Neurology

MULTIPLE SCLEROSIS

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Learning Objectives

1. Describe the epidemiology, etiology, pathophysiology, and clinical presentation of multiple sclerosis (MS).
2. Distinguish among relapsing-remitting MS, benign MS, secondary-progressive MS, and primary-progressive MS.
3. Interpret results from disability scales and magnetic resonance imaging scans to monitor the progression of MS and recommend treatment changes.
4. Evaluate the various treatment options of acute exacerbations with regard to indication, efficacy, and adverse effects.
5. Develop optimal treatment plans for individual patients with MS using the 2005 Consensus Statement from the Executive Committee of the Medical Advisory Board of the National Multiple Sclerosis Society.
6. Evaluate the disease-modifying drugs (DMDs) with regard to efficacy and adverse effects.
7. Assess the symptomatic problems associated with MS and their various treatment options.
8. Design methods for educating patients on their pharmaceutical regimens that improve adherence and outcomes.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune disorder characterized by central nervous system (CNS) demyelination and axonal damage. The term multiple sclerosis refers to two major characteristics of the condition: the multiple affected areas of the CNS that produce neurologic symptoms and the characteristic sclerosed areas that are the hallmark of the disease. French neurologist Jean-Martin Charcot, the father of neurology, first described MS in 1868, calling the condition sclérose en plaques.

Multiple sclerosis is the second most common cause of neurologic disability in the United States, incurring health care costs of more than $10 billion per year. In addition, MS is the leading cause of non-traumatic disability in young adults with a lifetime risk of 1 in 400. Recent advances in understanding the pathophysiology of MS coupled with the release of six disease-modifying drugs (DMDs) since 1993 have significantly improved the clinical outlook of the disease. Although DMDs are not a cure for MS, they can alter the natural course of the disease by decreasing the number and severity of relapses, slowing the progression, and decreasing the occurrence of new lesions.

Epidemiology and Risk Factors

Multiple sclerosis is a relatively common condition. An estimated 250,000–350,000 persons in the United States and more than 2.5 million persons worldwide have MS. The prototypical patient is a young woman of childbearing age. Multiple sclerosis is most often diagnosed in patients between the ages of 20 and 45, with the peak incidence in the fourth decade of life. Occasionally, the disease presents in childhood or in late adulthood. The literature describes patients as young as 10 months and as old as 80 being diagnosed with MS. Women are afflicted with MS more than men by a ratio of 2–3:1. However, men usually develop the first signs of MS at a later age and are more commonly diagnosed with the progressive form of the disease than women. Multiple sclerosis tends to affect Caucasians, especially those of Northern European descent, more than other ethnic groups. Multiple sclerosis is rare in tropical areas, and the prevalence increases in areas further away from the equator, excluding polar regions. Finally, genetics appears to play a role. The familial recurrence of MS is about 5%, with siblings being the most commonly reported relationship.

Etiology

Although the exact cause of MS is unknown, most experts agree that the condition is most likely caused by a combination of factors, including genetics, environment, and immune system derangement. Multiple sclerosis occurs when the immune system of genetically susceptible individuals becomes altered after exposure to certain viruses

Abbreviations in This Chapter

ABCR	Avonex, Betaseron, Copaxone, and Rebif
CNS	Central nervous system
DMD	Disease-modifying drug
MS	Multiple sclerosis
MRI	Magnetic resonance imaging

(e.g., measles, mumps, rubella, varicella, Epstein-Barr, or human herpes virus 6) that allow autoreactive T lymphocytes to become activated, cross into the CNS, and attack myelin. However, to date, no direct causal relationship has been observed between any of these infections and the development of MS. In addition, the only definitive genetic association with MS lies with the DR2 haplotype-DR5, DQ6. The risk conferred by this haplotype is small and inconclusive; however, its link to MS is well established.

Pathogenesis

The basic physiologic derangement in MS is the stripping of the myelin sheath surrounding neurons in the CNS by autoreactive T cells. Myelin, which is composed of tightly wrapped lipid bilayers with specialized protein components, facilitates nerve fiber conduction and provides insulation for axons (Figures 1-1 and 1-2).

Multiple sclerosis is believed to follow a biphasic disease process. In the early phase of the disease, autoreactive T cells ($CD4^+$ or $CD8^+$) cross into the CNS. Under normal circumstances, T cells do not enter the CNS. Once inside the CNS, T cells attack the myelin sheath. The primary targets of this attack appear to be myelin in the CNS and the oligodendrocytes (the cells that form myelin in the CNS). Demyelination, which results when the nerve is stripped of myelin, coupled with an inflammatory response leads to the formation of lesions. In most circumstances, myelin can be restored and axons are well preserved during this phase. However, every attack, even subclinical attacks, produces some damage, and it is the accumulation of damage from repeated attacks that accounts for long-term disability. As MS progresses, there is a transition to a neurodegenerative phase. This phase is characterized by irreversible axonal damage, which can lead to disease progression and permanent disability. Axonal damage can cause permanent disruption in the transmission of nerve impulses, leading to neurologic symptoms that reflect the affected area of the CNS (Figure 1-3).

Making the Diagnosis

The diagnosis of MS is based on the presence of CNS lesions that are disseminated in time and space (occurring in different parts of the CNS and found at least 3 months apart), with no better explanation for the disease process. Early symptoms of MS may include muscle weakness or numbness in the limbs, partial or complete loss of vision in

