live vaccines should be administered before initiating these agents, or therapy may be discontinued if a live vaccine is required for a patient with MS already receiving one of these treatments. The timing of therapy interruption and vaccination is unique for each agent, and specific guidance is available in the corresponding medication guide. Additionally, the National MS Society recently published guidance around safety, efficacy, and timing of COVID-19 vaccines in people with MS. Before receiving any vaccine, patients with MS, especially those receiving a DMT, should consult with a health care provider for specific and personalized recommendations (Ciotti 2020; Farez 2019). Pharmacists play an important role in educating patients and providers on the indication and appropriateness of vaccines, as well as assisting with coordinating the timing of vaccinations before, during, and after MS treatment.

Pipeline Therapies

As mentioned earlier, most of the currently available DMTs target inflammatory demyelination and are therefore most effective during the active, relapsing phase of MS. Another S1P modulator, ponesimod, which is highly selective for S1P₁, is awaiting FDA review in early 2021. To more significantly alter the progressive nature of MS, which leads to disability, newer mechanisms of action that target neurodegeneration and provide neuroprotection are essential. This is challenging, however, because the mechanism of neurodegeneration is not fully understood. In addition to ongoing studies of new agents for relapsing MS, research is extensive in the area of progressive MS and neuroprotective therapies. Agents such as ublituximab (a targeted anti-CD20 antibody) and ibudilast (an inhibitor of toll-like receptors and proinflammatory cytokines) are in late-phase development. Other therapies introduce novel mechanisms into MS treatment. These therapies include opicinumab (with anti-LINGO activity to promote myelin repair), an innovative modified T-cell therapy targeted for Epstein-Barr virus–infected cells, and transplantation with mesenchymal stem cells.

Access and Affordability

Although DMTs significantly improve outcomes for patients with MS, poor adherence to therapy reduces their potential benefit. One significant barrier to adherence is the high cost of treatment (Simacek 2018). The average annual wholesale price of most DMTs exceeded \$100,000 in 2020, not including any associated administration costs for the infusible therapies (IBM 2021). For some insured patients, this high cost of care has led to strict step-edit criteria imposed by insurance providers and large out-of-pocket costs in the form of deductibles, copays, and coinsurance. Most manufacturer-supported programs offer medication-specific financial assistance for those with non-government plans. The recent availability of generic medications has resulted in lower cost equivalent therapies, though many generic products lack this type of financial assistance. Pharmacists are in a key position to educate patients and providers on the clinical and financial similarities and differences among these agents and to identify, for each patient, the most cost-effective agent in each class of therapies.

Several nonprofit organizations, such as HealthWell Foundation and Patient Access Network Foundation, provide financial support for high medication costs for patients who meet specific criteria. These disease-specific grants often have limited funding throughout the year, however, making it difficult to secure this financial aid. When all other options have been exhausted, many manufacturers also offer patient assistance programs that provide medication for free to patients who are uninsured or severely underinsured, as well as to those whose insurance denies coverage because of failure to meet the formulary criteria.

Treating MS Symptoms

In addition to modifying the disease course, other important aspects in the comprehensive treatment of patients with MS are identifying and treating the associated symptoms. Symptom management can improve quality of life and limit the impact of MS disability. This is significant because it may allow for ongoing employment and productivity (Toosy 2014). However, symptomatic management of MS can be challenging because patient presentation and treatment response are variable and unpredictable. Symptoms can also overlap; hence, prioritizing and treating the most bothersome symptoms may provide the greatest impact on quality of life improvement. Depression is one of the most common symptoms of MS and may significantly affect quality of life, productivity, and medication adherence (Rae-Grant 2018). Depression screenings should routinely be performed early and late in the disease course. Clinical pharmacists should be attentive to signs of depression and refer the patient for the appropriate intervention or treatment.

