

Implications for Multiple Sclerosis in the Era of the Affordable Care Act: An Evolving Treatment Paradigm

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Abstract

The treatment paradigm for multiple sclerosis (MS) continues to evolve as additional pharmacotherapeutic options become available. Furthermore, treatment individualization has become more feasible as new medications with distinct mechanisms of action and improved adverse event profiles have reached the market. As such, clinicians should familiarize themselves with the available treatment options, paying particular attention to their various advantages and disadvantages. In order to offer patients optimal MS therapy, it is crucial for clinicians to stay current with the changing landscape of multiple sclerosis. This article provides a review of the available pharmacotherapeutic options for treating MS, discusses the impact of adherence to therapy, and describes the importance of managing comorbidities often experienced by patients with MS.

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For author information and disclosures, see end of text.

More than 20 years have passed since the approval of the first disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS), and since then, several new therapies have reached the market. Clinicians now have many options to choose from, making the individualization of therapy more feasible than previously possible. In the absence of clinical guidelines that incorporate newer therapies, becoming familiar with the various pharmacologic treatment options available will facilitate optimal and effective use.

Several landmark studies have confirmed that initiating therapy soon after the identification of clinically isolated syndrome (CIS) prolongs the time to clinically definite MS.^{1,4} While questions remain as to the long-term benefit of early initiation of therapy, it is clear that early identification and appropriate treatment improves patient quality of life (QOL). The objective of this article, the second in this supplement, is to review the treatment of MS.

Diagnosis of MS

The diagnosis of MS can be challenging, as every patient may present differently, many syndromes mimic MS, and initial symptoms are variable; however, sensory symptoms do occur in 43% of patients,⁵ and cognitive impairment is common among patients with CIS suggestive of MS (CISSMS). A study by Potagas et al demonstrated a 27.3% frequency of cognitive dysfunction among those with CISSMS; another by Feuillet et al found that 57% failed at least 2 neuropsychological tests, and were therefore considered to have significant cognitive impairment, based on their study design.⁶⁻⁸ The prevalence of cognitive dysfunction increases with age and duration of illness.⁹ Other common symptoms upon initial presentation of patients with MS include fatigue, pain, exercise intolerance, temperature sensitivity, bladder dysfunction, vertigo, erectile dysfunction, ataxia, and diplopia. Notably, optic neuritis is a common symptom that occurs in up to 20% of patients upon

initial presentation and 50% of patients during the course of disease.^{10,11}

There is no single reliable test to diagnose MS, and the diagnosis is typically one of exclusion.¹² Some common tests used to aid in the diagnosis of MS include magnetic resonance imaging (MRI), visual evoked potential, lumbar puncture, and ocular coherence tomography. MRI enables the visualization of brain and spinal cord plaques, a key feature of MS. In addition to diagnosing MS, MRI is useful for routine monitoring of disease activity, guiding treatment decisions, evaluating disease progression, and assessing the extent of brain atrophy. Gadolinium-enhanced T1-weighted lesions or T2-weighted lesions provide evidence of new areas with disease activity.¹³ Diagnostic criteria from the International Panel on the Diagnosis of Multiple Sclerosis, commonly referred to as the McDonald criteria, have been revised several times.¹² The McDonald criteria provide a framework to facilitate the diagnosis of MS, and use of the McDonald criteria has in turn led to the earlier diagnosis of disease.¹²

Disability is common in MS; therefore, evaluating disability in patients with MS is an important component of measuring disease progression. The Expanded Disability Status Scale (EDSS) is the most commonly and traditionally used scale to assess disability,¹⁴ and the EDSS is used in both clinical practice and research to evaluate the impact of drug therapy on disease progression. The EDSS scores patients on a scale of 0 to 10, with a score of 0 representing a normal neurological exam and a score of 10 representing death; EDSS scores of 4 and above indicate impaired gait, and higher scores represent more severe impairment (with 8 representing confined to a wheelchair and 9 confined to bed).

Historically, MS was categorized on the basis of disease pattern into 1 of 4 phenotypes developed by the US National Multiple Sclerosis Society (NMSS) in 1996: relapsing-remitting MS (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS). Approximately 85% of patients present initially with RRMS.¹⁴ In 2013, the International Advisory Committee on Clinical Trials of MS reevaluated the definitions of clinical subtypes of MS developed by the NMSS.¹⁵ The phenotypes that were outlined in 1996 were clinical descriptions of disease; information regarding correlation with imaging and biological markers was not provided.^{14,15} Thus, the International Advisory Committee on Clinical Trials of MS refined the phenotypes, incorporating descriptors

that include consideration of disease activity and disease progression. With the exception of PRMS, which was deleted as a phenotype, the Committee retained the original phenotypes but added descriptors of disease activity.¹⁵

Management of MS

Treatment Guidelines and Recommendations

Unfortunately, there are no curative treatments for MS. Current therapies are aimed at decreasing the frequency and duration of acute exacerbations, as well as slowing the progression of disability. Although several publications provide clinicians with guidance regarding the treatment of MS, few have been updated to include all the currently available oral medications. Notably, the Canadian MS Working Group published an updated set of recommendations in 2013.¹⁶

