

Management of Multiple Sclerosis

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According to the National Multiple Sclerosis Society, multiple sclerosis (MS) is a disease of the central nervous system (CNS) that disrupts signals within the brain and also the signals between the brain and the body.^{1,2} Due to the CNS pathophysiology that characterizes MS, individuals afflicted by the disease will likely experience symptoms that range from numbness and tingling to blindness and paralysis.³ Although MS itself is not typically fatal, the neurological disease is incurable and can have a profoundly negative impact on patient quality of life (QOL).^{4,6} Fortunately, MS is now a treatable condition and many new pharmacotherapies have entered the market in recent years, with additional agents currently in late-stage development.

MS is a complex disease with various symptoms that impact many human functions. As such, a multidisciplinary approach that combines pharmacologic and nonpharmacologic management, patient education strategies designed to minimize adverse effects of medications (Table) and to increase treatment adherence, patient support groups, and an emphasis on maintaining open and effective lines of communication between the patients and healthcare professionals is essential.^{7,8} According to Ross, every patient with MS should have a primary care physician and a neurologist in the multidisciplinary team to oversee their care. Nurses are also important members of this team, as patients with MS frequently look to their nurses for additional information regarding the disease and their care. The nurse is the facilitator for patient autonomy, teaching self-directed learning techniques and empowering patients to take responsibility for the treatment of their disease. In addition, the management of primary, secondary, and tertiary symptoms of MS may involve specialists from many areas, such as physical therapists, psychologists/neuropsychologists, occupational therapists, urologists/neurourologists, and vocational rehabilitation counselors (Figure 1).

Assessment and Management of Relapse

Relapsing-remitting multiple sclerosis (RRMS) is the most common subtype of MS, accounting for 85% of MS cases at initial diagnosis. Patients with RRMS will experience relapses (also called attacks, exacerbations, or flare-ups) separated by periods of full or partial recovery.^{1,9} According to the 2010 revision of the McDonald criteria for the diagnosis of MS, relapses are defined as “patient-reported or objectively observed events that are typical of an acute inflammatory demyelinating event in the CNS, current or

Abstract

Patients with multiple sclerosis (MS), a disease of the central nervous system that disrupts signals within the brain and also the signals between the brain and body, will likely experience symptoms that may negatively impact their quality of life (QOL). Due to the complexity of MS and its disease burden, multidisciplinary management that combines pharmacologic and nonpharmacologic strategies with patient education is necessary. Diagnosing relapses of MS in clinical practice can be difficult due to the multiple subtypes of MS, variations of symptomatology, and pseudo-relapses. Managing relapses also presents its own set of challenges, for example, evaluating if treatment is appropriate and determining which agent would be most effective for a patient if treatment is recommended. Patient education is essential for achieving optimal outcomes for patients with MS and improving patient QOL, and should increase awareness of: (1) the disease itself and its progression; (2) the signs and symptoms of MS; (3) current treatment strategies and plan of care; (4) the recognition and management of relapses; (5) the value of treatment adherence and impact of nonadherence; and (6) hope for the future. The management of active MS may be further complicated by the complex variety of pharmacotherapeutic options, and in some instances, by having to switch between agents and drug classes. Newer agents in development (eg, alemtuzumab, ocrelizumab, laquinimod) offer the opportunity to expand the therapeutic armamentarium, although further long-term data are required to evaluate any safety concerns associated with newer agents.

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Table. Adverse Events Associated With Multiple Sclerosis Disease-Modifying Therapies⁷

	IFN Beta	Glatiramer Acetate	Mitoxantrone	Natalizumab	Fingolimod	Teriflunomide	Tecfidera
Short-term	Injection site reactions, flu-like symptoms, hepatic injury, lymphopenia, depression	Injection site reactions, vasodilation, tachycardia, chest pain, nausea, asthenia, anxiety, infection	Fatigue, nausea, infection, cytopenia, hair thinning	Fatigue, headache, arthralgia, depression	Slow heart rate, elevated BP, macular edema, liver enzyme elevation, lymphopenia	Nasopharyngitis, alopecia, nausea, liver enzyme increase, paresthesia, back pain, diarrhea, arthralgia	Flushing, gastrointestinal symptoms, puritis, elevated LFTs, decreased lymphocyte counts
Long-term	Seizures, cardiomyopathy, thyroid disorders, anaphylaxis		Leukemia, cardiotoxicity risk	Risk of PML, liver toxicity	Infection, seizures	Neutropenia, risk of liver failure, teratogenicity based on leflunomide: Category X	Currently unknown