Treatment often requires a multidisciplinary and multimodal approach, combining pharmacologic and nonpharmacologic therapies (Table 7). In addition to these pharmacotherapies, studies are ongoing of using cannabinoids for MS-related spasticity and pain, prompting an increased use of cannabidiol (CBD) products in recent years. Nabiximols, an oromucosal spray consisting of CBD and tetrahydrocannabinol, is approved as a second-line antispasmodic agent among the European Union and other countries, though it is not FDA approved for use in the United States (Novotna 2011).

Modifiable Risk Factors

Multiple sclerosis clinicians should encourage patients with MS to follow a responsible and healthy lifestyle. This includes addressing any modifiable risk factors that might contribute to poor outcomes, including increased risk of disability (Rosso 2019). Cigarette smoking can increase the risk of developing MS as well as worsen MS disease activity and increase the rate of disease progression and disability; therefore, the importance of smoking cessation should be emphasized and continually encouraged. Vitamin D deficiency is also associated with an increased risk of MS development and disease activity, and supplementation of vitamin D₃ is recommended with the goal of achieving serum 25-hydroxyvitamin D concentrations near the upper limit of normal (or 30–60 ng/mL) (Pierrot-Deseilligny 2017). Several vascular comorbidities, including obesity and hyperlipidemia, have been linked to exacerbated central inflammation and disability in patients with relapsing MS (Stampanoni Bassi 2019). It is important to educate patients with MS about the negative consequences of obesity and to encourage and support a lifestyle consisting of routine exercise and healthy nutrition.

MS IN SPECIAL POPULATIONS

The CMSC also provides guidance for DMT use in pediatric-onset MS (POMS) and considerations for use before, during, and after pregnancy. Such considerations for disease management in these special populations are briefly introduced in the text that follows (Ford 2019).

Pediatric-Onset MS

About 3%–5% of all patients with MS have disease onset before 18 years of age, with most cases developing at the time of puberty at 13–16 years of age. Pediatric-onset MS is usually relapsing MS with a few distinctive features, such as greater lesion burden, more frequent relapses, and more neurocognitive symptoms than in adult counterparts. Clinical presentation, especially in younger children, differs from adults and makes the diagnosis challenging. Therefore, a thorough evaluation is critical to rule out MS mimics, such as neuromyelitis optica spectrum disorder and acute disseminated encephalomyelitis. Patients with POMS often recover from relapses more quickly than adults, and although they have an overall similar course of progression, disability onset usually occurs at an earlier age (McKay 2019).

The overall goals, treatment approach, and DMT selection process for patients with POMS are very similar to those for adult patients; however, there are a few additional considerations, including social support and access to care, shifting personal autonomy and responsibilities, and ongoing cognitive, motor, and immune development. In general, as in adult patients, DMT use in POMS is usually recommended early in the disease course and soon after diagnosis to slow long-term progression and disability. Selection of DMTs should follow a risk-benefit analysis that is both patient- and therapy-specific (Ford 2019).

Although several DMTs have routinely been used off-label in pediatric patients, in 2018, the FDA approved fingolimod as the first agent indicated for use in patients 10 years and older (Chitnis 2018). Fingolimod had more favorable reductions in relapse rates and MRI changes than IFN β intramuscularly weekly, and adverse effect rates in children were similar to those in adults. The approved fingolimod dose is lower (0.25 mg by mouth once daily) for patients weighing 40 kg or less, and it is recommended to complete immunizations before initiating therapy.

Interferons and glatiramer acetate are considered safe and appropriate off-label options for pediatric patients with less disease activity at onset or those with low risk-tolerance. For patients with POMS who present with highly active disease and those with a suboptimal response to another DMT, off-label natalizumab or rituximab should be considered (Ghezzi 2020). The potential benefits of natalizumab often outweigh the risks, especially for those without anti-JCV antibodies (Ghezzi 2015). Because of significant safety concerns, teriflunomide, alemtuzumab, and cladribine are not recommended in pediatric patients.