Current Pharmacologic Treatments

Treatment of Acute Exacerbations

Acute exacerbations of MS are typically treated with high-dose pulse corticosteroids (ie, methylprednisolone 500-1000 mg/day intravenous [IV]).¹⁷ Data have demonstrated that, at equipotent doses, oral and IV corticosteroids are associated with similar clinical and radiologic outcomes.^{18,19} A randomized trial by Beck et al evaluated low-dose oral prednisone (1 mg/kg/day) for 14 days, high-dose intravenous (IV) methylprednisolone (1 g/day) for 3 days followed by oral prednisone (1 mg/kg/day) for 11 days, or oral placebo for 14 days for the treatment of optic neuritis, and reported worse outcomes with low-dose oral corticosteroids (vs placebo and IV methylprednisolone).²⁰ Patients who received IV methylprednisolone experienced faster recovery of visual function versus placebo ($P = .0001$ for visual field; $P = .02$ for contrast sensitivity; $P = .09$ for visual acuity). In patients in the low-dose oral corticosteroid group, outcomes were similar to placebo. Furthermore, the rate of new episodes of optic neuritis was significantly higher in the group receiving oral prednisone (relative risk [RR] 1.79; 95% CI, 1.08-2.95) versus placebo. This finding was not reproduced in the IV methylprednisolone group. The use of high-dose IV corticosteroids also decreased the likelihood of relapse in the next several years prior to diagnosis of definite MS.²¹ Compared with placebo and oral prednisone, the adjusted rate ratio for the development of definite MS within 2 years of IV methylprednisolone was 0.34 (95% CI, 0.16-0.74) and 0.38 (95% CI, 0.17-0.83), respectively.²¹ Therefore, when a clinical decision is made

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to treat a relapse, high-dose corticosteroids are generally chosen. There are no definitive data supporting the use of an oral steroid taper following high-dose IV steroids.²² The rationale for using high-dose corticosteroids is based on the ability of high-dose steroids to induce apoptosis of T cells and reduce inflammation via decreased migration of inflammatory mediators from the periphery into the central nervous system.^{23,24} However, it should be noted that the optimal therapeutic regimen for the use of high-dose corticosteroids in patients with MS has not yet been determined, and additional randomized, controlled trials will be needed to sufficiently evaluate the adverse effect profiles, appropriate dosages, routes of administration, and risk-benefit ratios of specific corticosteroids for the treatment of acute relapses of MS.²⁵

Adrenocorticotropic hormone (ACTH) may be used as an alternative therapy to high-dose methylprednisolone (or similar therapeutic substitutes such as dexamethasone or prednisone). ACTH is currently available as a sustained-release formulation in gelatin for subcutaneous (SC) or intramuscular (IM) injection.^{26,27} ACTH was the first approved medication to treat MS relapse. At this time, ACTH is used only in patients with MS who are unable to take methylprednisolone due to venous access problems, lack of response to high-dose corticosteroids, or adverse effects of high-dose corticosteroids (usually psychiatric effects).²⁷ The orphan status of this therapy, which leads to its substantial expense, is the primary reason for the infrequency of its use.

IV immunoglobulin and plasma exchange are second-line options for the treatment of acute exacerbations of MS.^{28,29} These options are very expensive, and are considered in cases where patients are intolerant of or unresponsive to corticosteroids.

Long-Term Treatment

DMTs are the mainstay of chronic treatment for patients with MS, and currently, there are 11 FDA-approved DMTs. Treatment with DMTs reduces the frequency and severity of acute exacerbations and slows disease progression (**Table 1**).³⁰⁻⁴¹ The selection of treatment is dependent on healthcare provider choice, individual patient preferences, and other parameters. The **Figure**⁴²⁻⁴⁷ provides a summary of the annualized relapse rates seen in pivotal studies for each of the currently available pharmacotherapeutic options.⁴²⁻⁴⁷ One of the biggest challenges when comparing the efficacy of these agents is the dearth of head-to-head clinical trials. While it is tempting to compare relapse rates between

the various agents, doing so without acknowledging the limitations of indirect comparisons may result in inaccurate conclusions. For instance, the study cohorts between different clinical trials may vary greatly in their frequency of baseline relapse rate and MRI disease activity.⁴⁸ Although relapse rates on treatment in the studies appear lower with newer agents compared with older injectable agents (ie, interferons [IFNs], glatiramer acetate [GA]), these lower rates may also be related to temporal changes in the diagnosis and management of MS.⁴⁹ Whereas the pivotal studies completed in the 1990s that led to the FDA approval of IFN beta (IFN- β) and GA utilized the Poser criteria to identify eligible patients with MS, studies that occurred during the 2000s and later utilized the McDonald criteria to identify patients with MS. Patients diagnosed via the McDonald criteria may have had earlier diagnoses and less advanced disease.^{12,49}

Interferons

The IFNs have been a first-line treatment for MS for almost 2 decades. There are currently 4 approved formulations available in the United States: SC IFN- β -1b, IM IFN- β -1a, SC IFN- β -1a, and SC pegylated IFN- β -1a,^{33-35,39,40} and based on pivotal studies, efficacy is similar among the different formulations.^{43,50} However, well-designed clinical trials have also demonstrated modest differences indicating improved outcomes with more frequent dosing of the same molecule. One such trial is the Evidence of Interferon Dose-response-European North American Comparative Efficacy (EVIDENCE) trial. The results of this randomized multicenter trial of 677 patients with RRMS demonstrated that patients receiving SC IFN- β -1a (44 mcg 3 times weekly) were more likely to remain relapse free at 48 weeks compared with patients receiving IM IFN- β -1a (30 mcg once weekly) (OR 1.5; 95% CI, 1.1-2.1; $P = .009$). Patients in the IM IFN- β -1a group also had fewer active MRI lesions ($P < .001$ at 24 and 48 weeks).⁵¹ Despite the results of the study, however, it is difficult to draw definitive conclusions due to the short study duration (6 months) and the lack of outcomes regarding the progression of disability.⁵² The Independent Comparison of Interferon (INCOMIN) trial randomized 188 patients with RRMS to receive either SC IFN- β -1b (250 mcg every other day) or IM IFN- β -1a (30 mcg once weekly),⁵³ and found that treatment with IFN- β -1b was associated with reduced relapses (RR 0.76; 95% CI, 0.59-0.9; $P = .03$), T2 lesions on MRI (RR 0.6; 95% CI, 0.45-0.8; $P < .0003$), and progression in EDSS score of 1 point sustained