BP indicates blood pressure; IFN, interferon; LFT, liver function test; PML, progressive multifocal leukoencephalopathy.

historical, with a duration of at least 24 hours, in the absence of fever or infection.^{9,10} Furthermore, paroxysmal symptoms, historical or current, may also be considered relapses if they consist of multiple episodes that occur over a minimum of 24 hours.¹⁰ The potential signs and symptoms of relapse are numerous and will vary in presentation depending upon the location of the demyelinating event and inflammation.² Any disability that results from a relapse of MS can persist for several weeks or for months,¹¹ although recovery time may be hastened through pharmacologic intervention.¹²

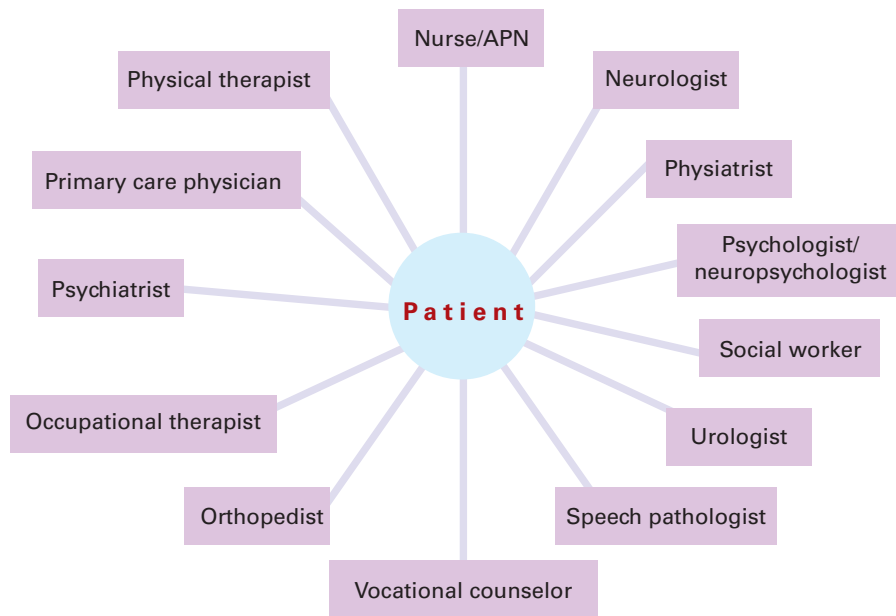
The diagnosis and treatment of MS relapses in clinical practice is challenging, as there are multiple manifestations of relapse, such as optic neuritis, paroxysms, and myelitis, and symptoms of relapse can vary even within each particular manifestation.¹³ Adding further complication to the treatment of relapses is the common misconception among many patients that disease remission is a symptom-free period, even though most individuals will always be symptomatic in some form.¹⁴ While fluctuations in symptoms, such as fatigue, may be caused by factors as common as stress or sleep deprivation, and may be mistaken for a relapse in MS,¹⁴ pseudo-relapses and infections can also make the diagnosis of an actual relapse more difficult. For instance, the transient worsening of symptoms due to overexposure to heat or overexertion are not representative of actual relapses of MS, but are most likely attributable to conduction blocks within demyelinated axons.¹⁴ Infections such as viral upper respiratory infections and simple urinary tract infections are often associated with pseudo-relapses in patients with MS¹⁴; however, systemic infections may provoke actual relapses by introducing a pro-inflammatory bias in immune responsiveness that is capable of triggering disease activity and exacerbations.¹⁵