Table 7. Treatment of Common MS Symptoms

Symptom	Pharmacotherapy	Nonpharmacologic and Alternative Therapies
Fatigue	Amantadine 100 mg twice daily Modafinil 100–200 mg per day Armodafinil 150–250 mg per day Methylphenidate 10–20 mg twice daily	Address underlying and contributing factors like mood or sleep disorders and medication adverse effects Maintain mobility and increase aerobic exercise Dietary acetyl-L-carnitine Occupational therapy for energy conservation strategies
Depression and mood disorders	SSRIs, SNRIs, TCAs at typical dosages Bupropion 100–450 mg per day, divided Mirtazapine 15–45 mg per day Pseudobulbar affect (PBA): Dextromethorphan 20 mg/ quinidine 10 mg twice daily	Address underlying and contributing factors like fatigue, cognitive impairment Psychotherapy with cognitive behavioral therapy Physical activity and exercise
Neuralgias and neuropathic pain	Gabapentin 100–600 mg up to four times per day, max 3600 mg per day Pregabalin 75–225 mg twice daily Duloxetine 60 mg per day Carbamazepine 300–1200 mg per day, divided Oxcarbazepine 600–1200 mg per day, divided TCAs at typical dosages	Massage therapy Acupuncture Hypnosis TENS DBS
Bladder dysfunction	Overactive bladder: Oxybutynin 5–15 mg per day, divided Tolterodine IR 2 mg twice daily; ER 4 mg per day Solifenacin 5–10 mg per day Mirabegron 25–50 mg per day Intradetrusor botulinum toxin injections Impaired emptying: Tamsulosin 0.4 mg at bedtime Nocturia: Desmopressin nasal spray or oral tablets at typical dosages	Bladder rehabilitation Pelvic floor exercises Chronic catheterization Percutaneous nerve stimulation
Bowel dysfunction	Bulk-forming agents: Methylcellulose, psyllium hydrophilic mucilloid Stool softeners: Docusate Osmotic laxatives: Lactulose, polyethylene glycol solution	Lifestyle modification to increase fluid intake and dietary fiber Establish a bowel routine Physical activity and exercise
Sexual dysfunction	Men: Phosphodiesterase type 5 inhibitors Intracavernosal or transurethral alprostadil Women: Topical lubricants Vaginal estrogen	Address contributing factors like depression, fatigue, bladder dysfunction, medication adverse effects Counseling
Spasticity	Baclofen 5–20 mg three or four times per day Tizanidine 2–6 mg three or four times per day Diazepam 2–10 mg up to four times per day Gabapentin 100–600 mg up to four times per day Botulinum toxin injections Intrathecal baclofen	Physiotherapy and physical therapy Physical activity, exercise, and stretching Orthotic devices

(continued)

Table 7. Treatment of Common MS Symptoms (*continued*)

Symptom	Pharmacotherapy	Nonpharmacologic and Alternative Therapies
Ataxia, tremor	Primidone 250 mg three or four times daily Propranolol 40–80 mg two or three times per day Carbamazepine 400–1200 mg per day, divided Oxcarbazepine 600–1200 mg per day, divided Topiramate 25–200 mg twice daily Clonazepam 3–6 mg per day Botulinum toxin injections	Physiotherapy, occupational therapy Weight bracelets, limb cooling DBS
Gait impairment	Dalfampridine ER 10 mg twice daily	Physical therapy Physical activity, exercise Mobility assistance devices like braces, canes, walkers, wheelchairs

DBS = deep brain stimulation; ER = extended release; IR = immediate release; TENS = transcutaneous electrical nerve stimulation.

Information from: Toosy A, Ciccarelli O, Thompson A. Symptomatic treatment and management of multiple sclerosis. *Handb Clin Neurol* 2014;122:513-62; Henze T, Rieckmann P, Toyka KV. Multiple Sclerosis Therapy Consensus Group of the German Multiple Sclerosis Society. Symptomatic treatment of multiple sclerosis. *Eur Neurol* 2006;56:78-105; Zecca C, Riccitelli GC, Disanto G, et al. Urinary incontinence in multiple sclerosis: prevalence, severity and impact on patients' quality of life. *Eur J Neurol* 2016;23:1228-34.