■ **Table 1.** Summary of Currently Available Disease-Modifying Therapies³⁰⁻⁴¹

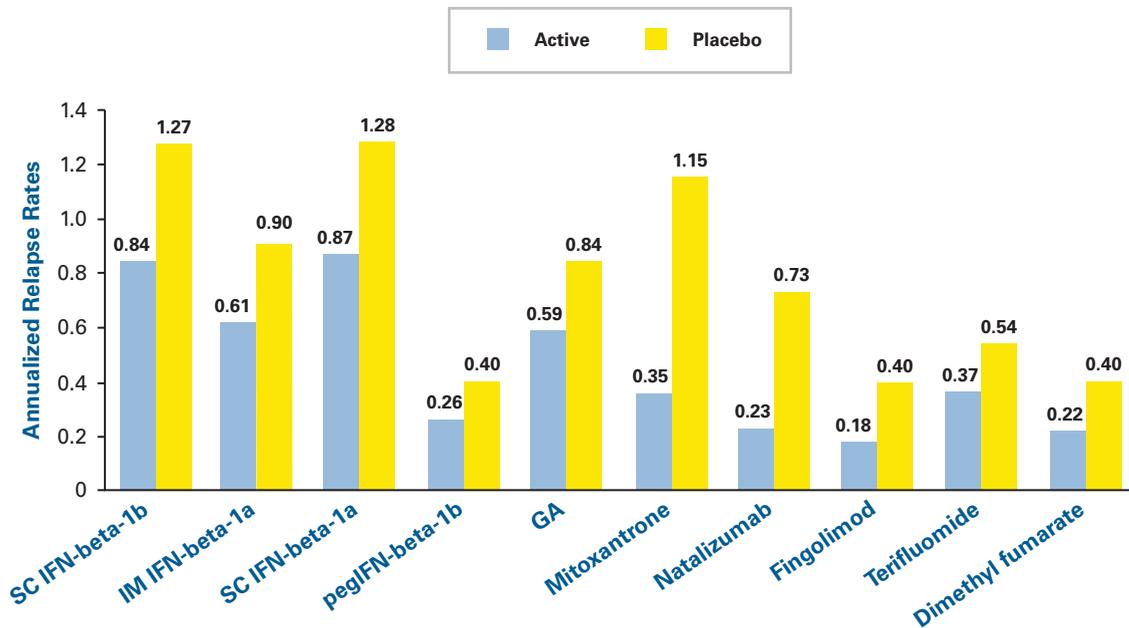
Drug (Trade Name)	Year Approved/ Indication	Mechanism of Action	Typical Dosage	Monthly Cost (\$) ^a	Comments
Interferon β-1b (Betaseron)	1993 Relapsing forms of MS; CIS	Unknown, may be related to anti-inflammatory properties	0.25 mg SC every other day	3740.75	First-line therapy; pregnancy category C; flu-like symptoms and injection site reactions common
Interferon β-1a (Avonex)	1996 Relapsing forms of MS	Unknown, may be related to anti-inflammatory properties	30 mcg IM weekly	5454.00	First-line therapy; pregnancy category C; flu-like symptoms and injection site reactions common
Interferon β-1a (Rebif)	1996 Relapsing forms of MS	Unknown, may be related to anti-inflammatory properties	22 or 44 mcg SC 3 times a week	5803.68	First-line therapy; pregnancy category C; flu-like symptoms and injection site reactions common
Glatiramer acetate (Copaxone)	1997 Relapsing forms of MS	Antigenically similar to MBP; induces and activate T-lymphocyte suppressor cells specific for myelin antigen; interferes with antigen-presenting functions	20 mg SC daily	6672.00	First-line therapy; pregnancy category B; skin reactions common
Mitoxantrone (Novatrone)	2000 RRMS; SPMS	Suppresses proliferation of T cells, B cells, and macrophages; impairs antigen presentation; enhances T-cell suppressor function; inhibits B-cell function, antibody production, and macrophage-mediated myelin degradation	12 mg/m ² IV every 3 months	131.25 ^b	Reserve for patients with rapidly advancing disease or who have failed other therapies; pregnancy category X
Natalizumab (Tysabri)	2004 Relapsing forms of MS	Monoclonal antibody against the alpha-4 subunit of integrin molecules; causes blockade of T-lymphocyte migration into the CNS	300 mg IV every 4 weeks	5614.80	
Interferon β-1b (Extavia)	2009 Relapsing forms of MS; CIS	Unknown, may be related to anti-inflammatory properties	0.25 mg SC every other day	5249.64	First-line therapy; pregnancy category C; flu-like symptoms and injection site reactions common
Fingolimod (Gilenya)	2010 Relapsing forms of MS	Binds to sphingosine 1-phosphate receptors 1, 3, 4, and 5; blocks the emergence of lymphocytes from lymph nodes and in turn amount available to enter the CNS; reduces inflammation	0.5 mg by mouth daily	5840.34	Second-line therapy; pregnancy category C; ensure varicella zoster immunity; extensive monitoring; FEV ₁ , pulse, blood pressure, ophthalmology examination, CBC, ALT, and AST
Teriflunomide (Aubagio)	2012 Relapsing forms of MS	Antiproliferative and anti-inflammatory effects; reduces the number of activated lymphocytes in the CNS	7-14 mg by mouth daily	5803.68	First-line therapy; pregnancy category X; requires accelerated elimination protocol in patients wishing to become pregnant or in the event of toxicity
Dimethyl fumarate (Tecfidera)	2013 Relapsing forms of MS	Anti-inflammatory and cytoprotective properties via activation of the Nrf2 pathway	120 mg by mouth twice daily for 7 days, then 240 mg by mouth twice daily	5913.60	First-line therapy; may cause flushing; pregnancy category C; CBC at baseline and annually (earlier if clinically indicated)
Pegylated interferon β-1a (Plegridy)	2014 Relapsing forms of MS	Unknown, may be related to anti-inflammatory properties	Initial dose of 63 mcg SC, then 94 mcg on day 15, and then the regular maintenance dose of 125 mcg on day 29 and every 2 weeks thereafter	NA	First-line therapy; pregnancy category C; flu-like symptoms and injection site reactions common