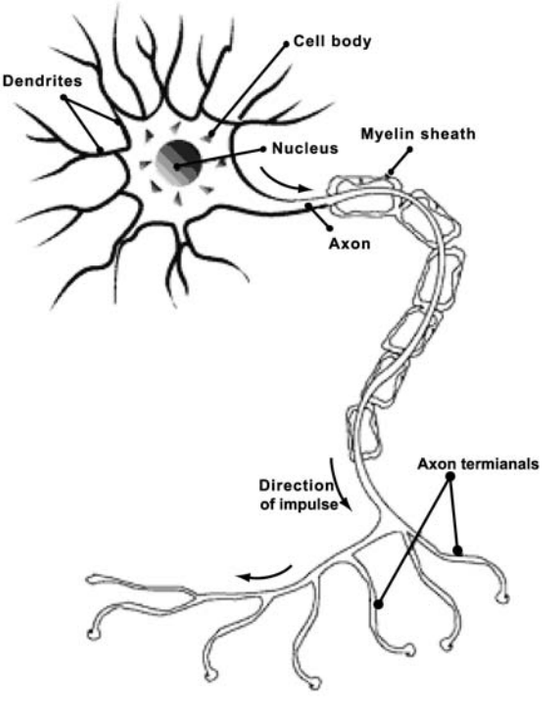

Figure 1-1. Nerve fiber conduction.
Nerve impulses originate in the nucleus and travel to axon terminals, where they are transmitted to other neurons and/or muscles. The myelin sheath facilitates the transmission of nerve impulses and insulates and protects axons. Without myelin, axons would have to be about 100 times larger to achieve the same speed of nerve transmission. When the myelin sheath is damaged in conditions such as MS, nerve fiber conduction can be impaired and/or lost.
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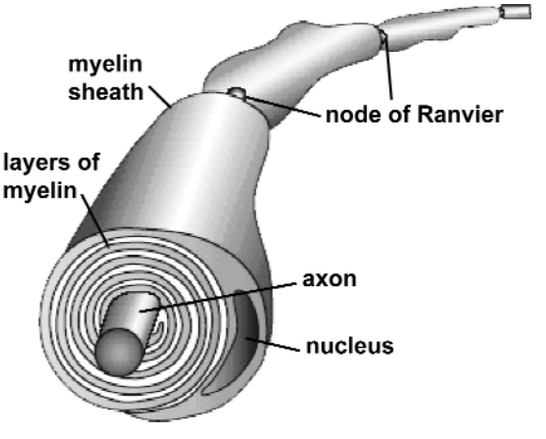

Figure 1-2. Cross section of a nerve.
Myelin, which is wrapped around the axon in many thin layers, is composed of protein and fatty substances. The nodes of Ranvier are regular breaks in the myelin sheath that surround the axons. Although the precise function of the nodes of Ranvier is unknown, it has been proposed that they may prevent the decay of nerve impulses, anchor the myelin sheath to the axon, and/or isolate each segment of myelin.
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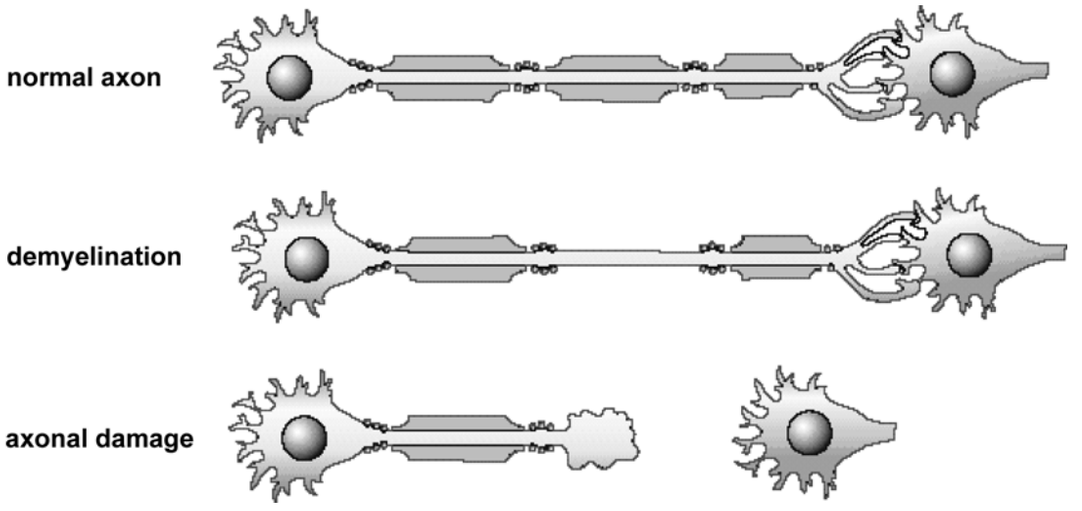

Figure 1-3. The stripping of myelin.
The picture on the top represents a normal axon with an intact myelin sheath. The middle picture depicts a demyelinated axon that has lost a portion of the myelin sheath. The bottom picture shows the final result of demyelination, known as axonal damage. The axon has been severed due to the loss of myelin.
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one eye, double vision, or instability. Symptoms may appear suddenly, or over the course of minutes to hours. Some patients may describe similar events that occurred previously. Because no one test is completely reliable in identifying MS, and a variety of conditions can mimic the disease (e.g., vascular disease, spinal cord compression, vitamin B_{12} deficiency, or CNS infections), diagnosis depends on physician expertise and clinical findings.

The McDonald criteria, which was adopted in 2001 by the International Panel on MS Diagnosis, incorporates both clinical and laboratory elements in the diagnosis of MS. Although the McDonald criteria requires the presence of at least two lesions that are separated by time and space, it allows for magnetic resonance imaging (MRI) studies, cerebrospinal fluid analysis, and evoked potential findings to be used as a means of identifying second attacks. The McDonald criteria calls for 1 of 3 potential diagnoses: 1) a diagnosis of MS, 2) a "possible" diagnosis of MS, or 3) no diagnosis of MS.

Magnetic resonance imaging scans are the most useful test for confirming the diagnosis of MS because they are highly selective in detecting MS lesions. However, not all patients with MS have lesions that can be seen on MRI. Early in the disease course, scans may be normal because the lesions are not yet large enough to be visualized on MRI. Magnetic resonance imaging scans with contrast are commonly used because they differentiate new lesions from old ones. Lesions that enhance (glow) after injection with the contrast material gadolinium indicate the presence of new lesions. Despite the usefulness of MRI scans, they should not be solely used to diagnose or rule out MS. Five percent of people with MS do not have evidence of the disease on MRI scans. In addition, spots on MRI scans suggestive of MS are based on changes in proton density (water content) and thus are intrinsically nonspecific. Therefore, spots on MRI scans can occur with any condition that results in changes in brain water content, including normal aging, migraine headaches, high blood pressure, head injuries, infections, or vasculitis.

Lumbar punctures can also help in the diagnosis of MS. Ninety percent of patients with definite MS have elevated amounts of immunoglobulin G proteins in their cerebrospinal fluid. In addition, oligoclonal bands are also commonly present in the cerebrospinal fluid of patients with MS. However, increased immunoglobulin G levels and the presence of oligoclonal bands are not specific for MS. These diagnostic tests are probably more useful in ruling out infectious or neoplastic conditions that mimic MS.

Evoked potential tests that measure the electrical activity of the brain in response to stimulation of specific sensory nerve pathways can assist clinicians in making a diagnosis of MS. These tests are particularly useful in identifying areas of demyelination that are clinically silent. Of the four sensory evoked potential tests (visual, brainstem, auditory, and somatosensory), the visual evoked potential test is most useful because it can provide objective evidence of optic nerve lesions that are not visible on MRI scans. The visual evoked potential test is not specific for MS, and other conditions (e.g., tumors compressing the optic nerve or other demyelinating diseases) can also produce abnormal results.

Clinical Presentation

Types of MS

The clinical presentation of MS is extremely variable among patients and usually varies over time, but invariably the disease can be categorized into four general categories: relapsing-remitting MS, benign MS, secondary-progressive MS, and primary-progressive MS (see Table 1-1 and Figure 1-4).