If a true clinical relapse is suspected in a patient with MS, the clinician must decide if the relapse is to be treated at all, and if so, which treatment should be selected. Investigators have studied the effects of corticosteroids on both short- and long-term recovery from optic neuritis in patients with MS, and the results have demonstrated significant improvements in short-term outcomes; however, no long-term benefits in terms of attaining pre-relapse functioning have been observed.¹⁶⁻¹⁸ Therefore, the decision to treat a relapse in MS often depends on the functional impact that the relapse may have on the patient's daily life. Typically, the standard of care and first-line treatment option for relapses in MS is 3 to 5 days of intravenous methylprednisolone (500-1000 mg/d), with or without an oral taper, or a high-dose oral steroid.¹⁴ Because high-dose oral and intravenous steroid regimens have shown similar efficacy in treating MS relapses,^{19,20} the decision of which agent to use is normally determined by patient and clinician preferences. Other treatments for relapses of MS include adrenocorticotrophic hormone, intravenous immunoglobulin, and plasma exchange; however, these treatments are usually reserved for those who are unresponsive to first-line therapies.¹⁴ It is important to note that combining comprehensive rehabilitation with standard, intravenous methylprednisolone therapy may result in improved performance on measures of disability and QOL over a 3-month period following a relapse in patients with MS.²¹

Patient Education

Epidemiologically, the majority of patients diagnosed with MS are between the ages of 20 and 50 years, and the disease is diagnosed in 2 to 3 times as many women as men.^{1,2} The newly diagnosed patient with MS is often in his or

■ **Figure 1.** The Various Professionals Involved in a Multidisciplinary Team Approach to MS Care



APN indicates advanced practice nurse; MS, multiple sclerosis.

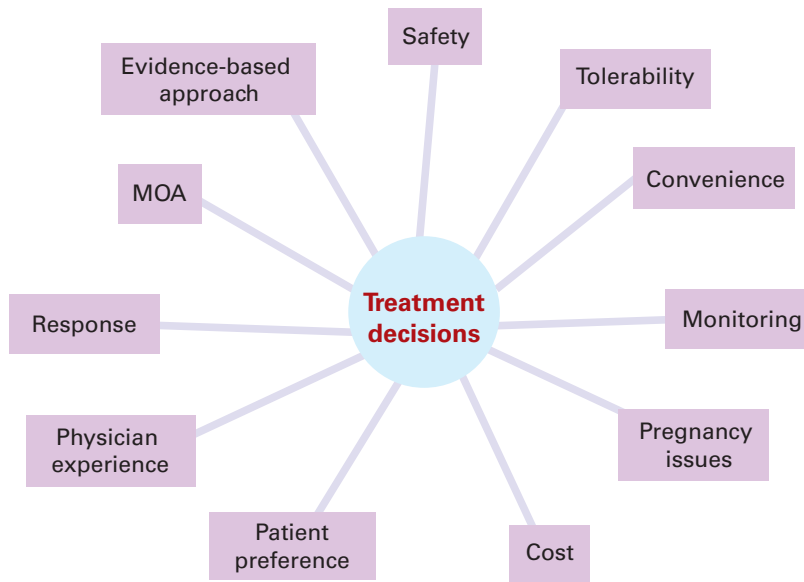
her peak productive years—young (between the ages of 20 and 50 years) and of the age to possibly start a career and/or a family.¹ For these patients, concerns about disability and a fear for their future are common.^{22,23} These circumstances provide an opportunity for healthcare professionals to educate patients with MS regarding a variety of topics to ensure informed treatment decisions, to maintain self-care, and to take control of their lives.²² Patients with MS require education that clearly explains the facts regarding the possible course and nature of the disease, its symptoms, and the importance of diagnostic tests.²² Another important area of education concerns assisting patients in finding support groups and developing appropriate support systems.²² Education regarding the nature of rehabilitative services and how to find those services will also be necessary.²² Regarding the treatment of MS, patient education topics include the plan of care, the potential side effects of pharmacotherapies and efforts needed to mitigate those effects, injection anxiety, social isolation, and treatment expectations.^{22,23} Patient education regarding realistic treatment expectations may be the most critical area of education,²³ and is necessary for treatment adherence and the success of long-term disease management. Patients should know that pharmacotherapies for MS are, at the moment, not designed to be curative, but can slow the progression of the disease and improve patient QOL. In addition, education regarding the risks of *not* treating MS or delaying treatment for MS should be provided to patients. It is important to keep in mind the 4 main goals of