MS and Pregnancy

Because most patients with MS are women and many receive the diagnosis during their childbearing years, family planning is an important topic of discussion. With respect to DMT, the decision of whether to continue or discontinue treatment before conception is quite challenging and must consider the risk-benefit for both the mother and the fetus. In general, pregnancy and delivery outcomes do not differ significantly among women with and without MS. It is also encouraging that MS activity and relapses decrease during pregnancy for most women. Therefore, the conventional approach is to discontinue DMT before conception and resume after delivery, especially for patients who have had a mild disease course. However, for patients with more highly active MS, continuing the current DMT, or using a bridge treatment with a safer alternative, up to conception may be warranted. In some instances, continuation of a DMT throughout pregnancy may be necessary.

Most currently available DMTs are either contraindicated (teriflunomide, cladribine) because of teratogenicity or strongly discouraged during pregnancy (S1P modulators, cladribine, alemtuzumab, ocrelizumab, ofatumumab) because of potential fetal risk. According to safety data and pharmacokinetic profiles, the recommended washout periods vary from 10 days with siponimod to 6 months with ocrelizumab, ofatumumab, and cladribine. Undetectable plasma concentrations of teriflunomide should be confirmed before conception. No washout is necessary for glatiramer, IFN β , and the fumarates, and a washout should be avoided with natalizumab because of the risk of rebound MS activity (Ford 2019). Patients who discontinue fingolimod, and possibly other S1P modulators,

may also be at risk of increased MS disease activity, especially during the trying-to-conceive phase. Therefore, many MS experts recommend changing to a safer alternative as a bridge to conception or for continuation throughout pregnancy (Tintore 2019). Patients who become pregnant while receiving DMT without completing the recommended wash-out period and those who continue treatment throughout pregnancy should be encouraged to enroll in the manufacturer's pregnancy registry.

Although information is limited, retrospective analysis and registry data show that IFN β and glatiramer are likely safe and may be considered during pregnancy. For patients with a history of significant relapses, particularly during a previous pregnancy, the benefit of high efficacy natalizumab may outweigh the potential fetal risks of thrombocytopenia and anemia (Ford 2019; Vaughn 2018). If prenatal relapses occur and require treatment, corticosteroids are considered safe, especially during the second and third trimesters, and plasmapheresis can be considered for serious MS events.

Although pregnancy often induces a remission phase of MS, disease activity increases within a few months after delivery. The best predictor of both prenatal and postpartum relapse risk is an individual patient's pre-pregnancy relapse rate and history (Voskuhl 2017). In general, it is recommended to resume a DMT soon after delivery, though this can be delayed if the mother chooses to breastfeed. The effect of breastfeeding, partial or exclusive, on postpartum MS activity is unclear. No DMTs have been approved for use during breastfeeding, though glatiramer and IFN β are not likely orally bioavailable to the infant and are therefore the safest options.

Patient Care Scenario

M.A. is a 32-year-old African American woman who was given a diagnosis of RRMS 1½ years ago after an episode of neurologic dysfunction, followed by MRIs that revealed several brain lesions and two large spinal cord lesions (one gadolinium enhancing), all typical of MS. A lumbar puncture revealed CSF-specific OCBs. At that time, she received intravenous methylprednisolone 1000 mg for 5 days and partly recovered. Her neurologist recommended DMT, but she declined for fear of adverse effects. The patient currently takes citalopram 20 mg daily for depression, gabapentin 300 mg three times daily for neuralgia,

and vitamin D supplementation. Recently, she had sudden onset of significant fatigue and urinary incontinence. A new MRI reveals gadolinium-enhancing lesions in her brain and spinal cord. M.A.'s neurologist has recommended a high-efficacy DMT after a course of high-dose intravenous steroids. Her anti-JCV index is 1.1, and her hepatitis B panel shows immunity. All other routine laboratory test results are normal. As the clinical pharmacist, you have been consulted to provide education regarding her indication for therapy and counseling on each DMT.