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CIS, clinically isolated syndrome; CNS, central nervous system; FEV₁, forced expiratory volume in 1 second; MBP, myelin basic protein; MS, multiple sclerosis; SC, subcutaneous.

^aBased on average wholesale price.⁴¹

^bBased on a body surface area of 1.7 m².

■ **Figure.** Annualized Relapse Rates Seen With Disease-Modifying Therapies Versus Placebo in Select Pivotal Trials^{42-47,a}



GA indicates glatiramer acetate; IFN, interferon; IM, intramuscular; SC, subcutaneous.

^aAnnualized relapse rates were significantly reduced with all disease-modifying therapies versus placebo ($P < .05$) in each of the respective studies. Interpretation of indirect comparisons should be made with caution.

for 6 months (RR 0.44; 95% CI, 0.25-0.80; $P = .005$) compared with SC IFN β -1a.

A significant shortcoming of this study was the small sample size ($n = 188$). According to Clanet et al, doubling the dose of weekly IM IFN β -1a did not appear to offer any additional benefit versus standard dosing.⁵⁴ SC pegylated IFN β -1a offers the advantage of less frequent dosing of 125 mcg every 2 or 4 weeks, and the ADVANCE trial demonstrated that pegylated IFN effectively reduced relapse rate and disease progression versus placebo, with dosing every 2 weeks being more effective than every 4 weeks.⁴³

The product labeling for IFN β -1b in North America is approved for “relapsing forms of MS” but also includes SPMS in Europe, which is due to a remarkably positive trial in European patients, which was stopped early because of the profound effects on disability progression.^{55,56} This multicenter, double-blind, placebo-controlled study enrolled and randomly allocated 358 patients with SPMS to placebo and 360 patients to IFN β -1b (8 million units every other day) and followed patient progression of disability (measured using EDSS) for up to 36 months. IFN β -1b delayed disease progression by 9 to 12 months in a study period of 2 to 3 years. The OR for confirmed disease progression was 0.65 (95%

CI, 0.52-0.83; IFN β -1b vs placebo). The proportion of patients with confirmed EDSS progression was significantly lower in the IFN β -1b group (38.9% vs 49.7%; $P = .0048$). Unfortunately, this finding could not be repeated in an older, more disabled North American cohort,⁵⁷ and a meta-analysis recently concluded a lack of convincing repeatability in the improvement of long-term disability outcomes, although short-term disability outcomes are improved.⁵⁸

The most common adverse drug events seen with IFNs include abdominal pain (8%-25%), depression (4%-30%), fatigue (30%-40%), fever (20%-31%), headache (50%-70%), injection site reaction (3%-90%), leukopenia (13%-35%), elevated serum glutamic-pyruvic transaminase (12%-30%), and elevated serum glutamic-oxaloacetic transaminase (4%-20%).^{33-35,39,40} The incidence rate of these adverse effects varies by IFN preparation. In general, all IFN β s are well tolerated among patients with MS, with the most common adverse effect being flu-like symptoms (49%-60%).^{33-35,39,40} While these flu-like symptoms may subside in some patients, a study by Caon et al reported continued symptoms in 37% of patients receiving high-dose IFN β at 5 years.⁵⁹ All IFN β agents are associated with a risk of neutralizing antibodies (NAbs) to IFN β ; IM IFN β -1a is the least antigenic of the 4 IFN β agents. While the pres-

ence of NAbs is associated with diminished treatment efficacy, according to some practitioners, the presence of NAbs alone (without signs and symptoms of treatment failure) should not dictate the decision of switching to an alternative agent, although others may disagree.^{16,60} Overall, long-term outcomes in studies of IFN β treatment have been very encouraging.^{61,62}

Glatiramer Acetate

GA, which first gained FDA approval for use in the US market in 1996, is considered a first-line treatment for RRMS.²⁶ Notably, however, the results of 2 large clinical studies (Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose in Multiple Sclerosis Patients [BEYOND] and Rebif versus Glatiramer Acetate in Relapsing MS Disease [REGARD]) did not show a difference between GA and IFNs in the primary outcome measure of relapse rates.^{63,64} However, MRI outcomes were superior with high-dose IFN β -1b (500 μ g SC every other day) and IFN β -1a in both studies (BEYOND; fewer gadolinium-enhancing lesions vs GA; 0.24 vs 0.41 lesions per patient per scan; 95% CI, -0.4 to 0.1; $P = .0002$ and REGARD; cumulative number of new T2 lesions; 3.3 vs 4.6; $P = .0009$). Although the combination of IFN and GA seems logical, given their differing mechanisms of action, in the Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis (COMBIRX) study, there was no benefit to combination IFN+GA treatment versus monotherapy with either agent.⁶⁵