MS management: (1) modifying/reducing relapses and delaying progression to disability; (2) treating relapses; (3) managing symptoms; and (4) maintaining an acceptable QOL. It should also be noted that inspiring hope for the future is also a critical component of patient education, as it can energize patients with MS and make healthy coping more feasible.²²

The management strategy for a patient with MS should be tailored based on the specific state of their disease, the therapeutic regimen, and the patient's individual characteristics. Treatment decisions for MS are often quite complex and should be made by balancing disease-related therapeutic considerations with patient circumstances, which may include convenience, cost, patient preference, response, and tolerability (Figure 2). Treatment decisions should also take into account the patient's goals and lifestyle in an effort to promote optimal adherence and persistence to therapy, while maintaining a balance between safety and efficacy for a chosen regimen. Additionally, patients should be aware of the availability of disease-modifying therapies (DMTs) for RRMS, and that therapy should be initiated as early as possible to reduce the frequency of relapses and to delay disease progression. Ultimately, the goals of treatment are to prevent further disability and to preserve function, and it is evident that successful management of MS is contingent upon a complex multitude of clinical, social, and cognitive factors.^{24,25}

Adherence, which is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen,²⁵ involves partnership, mutually

■ **Figure 2.** The Various Professionals Involved in a Multidisciplinary Team Approach to MS Care



MOA indicates mechanism of action; MS, multiple sclerosis. Benefits and risks should be taken into account when making treatment decisions.

established goals, and a therapeutic alliance as core elements. Unfortunately, there are numerous barriers to treatment adherence in MS, including communication problems, knowledge deficits, physical impairments, social and cultural variables, financial concerns, emotional distress, psychiatric disorders, and cognitive deficits.²² MS is a highly complicated disease and despite its substantial clinical and significant burden, MS may not be well understood among the patient population. Other common issues that affect treatment adherence include the fear of needles, which complicates or even prevents the use of injectable therapies, and misconceptions of low treatment efficacy. Fortunately, with the recent introduction of noninvasive oral agents for MS into the drug market, patients, especially those uncomfortable with the use of injectable DMTs, may be afforded a more positive outlook on disease management and a more flexible, “on-the-go” lifestyle, which may consequently improve adherence to DMTs. However, similar to injectable therapies for MS, even patients on oral agents may become less adherent to treatment regimens if treatment is perceived to be less effective.²²

A study published in 1997 by the *Archives of Neurology* found that up to 41% of patients reported new or increased depression within 6 months of starting interferon treatment, and demonstrated that patients experiencing symptoms of depression were more likely than those without symptoms of depression to discontinue treatment with interferon for MS. Of the patients who had experienced depression, significantly

more patients who received psychotherapy or management with antidepressant medication continued treatment with interferon compared with patients who did not receive treatment for their depression (86% vs 35%; $P = .003$).²⁶ The authors of the study suggested that treating patient-reported depression may increase adherence to DMTs.²⁶

More recently, the authors of a review published in 2007 by *The Journal of Neurological Sciences* noted that the most frequent cause of stopping treatment is perceived lack of efficacy, and that most withdrawals from treatment occurred during the first year.²⁷ This information illustrates the importance of patient education and the implementation of strategies to promote adherence, which include setting realistic expectations, explaining the critical role of adherence in treatment outcomes, recognizing and addressing barriers to optimal adherence, accounting for ethno-cultural barriers, advocating for patients by assisting with reimbursement, identifying available resources, and involving family members and loved ones.²²

Managing Active Disease

The pharmacologic management of active MS typically begins with the administration of immunomodulatory disease-modifying drugs (DMDs); however, not all patients will have an optimal response to initial therapy. For patients with persistent relapses or disease activity observed via magnetic resonance imaging (MRI), or those who have difficulty tolerating or adhering to their treatment regimen, switching agents