ANSWER

It is important to help M.A. understand her diagnosis and risk of ongoing MS activity and disease progression. One and one-half years ago, she presented with typical MS activity consistent with an MS event. Her MRIs revealed both DIS (lesions in several locations within the CNS) and DIT (old non-enhancing lesions and one new gadolinium-enhancing lesion). The presence of CSF-specific OCBs also shows DIT. Because of the incomplete recovery from her first MS event, as well as three additional poor prognostic risk factors (African American race, spinal cord lesions at onset, and two or more events in the first 2 years of onset), the treatment guidelines recommend a high-efficacy DMT to significantly reduce MRI and relapse activity and slow progression and disability.

Because M.A. is naive to DMT, alemtuzumab is not currently indicated. You confirm that she has no prior immunosuppressant use; therefore, with an anti-JCV antibody index of 1.1, M.A.'s risk of natalizumab-associated PML is 1 in 10,000 for the first 24 months of treatment. This is not a contraindication to therapy; however, after further discussion, she does not accept this risk.

You discuss ocrelizumab and ofatumumab, including the need for baseline immunoglobulin concentrations, with M.A. She prefers a self-administered DMT to infusion treatment but asks whether she has any oral options. You advise that a moderately high-efficacy DMT like

fingolimod or other S1P modulators can be considered if her neurologist agrees, and several factors must be considered, including drug interactions (e.g., citalopram), additional baseline assessments (ECG, eye examination, laboratory tests), and risk of rebound MS activity after discontinuation.

After an in-depth discussion of each high-efficacy DMT, M.A. decides on ofatumumab. You provide her with important education points, including dose and proper injection administration, use of premedications before her first dose and afterward as needed for injection-related reactions, infection risk, and contraceptive use during treatment. You advise her to discuss any plans for pregnancy with her neurologist so that a washout period can be discussed. You advise that live virus vaccines should be avoided during treatment and recommend that she receive any necessary vaccinations before therapy, if possible. You also discuss access to care and financial resources that may be available, if needed.

Finally, you counsel M.A. that urinary incontinence may be a sign of neurogenic bladder and could place her at risk of UTIs. Infection and fever can cause a pseudo-relapse and should be reported to her medical providers. You also encourage her to make positive lifestyle choices, including aerobic exercise and healthy nutrition, which will improve her fatigue and depression.

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CONCLUSION

Multiple sclerosis is heterogeneous in presentation and clinical course with a variable response to therapy, making diagnosis and treatment challenging. In 2013, the International Advisory Committee on Clinical Trials in Multiple Sclerosis updated terms to more specifically define the active and progressive phenotypes of MS. Soon afterward, the 2017 update to the McDonald criteria simplified the diagnostic process,

allowing for an earlier diagnosis. Disease-modifying therapies target inflammatory demyelination and are thus most effective during the active phases of MS to reduce disease activity; hence, early treatment is key to delay neurodegeneration and disability. Since 2017, five new moderately to highly efficacious DMTs have been approved for relapsing forms of MS, one of which (ocrelizumab) is also approved for PPMS. The DMT selection process can be challenging and must balance patient- and therapy-specific considerations.