Common adverse effects seen with GA in clinical studies include dyspnea (14%), influenza (14%), injection site reaction (8%), nausea (15%), palpitations (9%), rash (19%), and vasodilation (20%).³² While GA is generally well tolerated, injection site reactions are common, and up to 16% of patients experience a postinjection syndrome (ie, chest palpitations, anxiety, flushing, tachycardia, and shortness of breath).³² Long-term safety and efficacy were demonstrated in a 15-year analysis of an ongoing open-label cohort. No long-term safety concerns were identified and few patients experienced relapses or disease progression.⁶⁶ GA is classified as pregnancy category B and exposure during pregnancy has not been associated with an increase in spontaneous abortion or fetal abnormalities.⁶⁷ Relapse rates may be reduced when switching therapy secondary to lack of effectiveness; however, there is evidence that if the therapeutic switch is due to intolerable adverse effects, relapse rates may not change significantly.⁶⁸ With regard to switching from IFN to GA, a small study of 39 patients with RRMS found

that the annualized relapse rate remained similar to the “pre-switch” rate among patients switching because of adverse effects (0.33 vs 0.31; pre- vs post switch, respectively). However, patients who switched due to lack of effectiveness experienced a reduction in relapse rate (1.55 vs 0.62).

Mitoxantrone

In 2000, mitoxantrone, an anthracycline initially used as a chemotherapeutic agent, was approved for the treatment of aggressive RRMS, SPMS, and PRMS,⁶⁹ based largely on the results of the European Mitoxantrone in Multiple Sclerosis Group study.⁴⁶ This phase 3, multicenter, double-blind study randomized 194 patients with either RRMS or SPMS to placebo, mitoxantrone 5 mg/m², or mitoxantrone 12 mg/m² every 3 months for 24 months. Patients treated with mitoxantrone 12 mg/m² experienced a significant reduction in MRI end points (fewer gadolinium enhanced lesions at 24 months; 0% vs 16%) and number of relapses (24.08 vs 76.77; $P = .0002$) versus placebo. EDSS change was significantly lower in the mitoxantrone 12 mg/m² versus placebo group (-0.13 vs 0.23; $P = .0194$), as was the ambulation index (0.30 vs 0.77; $P = .0306$). Based on a systematic review of the literature, the authors concluded that mitoxantrone had partial efficacy in reducing relapse frequency and disease progression in patients with worsening RRMS, PRMS, and SPMS.⁷⁰ The typical dose of mitoxantrone is 12 mg/m² IV over 15 minutes every 3 months, with a maximum cumulative lifetime dose of mitoxantrone not to exceed 140 mg/m².⁷¹ Common adverse effects of mitoxantrone include nausea (76%), alopecia (61%), menstrual disorders (61%), amenorrhea (43%), respiratory tract infections (53%), and urinary tract infections (32%).^{36,71} Cardiotoxicity is a significant concern with mitoxantrone, and based on pooled data from various studies, with mitoxantrone use, the rate of left ventricular dysfunction is approximately 12% and the risk of heart failure is approximately 0.4%.⁶⁹ However, there is a wide range of incidence rates reported in the literature. In addition, the incidence rate of treatment-related leukemia with mitoxantrone is approximately 0.8%.⁶⁹ Given the significant risk of toxicity, it is generally recommended that mitoxantrone be reserved for patients who have rapidly declined or have failed other therapies.⁷¹

Natalizumab

Natalizumab has been compared with placebo and evaluated as add-on therapy to IFN in pivotal tri-

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als.^{72,73} The Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study randomized 942 patients in a 2:1 ratio to receive either natalizumab 300 mg or a matching placebo via IV infusion every 4 weeks for more than 2 years.⁷² Compared with placebo, natalizumab reduced the risk of sustained progression of disability by 42% over 2 years (hazard ratio [HR] 0.58; 95% CI, 0.43-0.77) and was associated with a lower annualized relapse rate (0.23 vs 0.73; $P < .001$).⁷² The accumulation of new or enlarging hyperintense lesions (on T2-weighted MRI) was reduced by 83% with natalizumab therapy and the number of lesions (detected by gadolinium-enhanced MRI) was reduced by 92% with natalizumab therapy. The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study evaluated the addition of natalizumab to IFN β -1a in patients who had at least 1 MS relapse in the past 12 months prior to randomization. Patients were randomized to receive IV natalizumab 300 mg every 4 weeks ($n = 589$) or a matching placebo ($n = 582$) in addition to IFN β -1a for up to 116 weeks. Treatment with natalizumab plus IFN β -1a resulted in a 24% reduction in the RR of sustained disability progression (HR 0.76; 95% CI, 0.61-0.96; $P = .02$), a lower annualized relapse rate (0.34 vs 0.75; $P < .001$), and fewer new or enlarging lesions in T2-weighted MRI (0.9 vs 5.4; $P < .001$) compared with IFN β -1a alone. Natalizumab was approved for use in patients with RRMS in 2004 and is considered an option for patients with an inadequate response or unable to tolerate first-line treatment (ie, IFN, GA).³⁷

Common adverse events reported in clinical trials in patients treated with natalizumab include abdominal discomfort (11%), arthralgia (19%), depression (19%), fatigue (27%), headache (38%), lower respiratory tract infection (17%), pain in extremity (16%), rash (12%), and urinary tract infection (21%).³⁷ Shortly after its 2004 approval, progressive multifocal leukoencephalopathy (PML) was reported in 2 patients receiving natalizumab, leading to the suspension of its FDA approval in February 2005. PML, although rare, is a serious iatrogenic event that can occur in approximately 1 of every 1000 natalizumab-treated patients.⁷⁴ Risk factors that increase the possibility of this adverse event include the prior use of immunosuppressants, testing seropositive for anti-John Cunningham virus (JCV) antibody, and the use of natalizumab for greater than 2 years.^{37,75} After a review of the available data, the FDA reapproved natalizumab in 2006 and required that the risk of PML be noted in the pre-

scribing information as a black box warning. The FDA also generally recommended restricting its use to patients with MS who failed other therapies or had aggressive disease. It should be noted that natalizumab is generally considered a highly effective therapy on the basis of its MRI efficacy, although head-to-head clinical trial comparisons with other therapies have not been conducted.