Relapsing-Remitting MS

Eighty-five percent of patients with MS are originally diagnosed with the relapsing-remitting form. This form of

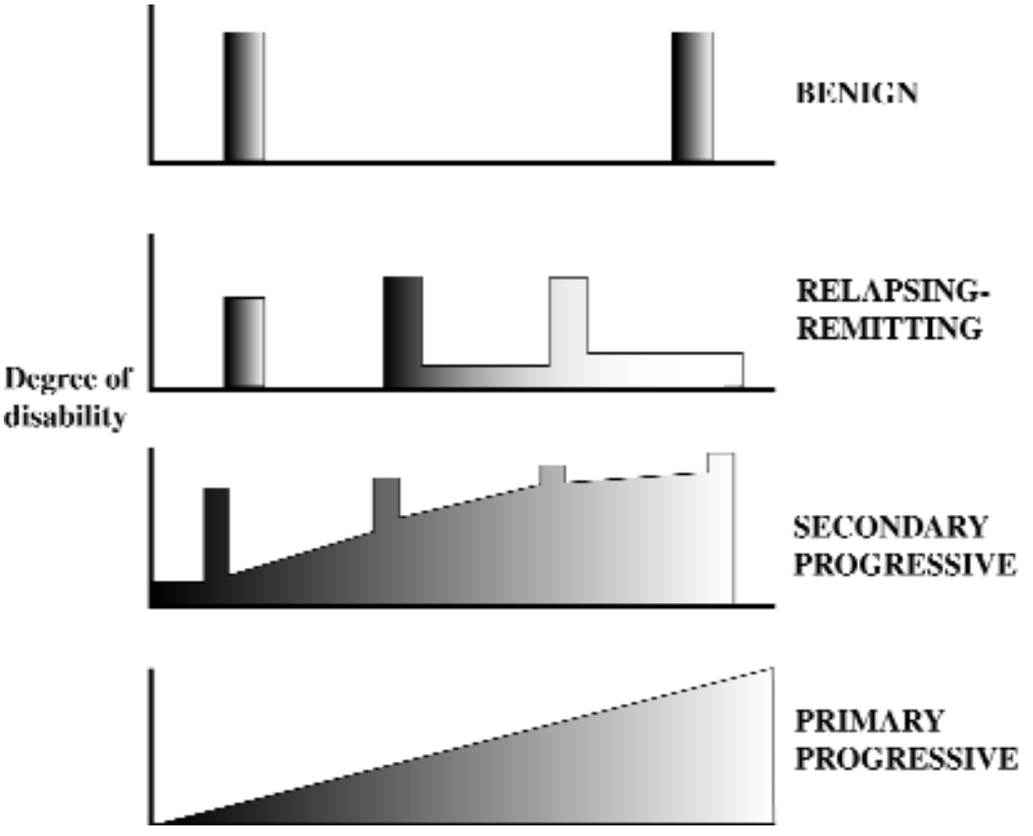

Figure 1-4. Types of multiple sclerosis.
In benign multiple sclerosis (MS), patients return to normal after attacks and experience no disability. In relapsing-remitting MS, patients experience relapses that can lead to increasing degrees of clinical deficits. In secondary-progressive MS, patients may continue to have relapses, but also experience a slow steady loss of neurologic function. In primary-progressive MS, patients experience a continuous worsening from onset, without distinct relapses and remissions. Reprinted with permission from the Multiple Sclerosis Foundation.

Table 1-1. Types of Multiple Sclerosis

Name	% of Patients at Onset	Features
Relapsing-remitting	About 85%	Characterized by relapsing-remitting episodes—new attacks (relapses) that occur and last for at least 24 hours and are separated from other new symptoms by at least 30 days; followed by periods of remissions when symptoms resolve or partially resolve
		Residual symptoms and an increasing degree of clinical deficit are common after attacks
Benign	Less than 5%	Abrupt onset, few exacerbations, and no permanent disability
Secondary-progressive		30%–50% of patients with relapsing-remitting MS eventually develop secondary-progressive MS
		Characterized by a gradual worsening of neurological symptoms
		Relapses can occur (especially early in this phase, but as the disease progresses relapses are less common and brain atrophy is more common
Primary-progressive	About 10%–15%	Progressive disease from onset without relapses and remissions
		Associated with a bad prognosis

MS = multiple sclerosis.

MS is characterized by attacks—new symptoms lasting at least 24 hours and separated from other new symptoms by at least 30 days—followed by remissions, during which symptoms resolve or partially resolve. Attacks are generally referred to as relapses or exacerbations, with the first attack (one single isolated episode of inflammation) being termed a clinically isolated syndrome. It is common for residual symptoms and an increasing degree of clinical deficit to persist after each attack.

Benign MS

A small subset of patients with relapsing-remitting MS, less than 5%, are eventually diagnosed with benign MS, an extremely rare form of MS characterized by an abrupt onset, few exacerbations, and no permanent disability. However, because of the variable clinical courses associated with MS, the diagnosis can change at any time.

Secondary-Progressive MS

Over the course of months to years, 30%–50% of patients with relapsing-remitting MS experience a gradual worsening of neurologic symptoms and are diagnosed with secondary-progressive MS. This type of MS most likely represents a neurodegenerative process initiated by earlier episodes of tissue injury. Patients with secondary-progressive MS continue to have relapses, especially during the early disease stages, but tend to experience increasing levels of disability. In addition, the incidence of new lesions (as seen on MRI) is less common, whereas, the development of brain atrophy is much more common in patients with secondary progressive MS.

Primary-Progressive MS

About 10%–15% of patients experience progressive disease without relapses and remissions from the onset and are diagnosed with primary progressive MS. Patients with primary progressive MS generally have a worse prognosis than patients diagnosed at the onset with relapsing-remitting MS.

Prognostic Indicators

It is often difficult to predict the prognosis of a patient with MS because the disease is far too variable and can change at any time. Although the course of MS is often unpredictable, there are some indicators that can predict a patient's prognosis. Patients diagnosed before age 40 tend to do better than patients diagnosed after age 40, and women have a better prognosis than men. Patients initially presenting with optic neuritis or numbness/tingling in the extremities have a better prognosis than patients who have motor or cerebellar symptoms at the disease onset. Not surprisingly, patients who have fewer attacks and those diagnosed with relapsing-remitting MS tend to fair better than those diagnosed with progressive MS.

The disease MS does not alter life expectancy; however, complications related to MS (e.g., urosepsis and pneumonia) may lead to shorter than expected life spans. Generally speaking, patients suffering from rapidly progressive MS tend to have shorter life expectancies than those diagnosed with relapsing-remitting MS or a slowly progressive form of the disease.