Practice Points

- Most patients with MS first develop RRMS, which then transitions to a progressive course secondarily (SPMS), though some patients may present with progression from the onset (PPMS). Even though CIS is the first clinical event in a patient who develops MS, CIS does not yet meet the full diagnostic criteria of DIS and DIT.
- Disease activity and progression both characterize the state of disease at any point in time and should be evaluated annually. Evidence of MS activity includes clinical relapse or MRI changes; therefore, active MS can be identified radiologically with or without the presence of the clinical sequelae.
- Comprehensive MS management includes treating acute relapses, modifying the disease course with DMT, minimizing symptoms to improve quality of life, and encouraging a healthy lifestyle to address modifiable risk factors.
- The updated 2017 McDonald criteria simplify the diagnostic process to support an early diagnosis of MS and encourage early DMT for improved outcomes.
- Although MS is highly variable in presentation and disease course, several prognostic factors associated with highly active MS can help identify patients who may be at higher risk of unfavorable outcomes.
- Current guidelines encourage high-efficacy DMTs for patients with highly active MS, those at risk of a poor prognosis, and those with a suboptimal response to other DMTs.
- Several newer DMTs are more efficacious for active and relapsing forms of MS than older platform therapies. These newer agents are more immunosuppressive, and their potential benefit must be weighed against their risk of adverse effects, including serious infections, malignancies, fetal risk, and rebound MS activity after discontinuation.
- DMT selection should be highly individualized and based on patient- and therapy-specific considerations. The AAN guidelines recommend a dedicated interaction for DMT education, especially for patients with newly diagnosed disease.
- Clinical pharmacists should be aware of the required baseline assessments, ongoing monitoring recommendations, disease and drug interactions, and vaccine considerations and recommendations for each DMT.

The AAN and the CMSC have provided guidelines for this risk-benefit treatment approach. In addition to modifying the disease course, comprehensive MS care includes addressing modifiable risk factors, minimizing symptoms, and treating acute relapses, as needed. Clinical pharmacists have an opportunity to partner with MS clinicians in developing individualized, patient-centric treatment plans that will significantly influence patient care and outcomes.

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Self-Assessment Questions

- A 58-year-old woman received a diagnosis of multiple sclerosis (MS) at age 32. She currently takes dimethyl fumarate 240 mg twice daily. The patient has not had an MS relapse in several years, and her recent MRI was relatively unchanged from 3 years ago. However, she reports ongoing and worsening fatigue and urinary incontinence, as well as more difficulty with concentration and word finding. These symptoms began 2 years ago and have become more noticeable and increased over the past 8 months. Which one of the following best evaluates this patient's ongoing and worsening symptoms?

 - Inflammatory demyelination within the CNS
 - Inflammatory demyelination within the peripheral nervous system
 - Neurodegeneration within the CNS
 - Neurodegeneration within the peripheral nervous system
 - A 28-year-old woman with recently diagnosed left optic neuritis is referred to a neurologist for further evaluation. Her medical history is unremarkable for previous neurologic events, though her current brain MRI reveals two active, gadolinium-enhancing lesions in the cortical region. The patient reports pain upon moving her left eye, as well as significantly blurred vision with loss of color vividness, impairing her ability to perform her job. Her neurologist orders methylprednisolone 1000 mg by intravenous infusion once daily for 3 days. Which one of the following best justifies the use of high-dose steroids for this patient?

 - Remyelinate her optic nerve
 - Delay the time to onset of relapsing MS
 - Reduce the likelihood of developing progressive MS
 - Accelerate recovery from the optic neuritis
 - Which one of the following patients with newly diagnosed MS is most likely to develop highly active MS?

 - 55-year-old African American woman with a 1-year history of neurologic disability
 - 43-year-old African American man with a 1-year history of two spinal cord relapses
 - 31-year-old white man with a 1-year history of two clinical relapses
 - 40-year-old white woman with three brain lesions resulting in one clinical relapse
 - Which one of the following statements best evaluates the use of sphingosine-1-phosphate (S1P) modulators in patients with MS?

 - Because of increased receptor selectivity, siponimod can be initiated without medical supervision of the first dose.
 - Because of increased receptor selectivity, siponimod has fewer drug interactions than fingolimod.
 - Fingolimod first dose should be repeated under medical supervision after a therapy lapse of 4 days or more.
 - Siponimod dose determination is weight based.
- Questions 5–7 pertain to the following case.**
- T.J. is a 38-year-old African American man with recently diagnosed relapsing MS. In addition to several lesions in his brain, he has significant lesion burden in his spinal cord and incomplete recovery from his last clinical relapse, which began 8 weeks ago, resulting in ongoing difficulties with walking and ambulation. T.J. is treatment naive, and his neurologist initially recommends a high-efficacy disease-modifying therapy (DMT).
- Which one of the following best justifies the recommendation of DMT for T.J.?