Fingolimod

The safety and efficacy of fingolimod, the first oral therapy approved for MS, were established in 2 large phase 3 studies. Both the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study and the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) study found that fingolimod reduced the frequency of relapses and improved MRI end points.^{47,76} The FREEDOMS trial randomized 1272 patients to fingolimod 0.5 mg daily, fingolimod 1.25 mg daily, or placebo. The annualized relapse rate was significantly reduced with both dosages of fingolimod versus placebo (0.18 and 0.16 vs 0.40, respectively; $P < .001$ for either dose vs placebo). In addition, a statistically significant reduction in the probability of disease progression over the 24-month study period (HR 0.70 and 0.68, 0.5 mg and 1.25 mg, respectively; $P = .02$ vs placebo, for both comparisons) was reported.

The TRANSFORMS study randomized 1292 patients to either fingolimod 1.25 mg daily, fingolimod 0.5 mg daily, or 30 μ g of IM IFN β -1a weekly. Annualized relapse rates were significantly reduced with both dosages of fingolimod versus IFN β -1a (0.20; 95% CI, 0.16-0.26 for fingolimod 1.23 mg daily and 0.16; 95% CI, 0.12-0.21 for fingolimod 0.5 mg daily vs 0.33; 95% CI, 0.26-0.42 for placebo; $P < .001$ for both groups vs IFN β -1a).⁷⁶ Since the 2 doses were similarly effective, but the higher dose was associated with an increased incidence of side effects, the lower dose was approved for marketing. Fingolimod is, therefore, the only MS therapy, including current oral therapies, with data substantiating a superior therapeutic benefit over another therapeutic class of DMTs.⁷⁶ Serious adverse events that may occur with fingolimod include bradycardia, cardiac conduction abnormalities, macular edema (especially in patients with diabetes mellitus), dyspnea (should be used with caution in patients with chronic obstructive pulmonary disease), and elevations in hepatic enzyme levels.³¹ The first dose of fingolimod (0.5 mg) should be given in the prescriber's office (or in a healthcare setting) and the patient should be monitored

for 6 hours due to the risk (albeit infrequent) of severe and/or symptomatic bradycardia (<1%) or significant cardiac arrhythmia. If a patient has not had varicella, it is recommended that they get vaccinated 1 month before starting fingolimod.³¹ There are small risks of significant toxicities (<1%) requiring complex safety planning associated with this agent compared with other therapies, and as a result, fingolimod is generally used as a second-line agent, although it is approved for first-line therapy in North America.

The most common adverse events reported with an incidence of greater than 10% in fingolimod clinical trials include back pain, cough, diarrhea, headache, influenza, and liver transaminase elevations.³¹ Long-term data beyond 4 years are limited with fingolimod, and increased but low rates ($\geq 1\%$) of herpetic infections and pneumonia have been seen in some trials. Due to its mechanism of action, treatment with fingolimod results in up to a 70% reduction in circulating lymphocytes, which are restricted to the lymph nodes and spleen, but the reduction in circulating lymphocytes does not appear to contribute to a major change in infection risk.

Teriflunomide

Teriflunomide, the active metabolite of the rheumatoid arthritis drug leflunomide, is an oral DMT that has been studied for the treatment of relapsing forms of MS in several large randomized controlled trials.^{44,77,78} Relapse rates were lower in patients treated with teriflunomide compared with placebo in the Teriflunomide Multiple Sclerosis Oral (TEMSo) trial. Also, relapse rates were similar (only in the 14-mg group) to IFN β -1a 30 mcg IM weekly in the TERifluNomidE and REbif (TENERE) trial. The TEMSo study was a phase 3, double-blind, placebo-controlled study that randomized 1086 patients to teriflunomide 7 mg/day, teriflunomide 14 mg/day, or placebo with a 108-week follow-up period.⁴⁴ Patients treated with teriflunomide (both doses) experienced significantly fewer relapses compared with placebo (annualized relapse rate, 0.37 vs 0.54 for both doses vs placebo, respectively; $P < .001$). Furthermore, the TEMSo study also reported significant reductions in MRI lesion volume (relative reduction vs placebo; 39.4% and 67.4%; teriflunomide 7 mg and 14 mg, respectively; $P < .001$ for both groups). Unlike other trials for relapsing MS, TEMSo expanded the spectrum of phenotypes to include SPMS patients with relapses, and teriflunomide demonstrated efficacy from the first symptom presentation through the spectrum of more disabled patients with MS. The TENERE

study reported similar annualized relapse rates in teriflunomide (14 mg/day) compared with IFN β -1a 30 mcg IM weekly (0.26 vs 0.22; $P = .59$).⁷⁸ Durability of response was supported by an 8.5-year follow-up study where relapse rates remained low (annualized relapse rate 0.28 and 0.2, teriflunomide 7 mg and 14 mg, respectively) in teriflunomide-treated patients.⁷⁹ Some common adverse reactions reported in clinical studies included elevations in alanine transaminase (ALT) (12%-14%), alopecia (10%-13%), diarrhea (15%-18%), influenza (9%-12%), nausea (9%-14%), and paresthesia (9%-10%).³⁸ The alopecia was described as generally mild and temporary thinning of the hair. Only about 1% of patients discontinued therapy due to the alopecia. More serious adverse effects are rare and include peripheral neuropathy, acute renal failure (which generally occurred only on a single blood test), increased blood pressure, infection, and bone marrow suppression.³⁸ Prior to initiating therapy with teriflunomide, it is recommended that patients be screened for tuberculosis, and monthly monitoring of transaminases during the first 6 months of treatment is also recommended to detect hepatotoxicity, which infrequently requires discontinuation. Many of the risk factors were derived from known reactions associated with leflunomide. Teriflunomide is likely less toxic than its parent compound leflunomide, presumably due to the absence of many potentially hepatotoxic and myelosuppressive metabolites.