Monitoring the Progression

Disability scales are commonly used to monitor the overall progression of MS. The MS Functional Composite combines the results from three individual measures (i.e., ambulation, arm and hand function, and cognition) into a single score. This disability scale is expected to eventually replace the traditional Kurtzke Expanded Disability Status Scale, a scale that takes only ambulation into account, ignores cognition, and requires advanced expertise to use.

Magnetic resonance imaging scans are extremely useful tools for monitoring disease progression in patients with MS. In clinical practice, MRI scans can confirm disease progression in patients for whom disease activity is not clear, and persistent MRI activity during treatment with DMDs can be suggestive of disease progression and/or worsening. The focus for evaluation is on lesions in two areas, T1 and T2. The T1 hypointensities are dark or hypointense lesions. The T1 hypointensities that persist for 6 months or longer represent areas of tissue destruction and are called black holes. Newer lesions can be associated with transient T1 hypointensities representing edema. Bright areas (hyperintensities) on T2-weighted scans may represent a mixture of tissue pathologies, including active/chronic demyelination, tissue destruction, and edema. Regardless of type, gadolinium-enhancing lesions reflect breakdown of the blood-brain barrier and indicate the presence of active inflammation. The location of the lesions and the ensuing damage caused by the lesions are a better predictor of a poor clinical course than the actual number of lesions. Advancing methods of MRI (e.g., diffusion tensor imaging, magnetization transfer imaging, and MRI spectroscopy) are more specific than traditional MRIs. They are better able to assess tissue injury and recovery following treatments.

Clinical Management

The clinical management of MS should be considered as three parallel pathways. First, relapses (acute exacerbations) should be treated with appropriate therapies. Next, DMDs should be used to alter the natural history of the disease and to prevent/minimize neuronal damage. Finally, symptomatic problems associated with MS should be managed with additional medications to prevent and/or treat complications.

Treating Acute Exacerbations

The unpredictable nature of MS makes it difficult to anticipate when acute exacerbations (sudden events that produce functional decline) will occur. However, certain factors (e.g., infections, hyperventilation, fever, lack of sleep, stress, malnutrition, anemia, or childbirth) have been reported to aggravate symptoms and precipitate acute attacks.

Corticosteroids are considered the mainstay of treatment for acute exacerbations. These drugs exert their effect by decreasing edema in areas of demyelination, restoring the integrity of the blood-brain barrier, inducing T-cell apoptosis, and diminishing the release of proinflammatory cytokines. Numerous controlled, clinical trials found that corticosteroid therapy hastens the recovery time from acute attacks, and that high-dose corticosteroids are significantly more effective than moderate-dosed regimens in achieving

Table 1-2. Minimizing the Adverse Effects of Corticosteroids

Metallic taste in mouth: Chocolate milk and/or candy can decrease this sensation
Insomnia: Short-acting hypnotic drugs or benzodiazepines can be useful; avoid recommending over-the-counter antihistamines as they can worsen the metallic taste in the mouth
Gastrointestinal upset: Tell patients to avoid all products that typically upset their stomach (e.g., spicy foods, caffeine) and to minimize exposure to nonsteroidal anti-inflammatory drugs; suggest over-the-counter histamine-2 blockers or antacids.
Headaches/body aches: Suggest acetaminophen and tell patients to avoid nonsteroidal anti-inflammatory drugs.

Fox RJ, Bethoux F, Goldman MD, Cohen JA. Multiple sclerosis: advances in understanding, diagnosing, and treating the underlying disease. Cleve Clin J Med 2006;73:97.

this goal. However, although high-dose corticosteroids have proven to shorten the duration of acute attacks, they have not been demonstrated to alter the progression of the disease.

The American Academy of Neurology recommends intravenous methylprednisolone (500–1000 mg/day for 3–10 days) for treating acute exacerbations. Patients usually improve within the first 3–5 days of corticosteroid therapy. Some evidence suggests that equivalent doses of oral corticosteroids (e.g., dexamethasone and prednisone) are comparable pharmacokinetically to intravenous methylprednisolone; however, definitive studies using this administration route for acute exacerbations of MS are lacking.

The adverse effects of corticosteroids should not be underestimated despite the obvious benefits of the drugs. Short-term treatment sometimes produces a metallic taste in the mouth, insomnia, altered mood, headaches/body aches, and gastrointestinal pain. Clinicians should educate patients, before treatment, about these adverse effects and offer suggestions to help patients minimize the problems (Table 1-2).

Corticosteroids should be used with caution in some patient populations (e.g., patients with brittle diabetes or severe osteoporosis). In addition, high-dose corticosteroids are effective in only about 75% of patients. Alternatives to corticosteroids do exist and should be considered for patients who do not respond or who are not considered viable candidates for corticosteroid therapy. Studies have shown that plasma exchange is effective in about 40% of patients who have previously failed high-dose intravenous methylprednisolone therapy. Similarly, numerous clinical trials have shown that intravenous immune globulin reduces the intensity and duration of acute exacerbations.

Altering the Natural History of the Disease

The primary goal of DMDs is to alter the natural course of MS by reducing the frequency and severity of relapses, preventing the chronic progressive phase, and slowing the progression of disability. Currently, six DMDs are approved for the treatment of MS, including the two interferon-β1a groups (Avonex and Biogen Idec; Rebif and Serono), interferon-β1b (Betaseron; Berlex), glatiramer acetate (Copaxone; Teva Neuroscience), natalizumab (Tysabri; Biogen, Elan Pharmaceuticals), and mitoxantrone (Novantrone; Serono).

The DMDs can be divided into two categories: immunomodulators and immunosuppressants. The immunomodulators, which modify the immune system, are dosed continuously; they include all of the interferon-β products, glatiramer acetate, and natalizumab. The interferon-β products and glatiramer acetate, which are frequency called the ABCR drugs based on their proprietary names, are considered first-line treatments for relapsing-remitting MS, whereas natalizumab is indicated only for patients who have not responded adequately to, or who cannot tolerate, the ABCR drugs. Mitoxantrone is the only drug approved for marketing in the United States to treat the worsening forms of relapsing-remitting MS and progressive MS. Unlike the immunomodulators, mitoxantrone is administered in pulse doses up to a maximum lifetime dose of 140 mg/m^2.