 - High-efficacy DMT can reverse his symptoms and accelerate recovery from his last relapse.
 - Because he likely has primary progressive MS (PPMS), high-efficacy therapy is preferred.
 - High-efficacy DMT should be considered initially because he has highly active MS.
 - An "induction-style" treatment approach is preferred because he has relapsing MS.
 - T.J. understands and accepts the risks and requirements of several high-efficacy DMTs. His prescreening tests show that CBC, absolute lymphocyte count, and renal and liver test results are all within normal limits. None of the laboratory test results indicates concern for infection. A JCV antibody index is positive with a value of 1.2. Which one of the following best assesses T.J.'s risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML)?

 - Natalizumab is contraindicated because his anti-JCV antibody test is positive.
 - Natalizumab-associated PML risk cannot be estimated because he is treatment naive to DMT.
 - His anti-JCV index is low positive, so he can receive a maximum of 24 doses of natalizumab.
 - His estimated risk of PML is 1 in 10,000 for up to 24 months if his anti-JCV antibody index remains ≤ 1.5 .
 - T.J. begins therapy with a high-efficacy, infusible monoclonal antibody. Three months later, at his next follow-up, he continues to have difficulty ambulating without assistance. This has significantly affected his quality of life. Which one of the following is best to recommend for T.J.?

 - Change to ofatumumab 20 mg every 4 weeks.
 - Begin physical therapy and initiate dalfampridine 10 mg twice daily.

- C. Initiate a 5-day course of intravenous methylprednisolone 1000 mg and repeat the MRI.
- D. Initiate escitalopram 10 mg per day for probable depression.

Questions 8 and 9 pertain to the following case.

H.T., a 48-year-old single father of three children, was given a diagnosis of highly active relapsing MS about 10 years ago. He currently receives ocrelizumab infusions, and his MS has been stable for several years. As the clinical pharmacist at a comprehensive MS center, you notice that H.T. has rescheduled his infusion appointment several times since his last infusion, which was almost 10 months ago.

8. Which one of the following is the most appropriate next step to take for H.T.?
 - A. Notify his MS provider that he is no longer receiving ocrelizumab therapy.
 - B. Recommend that he discontinue ocrelizumab because his MS is stable.
 - C. Recommend that he receive a split dose at the time of his next infusion.
 - D. Follow up with the patient to determine whether there are any barriers to adherence.
9. Three weeks later, H.T. presents for his ocrelizumab infusion. He expresses difficulty with his busy schedule and making time for his infusions. He wants to know if he can spread the appointments out to every 12 months instead of every 6 months. Which one of the following is best to recommend for H.T.?
 - A. Change to extended-interval-dosing ocrelizumab.
 - B. Change to extended-interval-dosing natalizumab.
 - C. Change to oral teriflunomide.
 - D. Change to subcutaneous ofatumumab.
10. A 32-year-old woman (height 68 inches, weight 82 kg) has a diagnosis of relapsing MS. Her neurologist recommends cladribine after an MRI reveals new gadolinium-enhancing lesions while the patient is taking fingolimod 0.5 mg daily. Her MS treatment history includes interferon-beta (IFN β) and natalizumab, and you have confirmed that the patient has been adherent to fingolimod since she began taking it more than 2 years ago. Which one of the following is the best cladribine dosing regimen to recommend for this patient's course 1?
 - A. 10 mg daily for 5 days, followed 23 days later by 10 mg daily for 5 days
 - B. 20 mg daily for 5 days, followed 23 days later by 20 mg daily for 5 days
 - C. 20 mg daily for 3 days, then 10 mg daily for 2 days; followed 23 days later by 20 mg daily for 2 days, then 10 mg daily for 3 days
 - D. 20 mg daily for 4 days, then 10 mg daily for 1 day; followed 23 days later by 20 mg daily for 3 days, then 10 mg daily for 2 days