Teriflunomide is classified in pregnancy category X and should not be used in pregnant women, women who do not use reliable contraception, and women who are trying to become pregnant,³⁸ as it may take up to 2 years to reduce plasma concentrations to safe levels for pregnancy in women contemplating pregnancy. To expedite drug elimination in patients contemplating pregnancy, an accelerated elimination protocol using activated charcoal or cholestyramine for 11 days reduces teriflunomide half-life to approximately 24 hours. After 11 days of the accelerated elimination protocol, plasma concentrations are reduced by over 98%.³⁸ Accelerated elimination may also be used in situations where patients experience hepatotoxicity or other serious side effects. While long-term safety data are limited, experience with leflunomide in rheumatoid arthritis suggests that no major differences from the existing safety profile are likely.

Dimethyl Fumarate

Two large randomized controlled trials (Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis [CONFIRM])

■ **Table 2.** Emerging Agents for Multiple Sclerosis^{16,81,82}

Drug	Proposed Indication	Mechanism of Action	Phase of Clinical Trial
Almetuzumab	RRMS	Monoclonal antibody targets CD52 present on lymphocytes and monocytes (and other white blood cells), resulting in rapid depletion of these cell lines	3
Daclizumab	RRMS	<ul style="list-style-type: none"> • Monoclonal antibody directed at CD25 • Antagonism of CD25 leads to selective inhibition of activated T cells and expansion of CD56 (regulatory subset of natural killer cells) 	3
Laquinimod	RRMS	Reduces leukocyte migration into the central nervous system	3
Ocrelizumab	RRMS, PPMS	<ul style="list-style-type: none"> • Monoclonal antibody structurally similar to rituximab • Binds to CD20 on B cells and depletes circulating levels of B cells 	3
Rituximab	RRMS, PPMS	<ul style="list-style-type: none"> • Monoclonal antibody targeted against CD20 expressed on B cells • Depletes circulating levels of B cells 	2/3

PPMS indicates primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

and Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis [DEFINE]) established the safety and efficacy of dimethyl fumarate for the treatment of MS over a period of 2 years.^{42,80} In the CONFIRM study, patients were randomized to receive dimethyl fumarate 240 mg 2 or 3 times daily, GA, or placebo. Relapse rates were as follows: dimethyl fumarate twice daily, 0.22; $P < .001$; dimethyl fumarate 3 times daily, 0.20; $P < .001$; GA, 0.29; $P = .01$; all vs placebo, 0.4). In addition, the number of new or enlarging T2-weighted hyperintense lesions was significantly reduced in all treatments groups versus placebo ($P < .001$ for all comparisons). Furthermore, progression of disability was reduced with dimethyl fumarate 240 mg twice daily or 3 times daily versus placebo in the DEFINE trial (HR 0.62; 95% CI, 0.44-0.87; $P = .005$; HR 0.66; 95% CI, 0.48-0.92; $P = .01$; twice daily and 3 times daily, respectively). Dimethyl fumarate may decrease lymphocyte count by up to 30% within the first year of treatment³⁰; initiation of treatment with dimethyl fumarate should be postponed in the setting of infection. In clinical trials, a large proportion of patients experienced flushing (40%) at some point in therapy,³⁰ and while only 3% of patients in clinical trials discontinued therapy due to this adverse effect, it is important to counsel patients about the possibility of flushing. Low-dose aspirin may be beneficial in reducing the severity of this side effect. In addition to flushing, other common adverse effects with dimethyl fumarate (incidence >10% in clinical trials) include abdominal pain, diarrhea, and nausea.³⁰ Gastrointestinal (GI) side effects are the most

common cause of discontinuation and failure to achieve an adequate dose or an appropriate therapeutic regimen (240 mg twice daily). GI side effects may be reduced by taking the medication with food, especially fatty foods. Patients unable to titrate to a full dosage by 4 to 6 weeks due to GI side effects may require an alternative therapy. Given its relatively recent approval by the FDA in March 2013, long-term safety data with dimethyl fumarate are extremely limited.

Emerging Agents

Several agents are currently under investigation for the treatment of MS, including laquinimod, daclizumab, almetuzumab, rituximab, and ocrelizumab.^{16,81,82} As clinical data supporting these agents evolve, it is likely that the armamentarium of pharmacotherapeutic agents used to treat MS will expand, particularly with more highly effective therapies aimed at refractory patients. **Table 2**^{16,81,82} summarizes the mechanisms of action, indication, and current stage in development of select emerging agents.