Accumulating evidence suggests that the best time to initiate therapy with a DMD is early in the disease process. Data indicate that irreversible axonal damage may occur early in relapsing-remitting MS and that drug therapies appear to be more effective in preventing new lesions than in repairing old lesions. Based on these findings, the National Multiple Sclerosis Society recommends that therapy with DMDs be initiated as early in the disease process as possible. These recommendations along with others regarding the use of DMDs can be found in the 2005 Consensus Statement from the Executive Committee of the

Table 1-3. A Summary of the Major Points of the 2005 Consensus Statement From the Executive Committee of the Medical Advisory Board of the Multiple Sclerosis Society

Initiate treatment with a DMD as soon as possible following diagnosis of MS with a relapsing course. Consider treatment for selected first-attack, high-risk patients.
Access to therapy should not be limited by relapse frequency, age, or level of disability.
There should be access to/coverage for all FDA-approved drugs. Patients should be allowed to change therapies.
Immunosuppressant therapy with mitoxantrone should be considered for worsening or progressive MS.
None of the DMDs are approved for use in women who are pregnant, nursing, or attempting to become pregnant.
Treatment should not be stopped while insurers evaluate for continuing coverage.
Therapy should continue indefinitely except in the event of clear lack of benefit, intolerable adverse effects, new data, or better therapies

DMD = disease-modifying drug; FDA = Food and Drug Administration; MS = multiple sclerosis.

Table 1-4. Comparing Interferon-β Products

Type of Interferon	Proprietary Name	Dose/Route/Frequency	Approved
Interferon-β 1b (high-dose)	Betaseron	0.25 mg SQ QOD	1993
Interferon-β 1a (low-dose)	Avonex	30 mcg IM QW	1996
Interferon-β 1a (high-dose)	Rebif	44 mcg SQ TIW	2002

IM = intramuscularly; QOD = every other day; QW = every week; SQ = subcutaneously; TIW = 3 times/week.

Medical Advisory Board of the National Multiple Sclerosis Society. Table 1-3 summarizes the major points from the 2005 Consensus Statement.

Interferon-β Products

Currently, three interferon-β products are approved for treating MS: Avonex, Betaseron, and Rebif (Note: because of the similarities in generic names, proprietary names will be used henceforth to differentiate between the three interferon-β products). Numerous large, independent, multicenter, multicountry trials have consistently demonstrated that interferon-β products reduce the number of exacerbations and improve MRI measures of disease activity in the brain. interferon-β products are considered first-line treatments for relapsing-remitting MS and are also indicated for patients who cannot tolerate glatiramer acetate.

The interferon-β products that have antiviral and immunoregulatory functions belong to a class of peptides that are involved in various biological processes (e.g., defense against viral infections, cell growth regulation, and modulation of immune response). The exact mechanism(s) by which interferon−β products exert their beneficial effects in MS are not known. It appears that the interferon-β products decrease T cell production of interferon-γ (a pro-inflammatory cytokine), decrease the production of pro-inflammatory T-helper 1 lymphocytes and increase the production of T-helper 2 anti-inflammatory lymphocytes, and decrease T lymphocytes trafficking into the CNS.

The major differences between the three interferon-β products lie in administration route, dosage, and frequency of administration (Table 1-4). Betaseron, the first DMD approved for use in MS, and Rebif are both high-dose interferon-β products, whereas Avonex is a low-dose interferon product. Much debate exists regarding which interferon-β product(s) are most effective. Two randomized, prospective, multicenter, Phase 3 trials that compared the different interferon-β products were published in 2002. Results from these two studies suggest that the high-dose interferon-β products (Betaseron and Rebif) have greater efficacy than the low-dose interferon-β product (Avonex). Further evidence suggests that the dosing interval may be the contributing factor, as a recent study of standard-dose Avonex versus double-dose Avonex found that the double-dose product was no more effective than the standard-dose one. This evidence is consistent with previous data showing that sustained levels of interferon-β (with a greater area under the curve drug concentration) are more efficacious than brief periods of interferon-β exposure.

Influenza-like symptoms (e.g., fever, chills, tiredness, malaise, and muscle aches) are the most common adverse reactions associated with interferon-β products, occurring in about 60% of people. Not surprisingly, influenza-like symptoms are more often associated with the high-dose interferon-β products. Over time, influenza-like symptoms tend to decrease. Treatment with antipyretic drugs (e.g., ibuprofen or acetaminophen) and/or low-dose oral corticosteroids may decrease these influenza-like symptoms. Other adverse effects associated with the interferon-β products include injection site reactions, increased spasticity, mild anemia, thrombocytopenia, and menstrual irregularities. These adverse effects are usually not severe and rarely warrant discontinuation of the drug. In rare cases, interferon-β products can cause liver damage; therefore, patients should have their liver enzymes checked periodically. Because interferon-β products can cause depression, the products should be used cautiously in patients with mild to moderate depression and avoided in patients with severe depression.

Neutralizing antibodies can develop against any interferon-β product and can, in theory, decrease the effectiveness of the drugs. Although study results are variable, Avonex appears to be associated with the lowest incidence of neutralizing antibodies. However, to date, no agreed-upon assay, cutoff value, or recommended time frame to evaluate neutralizing antibodies exists. The recent National Multiple Sclerosis Society Consensus Guidelines do not endorse changing therapy for patients with elevated levels of neutralizing antibodies who are otherwise stable and doing well.

Glatiramer Acetate

Glatiramer acetate, a non-interferon-β product, is a synthetic mixture of polypeptides produced by the random combinations of four amino acids that are frequently found in myelin basic protein. Exactly how glatiramer acetate works is not completely understood. It has been hypothesized that the glatiramer acetate molecule influences immature CD4 T cells to become less inflammatory. This action suppresses the immune attack on myelin and prevents demyelination and nerve fiber damage. In addition, some evidence suggests that glatiramer acetate also has neuroprotective properties because it stimulates CD4 T-cells to produce a neuroprotection factor (known as brain-derived neurotrophic factor) that helps to protect the brain from axonal loss.

Glatiramer acetate should be administered subcutaneously at 20 mg once daily. It is considered a first-line treatment for relapsing-remitting MS and is also indicated for patients who cannot tolerate interferon-β products. In January 2005, 8-year data regarding the efficacy of glatiramer acetate were released. These data, which represent the longest-term data available on any of the commercially available DMDs, demonstrated that glatiramer acetate reduces relapse rates and slows the

accumulation of disability in patients with MS. In addition, the data supported the initiation of glatiramer acetate, as early in the disease process as possible, in the treatment of patients with MS.

Glatiramer acetate is generally well tolerated, with injection site reactions being the most bothersome adverse effects. Unlike the interferon-β products, glatiramer acetate is not associated with influenza-like symptoms. Glatiramer acetate does not require routine laboratory monitoring and does not produce neutralizing antibodies. However, at some point in therapy, 10%–15% of patients treated with glatiramer acetate experience a post-injection reaction consisting of chest pain, palpitations, and/or trouble breathing within minutes of administering a dose. This reaction usually happens only once and typically resolves within 30 minutes without residual adverse consequences. When counseling patients, pharmacists should make a point to educate patients about the possibility of this reaction. Data suggest that patients experiencing the post-injection reaction who were aware the reaction could occur were likely to continue therapy than those who had the reaction, but were not made aware of it.