11. Which one of the following patients is most likely to benefit from alemtuzumab?
 - A. 45-year-old with a history of Epstein-Barr viral infection who has relapsing MS, treatment refractory to natalizumab and ocrelizumab
 - B. 55-year-old with relapsing MS who has recurrent infections since completing treatment course 1 of cladribine
 - C. 35-year-old with relapsing MS whose condition has been stable on fingolimod but who cannot adhere to the routine laboratory monitoring protocol
 - D. 65-year-old with PPMS who has developed worsening disability while receiving ocrelizumab infusions

Questions 12 and 13 pertain to the following case.

P.C. is a 35-year-old woman who is referred to the neurologist for probable MS. On the basis of her clinical presentation and MRI, she is given a diagnosis of relapsing-remitting MS (RRMS). P.C. is extremely risk-averse and prefers nonpharmacologic and alternative medicine treatments. She declines to consider DMT and insists on a watch-and-wait approach.

12. The neurologist asks you to meet with P.C. to review the available DMTs and best plan of care. Which one of the following is best to recommend for P.C.?
 - A. Follow up with her neurologist in 1 year and recommend ocrelizumab at that time for its infrequent dosing requirements.
 - B. Follow up with her neurologist in 1 year and treat any MS symptoms as needed.
 - C. Schedule a follow-up with the clinical pharmacist in 1 month and recommend glatiramer acetate for its safety profile.
 - D. There is no need for a follow-up with the neurologist or pharmacist because the patient has declined MS treatment.
13. In addition considering a DMT, which one of the following is best to recommend for P.C.?
 - A. Vitamin D supplementation, smoking cessation, and routine exercise
 - B. Vitamin D supplementation, smoking cessation, and a high-fat diet
 - C. Smoking cessation, routine exercise, and a high-fat diet
 - D. Vitamin D supplementation, routine exercise, and a high-fat diet
14. A 9-year-old Hispanic boy has a medical history of obesity, hypertension, and impaired glucose tolerance. After extensive testing and exclusion of other diagnoses, he was recently given a diagnosis of relapsing MS. The patient has significant spinal cord disease and, despite

5 days of high-dose intravenous steroids, has not fully recovered from his last MS relapse. His laboratory test results today are unremarkable, except for an elevated fasting blood glucose of 130 mg/dL and a negative anti-JCV index. His blood pressure is 135/85 mm Hg. You discover that he is nonadherent to lisinopril and metformin. The patient and his parents are willing to consider all DMT options. Which one of the following is best to recommend for this patient?

- A. Initiate fingolimod, change his antihypertensive regimen, and recheck anti-JCV index in 6 months.
- B. Initiate natalizumab, prioritize physical activity and healthy nutrition, and recheck anti-JCV index in 6 months.
- C. Initiate fingolimod, prioritize physical activity and healthy nutrition, and recheck anti-JCV index in 6 months.
- D. Initiate glatiramer acetate, change his antihypertensive regimen, and recheck anti-JCV index in 6 months.

15. A 31-year-old African American woman was given a diagnosis of relapsing MS at 17 years of age. Her treatment history includes clinical failure of glatiramer acetate and IFN β . She has taken fingolimod 0.5 mg once daily for the past 6 years, with no relapse symptoms and only minor MRI changes since then. She and her husband would like to begin family planning, and her neurologist asks for your advice regarding a treatment plan. Which one of the following is best to recommend for this patient?

- A. Continue fingolimod until confirmation of pregnancy and then discontinue.
- B. Discontinue fingolimod and wait 2 months before trying to conceive.
- C. Change from fingolimod to siponimod and continue until confirmation of pregnancy.
- D. Change from fingolimod to glatiramer and wait 2 months before trying to conceive.