Treatment of Comorbid Conditions

Patients with MS often have comorbid conditions,⁸³ including neuromuscular function impairments, pain, cognitive dysfunction, and mental health issues.⁸⁴ Up to 50% of patients with MS experience depression.⁸⁵ Acknowledging, evaluating, and treating depression is important, as the use of IFNs in patients experiencing depression may increase symptoms of depression and suicide risk.^{33-35,39,40} Other commonly encountered comor-

■ **Table 3.** Strategies to Enhance Patient Adherence to MS Therapy^{97,113-115}

Barrier	Enhancement strategy
Perceived lack of efficacy	<ul style="list-style-type: none"> • Inform patients of therapeutic options, the importance of adherence, and expected adverse effects.¹¹³ • Setting realistic goals is critical, as MS patients often have unrealistic goals.⁹⁷
Needle phobia	<ul style="list-style-type: none"> • Educate patients on appropriate injection techniques. • Consider recommending an auto-injector device.¹¹⁴ • Consider oral therapy options.
Adverse reactions	Flu-like symptoms are common with interferons; gradual dose titration and the use of nonsteroidal anti-inflammatory drugs may help minimize these symptoms. ¹¹⁵
Cost	<ul style="list-style-type: none"> • Refer patient to manufacturer discount programs. • Identify patient eligibility for assistance programs.
Inconvenience	Identify patient preferences to determine the treatment option/drug formulation closest to the patient's expectations.

MS indicates multiple sclerosis.

bidities include visual problems, hearing loss, seizures, fatigue, paresthesia (including neuropathic pain), bladder/bowel/sexual dysfunction, gait problems, spasticity, and vertigo.⁸⁴ Sleep disorders are also commonly seen in MS patients, and may contribute to complaints of tiredness/fatigue.^{86,87} Treatment of these comorbidities should mirror the standard of care for each individual condition. With the exception of dalfampridine, a potassium channel blocker that has demonstrated benefits for managing spasticity and heat intolerance, and has improved walking (distance, gait endurance, and speed) in clinical trials of patients with MS,⁸⁸ there are currently no agents specifically approved for the treatment of MS-related symptoms. However, although not specifically indicated for patients with MS, many treatments for comorbid conditions commonly experienced by patients with MS have been evaluated in studies, and are available commercially.

Other Treatment Considerations

Epidemiological studies have identified an association between low serum 25-Hydroxyvitamin D (25[OH]D) levels and the risk of MS.^{89,90} Furthermore, studies have also demonstrated that low serum 25(OH)D levels are associated with higher rates of acute exacerbations of MS and disability progression.^{91,92} Answering the question of whether supplementation with vitamin D actually improves outcomes in patients with MS will require further clinical evaluation; nonetheless, it seems reasonable that patients with low serum 25(OH)D receive vitamin D supplementation.¹⁶ Other modifiable risk factors for MS include smoking, excess body weight, and high sodium intake.⁹³⁻⁹⁵ Smoking is associated with the development of MS (20%-60% increased risk) and worse outcomes in

patients with MS.⁹⁵ For example, the risk of conversion from relapsing-remitting to secondary-progressive disease is 3.6 times greater in smokers versus nonsmokers.⁹⁵ Smoking cessation is associated with slower disease progression.⁹⁶ In a study by Manouchehrinia and colleagues, ex-smokers who quit smoking either before or after the onset of MS had a significantly lower risk of reaching EDSS scores of 4 (HR 0.65; 95% CI, 0.50-0.83) and 6 (HR 0.69; 95% CI, 0.53-0.90) than current smokers.⁹⁶ Therefore, smoking cessation should be suggested for all patients with MS.

Impact of Adherence on the Management of MS

Medication adherence and treatment efficacy are closely linked, especially in the optimal management of MS. Patients with MS are most likely to discontinue therapy within the first 6 months of initiating treatment; 9% to 25% of discontinuations occur during this time frame.^{97,98} It is common for those who are on therapy for MS to miss doses; a study published in 2008 by Tremlett et al reported that 73% of patients missed at least 1 dose of therapy over a 6-month period.⁹⁹ Furthermore, discontinuation rates approach 40% after 1 year of therapy and 50% after 4 years of therapy.^{100,101} Patterns have also been noted, with discontinuation due to the treatment failure occurring later in therapy (median 35 months) versus discontinuation due to adverse effects, which occurs earlier in therapy (median 13 months).¹⁰²

Numerous barriers may contribute to reduced adherence rates in patients with MS, such as cognitive impairment,¹⁰³ depression,¹⁰⁴ concerns regarding treatment efficacy,^{100,105} adverse events,¹⁰⁶ the convenience of the route of administration of medication,^{107,108} and financial burden.¹⁰⁹ Cost is an important factor influencing

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treatment access and adherence; it has been shown that patients with MS who were employed or had higher incomes were 2 times more likely to be on DMT treatment.¹¹⁰ Higher cost sharing due to insurance restrictions has also been shown to decrease adherence, as well as increase the overall cost of medical care.¹¹¹ The cost of many of the DMTs is substantial, as shown in Table 1,³⁰⁻⁴¹ and is a major contributor to nonadherence in this patient population.

As with the treatment of any chronic disease, nonadherence adversely impacts patient outcomes. Al-Sabbagh and colleagues evaluated the impact of medication persistence on the incidence of severe MS relapses using data from a national managed care database. The results showed that patients with gaps in therapy of 90 days or longer had approximately a 2-fold increase in the probability of having a severe relapse (usually requiring a hospitalization).¹¹² Incorporating strategies to improve adherence to therapies in patients with MS has the potential to significantly impact their QOL and health-care resource utilization (Table 3).^{97,113-115}

Conclusion

The treatment paradigm for MS will continue to evolve as additional pharmacotherapeutic options become available for this challenging disease. Options for MS treatment once consisted of only a handful of injectable drugs. The introduction of oral medications as well as ongoing research for emerging agents carry beneficial clinical and economic implications for the MS community. However, as with the treatment of any chronic condition, the long-term management of patients with MS is not without its challenges, with side effects, access, affordability, and adherence being key issues. As more understanding is gained regarding this chronic, demyelinating autoimmune disease, it is paramount for clinicians, healthcare providers, and managed care professionals to remain abreast of and adapt to the current best practices in this evolving therapeutic landscape.

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