Natalizumab

Natalizumab was initially granted accelerated approval by the FDA in November 2004 as a treatment for relapsing-remitting MS. The accelerated approval was based on 1-year evidence from two clinical trials: the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) monotherapy trial with Avonex. Less than 3 months later, natalizumab was withdrawn by the manufacturer after three patients enrolled in the clinical trials developed progressive multifocal leukoencephalopathy, a serious, and potentially fatal, viral infection of the brain. In June 2006, the FDA approved an application for resumed marketing of natalizumab through a special restricted distribution program, called the TOUCH Prescribing Program (Table 1-5). The new labeling for natalizumab states that the product should be used only as monotherapy because administering the product with other DMDs could potentially increase the risk of developing progressive multifocal leukoencephalopathy. In addition, the new labeling states that natalizumab should be used only in patients who have not responded adequately to, or who cannot tolerate, the other DMDs.

Natalizumab is the first humanized monoclonal antibody approved for treating MS. It should be administered by intravenous infusion every 4 weeks at 300 mg. Infusion reactions (e.g., rash, drowsiness, fever, chills, nausea, flushing, decreased blood pressure, shortness of breath, or chest pain) are common with natalizumab. Such reactions usually occur within 2 hours of the start of the infusion and generally subside when the drug is stopped and/or treatment is given. Patients should be monitored for signs of infusion reactions during the infusion and for 1 hour after the infusion. Common adverse effects associated with natalizumab include headache, fatigue, urinary tract infection, depression, lower respiratory tract infection, joint pain, and abdominal discomfort.

Because natalizumab is a humanized product, antibodies can be produced by the body against the drug. Fewer than 10% of people produce antibodies to natalizumab. Persistently positive antibodies are associated with a decrease in effectiveness of natalizumab and an increase in infusion reactions.

Mitoxantrone

Mitoxantrone, a synthetic anthracenedione, decreases the migration of T cells into the CNS by arresting the cell cycle and interfering with DNA repair and RNA synthesis. The drug is effective in reducing clinical relapses and progression of disability in patients with worsening relapsing-remitting MS and progressive MS. Mitoxantrone is not considered a replacement for interferon-β products or glatiramer acetate, but it is often used in conjunction with them. Only in certain cases (e.g., when patients are progressing and worsening, but not relapsing) should mitoxantrone therapy replace interferon-β products or glatiramer acetate. Mitoxantrone should not be used in conjunction with natalizumab because the combination theoretically increases the risk of progressive multifocal leukoencephalopathy.

Mitoxantrone is dosed by intravenous infusion at 12 mg/m^2 every 3 months up to a maximum cumulative dose of 140 mg/m^2. Because mitoxantrone is cardiotoxic, it should be used only in patients who have normal cardiac function. Mitoxantrone should not be used in patients who have a left ventricular ejection fraction of less than 50%. Although the risk of cardiotoxicity appears to be related to the lifetime dose, it can occur any time during therapy. In addition, blood dyscrasias (particularly secondary acute myelogenous leukemia) have been associated with mitoxantrone use. In May 2005, the FDA requested that a Black Box Warning be added to the labeling of mitoxantrone, which provided additional information about the potential risk of cardiotoxicity and secondary acute myelogenous leukemia. The new labeling states that repeated testing of cardiac function should be performed

Table 1-5. Requirements of the TOUCH Prescribing Program

Natalizumab can only be prescribed, distributed, and infused by prescribers, infusion centers and pharmacies registered with the program.
Natalizumab can only be administered to patients who are enrolled in TOUCH.
Before initiating the therapy, patients must have MRI scans. These scans can help differentiate potential future MS symptoms from PML.
Patients on natalizumab should be evaluated 3 and 6 months after the first infusion and every 6 months, thereafter, and their status will be reported regularly to Biogen Idec.

MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
Adapted from *www.fda.gov/cder/drug/infopage/natalizumab/riskmap.pdf*.

before each dose, along with the baseline testing of cardiac function that was recommended in the original labeling. Mitoxantrone should not be given if the ejection fraction falls below 50% or if there is a 5% or greater decline from the patient's baseline ejection fraction. Other adverse effects associated with mitoxantrone include nausea, leukopenia, alopecia, menstrual irregularities, and urinary and respiratory tract infections.

When counseling patients about taking this drug, it should be explained that mitoxantrone may impart a blue-green color to the urine that lasts about 24 hours after drug administration and that may cause the sclera of the eyes to appear bluish. In addition, all women of child-bearing age should be reminded to avoid becoming pregnant while taking mitoxantrone. If women become pregnant while taking mitoxantrone, they should be instructed to contact their physician immediately.

Combining Therapies

Patients are generally treated with only one DMD at a time; however, in certain circumstances a second DMD may be prescribed. For example, patients who are experiencing a worsening of their relapsing-remitting disease commonly receive pulse mitoxantrone infusions in addition to their currently prescribed ABCR drugs. Data suggest that combination therapy slows and (sometimes) even halts disease progression. On the other hand, patients should never receive natalizumab with one of the other DMDs because the combination significantly increases the risk of progressive multifocal leukoencephalopathy infections. With regard to combining the interferon-β products with glatiramer acetate, data are lacking but hopefully forthcoming. In 2006, the National Institutes of Health began recruiting patients for the Combi Rx trial. This study is designed to evaluate whether glatiramer acetate plus Avonex reduces relapse rates more than either drug alone.

Non-Approved Therapies

Non-approved therapies that lack definitive scientific evidence are sometimes used in the treatment of MS. The immunosuppressant cyclophosphamide ranks as the most commonly prescribed non-approved therapy for MS in the United States. Although several non-blinded studies claimed that monthly intravenous infusions of cyclophosphamide slowed progression, other blinded studies have shown no benefit. Because of these inconsistent results and the high potential for serious adverse effects (e.g., hemorrhagic cystitis and malignancy), cyclophosphamide is typically reserved for patients with aggressive disease who have not responded to approved treatments.

Numerous oral therapies, including methotrexate, azathioprine, cyclosporine, and mycophenolate, have also been studied in MS. However, little or no controlled, clinical data exist supporting their use. These drugs are primarily prescribed to patients who cannot tolerate or for whom therapy failed with them.

DMDs in the Pipeline

Numerous clinical trials are presently under way examining "new and improved" DMDs in the hopes of finding alternative treatments that are easier to administer, have fewer adverse effects, and are more efficacious. Cladribine, fingolimod, and laquinimod are three orally administered DMDs that have shown promise in treating MS. A Phase 3 trial (known as CLARITY–CLAdRIbine Tablets in Treating MS OrallY) is currently under way in the United States examining the safety and efficacy of cladribine. The results from a Phase 2 trial evaluating the safety and efficacy of fingolimod found the product to be both safe and efficacious. As a result, a Phase 3 clinical trial evaluating fingolimod is under way in Europe and Canada.