may be the best option. A proposed algorithm from Spain has suggested that the first step in a switching strategy would be to switch from one first-line agent (ie, interferon betas, glatiramer acetate [GA], fingolimod, natalizumab) to another.²⁸ For example, patients initially treated with interferon betas may have their drug dosage or frequency increased, or those already on high-dose interferon beta may be switched to GA.²⁸ Similarly, patients who have been treated suboptimally with GA may be switched to an interferon beta.²⁸ In cases where the aforementioned recommendations are ineffective, switching to a second-line agent (ie, natalizumab or fingolimod) is suggested; however, while the second-line agent may be more effective, toxicity to the patient is also increased.²⁸ Fortunately, washout periods between switches are rarely needed, with the exception of switching from an immunosuppressive DMD to natalizumab, which requires immune system recovery.²⁹ Treatment cost is also an important consideration when deciding on therapeutic switches. Evidence suggests that non-pharmaceutical medical costs are greater for those who switch treatments for MS compared with persistent users of initial therapy.³⁰ Additionally, a study published in 2010 found that the initiation of therapy with fingolimod with continuous use for 2 years was associated with a lower cost per relapse avoided compared with treatment with an interferon beta (intramuscular interferon beta-1a) for 1 year followed by a switch to fingolimod.³¹

Emerging Therapies

Although several DMDs have demonstrated significant efficacy on clinical and MRI disease activity and are currently available for the treatment of patients with MS, more effective and tolerable therapies are still needed.³² Therefore, the drug pipeline for MS therapy continues to evolve to suit the needs of the patients and providers, with 3 DMDs (alemtuzumab, ocrelizumab, and laquinimod) currently in advanced development. The humanized monoclonal antibody alemtuzumab targets the glycoprotein antigen CD52, which is located on the surface of mature T and B lymphocytes and monocytes. The results of a study published in 2010 found that alemtuzumab induced the production of neurotrophic factors in reconstituted autoreactive T cells.³³ The results of one phase III trial of laquinimod, a synthetic, orally active, small-molecule, anti-inflammatory agent, showed that it was unable to significantly reduce relapses among patients with MS beyond those seen with placebo.³⁴ However, final results of another phase III trial showed that oral laquinimod administered once daily was able to slow the progression of disability and reduce the rate of relapse in patients with RRMS.³⁵

Investigational agents offer hope for improved patient outcomes, but are also associated with new challenges, and prominent among those challenges are safety concerns. While research and development for MS continues to move forward, patients receiving alemtuzumab in its phase III trials were required to undergo 1 month of prophylaxis with oral acyclovir after each infusion cycle due to concerns regarding opportunistic infections, and phase III trials with ocrelizumab for rheumatoid arthritis and lupus nephritis were partially or completely put on hold in 2010 due to opportunistic infections.³⁶ Malignancies are another concern, as a case of melanoma has been reported following treatment with alemtuzumab.³⁷ For those treated with alemtuzumab, lymphocytopenia is an additional safety issue due to prolonged lymphocyte depletion that may last for years following a single dose.³⁸ Further, treatment with alemtuzumab has been associated with emergent autoimmune diseases in the form of antibody-mediated autoimmune complications, such as thyroid disorders, immune thrombocytopenic purpura, and Goodpasture syndrome.^{38,39} Beyond the issues of safety, the selection of first-line therapies will undoubtedly become even more complicated due to the broadened scope of relative efficacy, different mechanisms of action, and various risk profiles. The decision-making process for treatment selection, sequencing, and combination for optimal benefits will undoubtedly increase in complexity as the agents currently in development for MS make their way into the market.

Summary

The complexity of MS and the diversity of its signs and symptoms require a multidisciplinary approach to treatment that combines pharmacologic and nonpharmacologic strategies, as well as improved patient education. The diagnosis and treatment of relapses in clinical practice presents a host of challenges due to the multiple manifestations of relapses, the variations of signs and symptoms within each particular relapse manifestation, and the presence of pseudo-relapses and infections. Whether or not treatment for relapse should be initiated is also a controversial topic, and if the relapse is to be treated, the selection of a treatment option requires careful and informed consideration. The treatment of active disease can also be further complicated based on the number and type of pharmacotherapeutic options available. Ultimately, a treatment decision should be personalized to the patient and contingent upon the balance between its risks and benefits. With the newer agents that are currently in the drug development pipeline, the expanded therapeutic armamentarium offers clinically beneficial opportunities, but also presents substantial challenges to clinicians and

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providers due to new questions regarding appropriate use and positioning in therapeutic algorithms. As such, additional long-term studies and clinical data will be required to elucidate any safety efficacy concerns associated with these newer agents for MS.

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