Data also suggest that the hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) may possess some disease-modifying properties. In fact, a study published in The Lancet found that simvastatin significantly decreased the number and volume of new lesions detected by MRI. With regard to the efficacy of hydroxymethyl glutaryl coenzyme A reductase inhibitors, most clinicians agree that it is highly unlikely that research will demonstrate that these products are as effective as the currently available DMDs. However, data do suggest that they may have a synergistic effect when added to the currently available DMDs.

Finally, several monoclonal antibodies (including daclizumab and rituximab) appear to show promise in the treatment of MS. Daclizumab is currently being studied in a Phase 2 clinical trial, and rituximab is being evaluated in a Phase 3 clinical trial.

Symptom Management

Patients with MS tend to experience many symptomatic problems secondary to their disease that can interfere with activities of daily living and decrease their quality of life. Some of the more common symptomatic problems associated with MS include spasticity, bladder and bowel dysfunction, fatigue, pain, tremors, cognitive dysfunction, depression, and sexual dysfunction. Because no two patients with MS are exactly alike, symptomatic problems tend to vary tremendously from individual to individual.

Symptomatic problems can be divided into those that are caused directly from the disease itself (primary symptoms) and those that are not. Primary symptoms result from the myelin destruction and neuronal damage in the particular areas of the CNS, whereas secondary and tertiary symptoms are manifestations of primary symptoms. Examples of primary symptoms include tremors resulting from cerebellum lesions or lower limb weakness due to lesions in the spinal cord. It is not uncommon for primary symptoms to cause secondary symptoms (e.g., falling and breaking a hip because of a leg tremor or slow gait due to weakness in the legs). Tertiary symptoms, which have a negative impact on life in general, can follow secondary symptoms. Depression, frustration, and/or vocational/marital problems are common components of tertiary symptoms. Examples of tertiary symptoms include refusing to leave home because of fear of falling or continually canceling social activities because of embarrassment of slow gait. Tertiary symptoms generally occur when primary problems are ignored or not treated.

Spasticity, a velocity-dependent increase in muscle tone derived from hyperexcitability of the stretch reflex, primarily affects the lower limbs and can lead to pain, stiffness, tremor, clonus, impaired balance, and spasms.

Spasticity can be induced by many noxious stimuli, including urinary tract infections, constipation, ingrown toenails, pressure ulcers, and poorly fitting assistive living devices (e.g., wheelchairs or braces). Because the interferon-β products enhance nerve conduction in the spinal cord, they can also exacerbate spasticity.

The goal of therapy when treating spasticity is to reduce symptoms to improve patient comfort and function rather than to completely eliminate spasticity. Of interest, some degree of spasticity actually helps patients with lower extremity weakness walk because it offers some limb stabilization.

Rehabilitation, which is considered key to managing spasticity, should be tailored to each patient's degree of impairment and disability. However, rehabilitation rarely alleviates all symptoms. Drugs that decrease spasticity are often used as adjuncts to rehabilitation. With regard to drug management of spasticity, one should attempt monotherapy initially, starting at the lowest possible dose, and slowly escalating the dose upward as needed.

Orally administered baclofen is considered the first-line treatment for spasticity. Because baclofen can cause significant weakness, dosages should be started low (e.g., 5–10 mg 3 times/day) and titrated upward slowly, as needed, to a maximum of 120 mg/day. Common adverse effects of baclofen include somnolence and confusion. Over time, these adverse effects tend to lessen dramatically. When patients are counseled about baclofen, they should be reminded to avoid suddenly stopping the drug because abrupt withdrawal can lead to hallucinations, seizures, and death.

Tizanidine is also frequently used to treat spasms. It appears to be as effective as baclofen, but tends to cause significantly less weakness. The starting dose of tizanidine is 2 mg at bedtime. This drug causes extreme sedation; therefore, doses must be gradually increased to a maximum of 36 mg/day (given in 3–4 divided doses each day). Common adverse effects of tizanidine include sedation, dry mouth, hypotension, and constipation. In severe cases of spasticity, baclofen and tizanidine can be combined.

Other products that are also sometimes used to treat spasms include diazepam, clonazepam, dantrolene, and clonidine. The benzodiazepines (diazepam and clonazepam) are most commonly used to treat nocturnal spasms that are refractory to baclofen and tizanidine. Dantrolene is typically reserved for patients who cannot walk and are therefore not affected by the muscle weakness that it causes. All of these products (e.g., diazepam, clonazepam, dontrium, and clonidine) can cause drowsiness. Patients should be reassured that the drowsiness usually decreases with time.

Botulinum toxin (type A or type B) is increasingly being used to treat MS spasticity, especially in patients with focal target areas (e.g., difficulty with self-catheterization and hygiene due to spasticity of the hip adductors). The drug is delivered by intramuscular injection; however, localization with electromyelography or electrical stimulation may be needed to find small or deep muscles. The effects of botulinum toxin occur within a few days to up to 2 weeks after injection, and typically last from 3 to 6 months. Periodic repeat injections are needed to maintain the benefit. Botulinum toxin is usually safe and well tolerated, with local muscle weakness and atrophy being the most commonly reported adverse events. Although botulinum toxin is not an approved treatment for spasticity, many insurance companies will pay for its use in patients with MS.

Patients who cannot tolerate or who are unresponsive to oral monotherapy or combination therapy with anti-spasm drugs usually benefit from intrathecal baclofen. This form of baclofen is markedly more effective and better tolerated than oral baclofen in patients suffering from severe spasms who are wheelchair bound. Intrathecal baclofen is delivered through a surgically implanted catheter and pump.

Bladder dysfunction is considered one of the most common symptomatic problems associated with MS; an estimated 96% of patients have bladder symptoms at some point in the disease. Left untreated, bladder dysfunction can exacerbate the underlying disease course and cause secondary infections.

Bladder dysfunction problems include failure to empty, failure to store, or a combination of the two. Failure to empty (detrusor hyperreflexia) is the most common bladder problem seen in patients with MS. Patients commonly complain of urinary urgency and frequency and of voiding only small amounts of urine. Over time, urgency can become more difficult to control and can lead to incontinence. Anticholinergic drugs (e.g., oxybutynin and tolterodine) are commonly prescribed for failure to store problems. The most common adverse effects associated with these drugs include dry mouth and constipation. Pharmacists should remind patients to increase their fluid intake while taking anticholinergic drugs. Although these drugs are usually effective, patients with large postvoid residual volumes (greater than100 mL) may also need to use intermittent self-catheterization because large urine residual volumes increase the risk of developing urinary tract infections.

Failure to store (detrusor sphincter dyssynergia) is a less common bladder dysfunction problem in patients with MS. The condition, which primarily occurs only in men, causes hesitancy, retention, and overflow incontinence. α-Blockers (e.g., terazosin and tamsulosin) are the drugs of choice for failure to store problems. Pharmacists should tell patients that these products decrease blood pressure and can cause severe dizziness, especially after the first dose. When α-blockers are not effective, adjunctive measures (e.g., pads, undergarments, or condom catheters) may improve the patient's quality of life by minimizing the embarrassing effects of overflow incontinence.

Bowel dysfunction, including diarrhea, constipation, and fecal impaction, occurs in about 70% of patients with MS. Treatments should focus on treating the underlying complaint (e.g., diarrhea or constipation). Bowel regimens with a high-fiber diet, exercise, and drugs such as laxatives and stool softeners are commonly used to treat bowel dysfunction problems. Patients should be cautioned to avoid using overly strong products because such drugs can cause diarrhea and fecal incontinence. Practitioners might suggest the use of daily or every other day bowel programs if constipation is an issue.

Fatigue, one of the most common complaints of patients with MS, often limits activities of daily living, job

performance, and quality of life. About 90% of patients with MS experience fatigue. Although MS-related fatigue is a common problem, clinicians should evaluate patients for coexisting medical conditions (e.g., thyroid disease, anemia, and sleep disturbances) that could cause or contribute to fatigue. The degree of MS-related fatigue varies from patient to patient. Although the exact cause is unclear, it is known that MS-related fatigue worsens before and during exacerbations and with external and core temperature increases. Not surprisingly, spasticity and weakness can also worsen MS-related fatigue.

Multiple sclerosis-related fatigue is best treated with a combination of low-impact aerobic exercise and anti-fatigue drugs. First-line drugs used to treat fatigue include amantadine or modafinil. Because modafinil can reduce the efficacy of hormonal contraception, women of childbearing age who use oral contraceptives should be reminded to use a back-up or alternative form of contraception. Other drugs used to treat MS-related fatigue include methylphenidate, fluoxetine, and 4-aminopyridine.

Neurogenic pain, defined as pain along the course of a nerve, occurs in an estimated 80% of patients. Neurogenic pain typically starts out with numbness and tingling, particularly in the extremities, but can progress to an extreme burning type of pain. Ironically enough, neurogenic pain is a good prognostic indicator for MS. Traditional pain medications (e.g., hydrocodone, morphine, and codeine) are not usually effective in treating neurogenic pain. Gabapentin or pregabalin is considered the first-line drug for neurogenic pain. Other products commonly used to treat neurogenic pain include carbamazepine, duloxetine, amitriptyline, oxcarbazepine, and nortriptyline. Patients should be reminded that these products do cause sedation, but that the sedation decreases with time.

Tremors, which affect the legs more often than the arms, occur in an estimated 75% of patients with MS. Unfortunately, tremors can be extremely disabling but generally respond well to drugs. Drugs used to treat tremors include clonazepam, propranolol, gabapentin, and primidone. In addition, some patients may benefit from adaptive equipment and gait training provided by occupational and physical therapists.

Depression is common in chronic diseases, including MS. Up to 50% of all patients with MS suffer from depression. Although the exact cause of MS-related depression is not fully understood, researchers have hypothesized that it could be a psychological reaction to a chronic illness, part of the grieving process, an adverse effect from drugs used to treat MS (e.g., interferon-βs), and/or related to the neuropathology of MS. Treatments of MS-related depression include both psychotherapy and pharmacotherapy. Multiple sclerosis-related depression typically responds well to antidepressant drugs (e.g., selective serotonin reuptake inhibitors, selective serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants). In recognizing that concurrent MS symptoms can cause depression, tricyclic antidepressants or the selective serotonin/norepinephrine reuptake inhibitors should be considered for patients who also suffer from pain and/or insomnia.

Sexual dysfunction, which occurs in 75% of all patients with MS, can affect both men and women. Male sexual dysfunction commonly manifests as erectile dysfunction, ejaculatory disorders, and difficulty in achieving orgasm, whereas women most often experience abnormal sensations, decreased lubrication, difficulty achieving an orgasm, and anxiety about incontinence. In general, MS-related sexual dysfunction can be caused by a variety of factors, including depression, fatigue, neurological impairment, pain, and drugs (e.g., alcohol, baclofen, β-blockers, selective serotonin reuptake inhibitors, and tricyclic antidepressants). Ironically, many drugs used to treat symptomatic problems can cause sexual dysfunction.

Male sexual dysfunction is much easier to treat than female sexual dysfunction due to the availability of the phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil). In clinical trials, sildenafil was no more effective than placebo in treating female sexual dysfunction. Because lack of lubrication can cause some female sexual problems, lubricants can be helpful to some women.

Special Populations

Pediatric MS

The estimated prevalence of childhood-onset MS ranges from 0.3% to 17%, although experts in the field estimate that the prevalence can be narrowed to 2%–5% of all cases. When MS is diagnosed in children, it most commonly occurs between the ages of 10 and 18. Disease onset before age 10 is considered exceptional, occurring in only 0.2%–0.7% of patients.

None of the ABCR drugs are approved for use in children. In fact, only limited data are available regarding the use of these products in pediatric patients. Although the ABCR drugs are not approved for use in children, most clinicians support their use because data (mainly in adults) clearly show that early initiation significantly slows the progression of the disease. When initiating therapy with one of the ABCR drugs in children, the dosing is perhaps the most challenging dilemma because only a few studies are available to guide practice. For patients between ages 7 and 18, it is generally suggested to begin therapy at 25%–50% of the recommended adult dose and gradually increase to the full dose. For children younger than age 7, it is usually advised to begin therapy at 25% of the recommended adult dose and then increase to 50% of the adult dose. Doses should be reassessed and increased as children age and mature.

Pregnancy and MS

The decision to become pregnant and have children can be a difficult one, especially for women who have MS. The degree of physical disability present is an obvious factor that needs to be examined when patients are considering pregnancy. Because no two patients with MS are alike, patients wanting to become pregnant should consult with both their MS physician and obstetrician. For the most part, pregnancy does not make the disease process worse. In fact, pregnancy is sometimes considered a “honeymoon” period for patients with MS because women typically have fewer MS relapses while pregnant. Sometimes MS symptoms will even abate during pregnancy.

The decision whether to use the ABCR drugs in women who are attempting to become pregnant, who are pregnant, or who are breastfeeding is a complicated one. Patients should consult both their MS physician and obstetrician when making these decisions. Typically, patients are advised to discontinue their ABCR drugs before attempting to become pregnant and to resume them after delivery. Likewise, lactating women are generally advised to not use their ABCR drugs while nursing. Of note, no data exist in humans linking ABCR drugs to fetal or infant problems; however, data exist in animals linking high-dose interferon-β products to spontaneous abortions. The interferon-β products are in the FDA Pregnancy Category C. Glatiramer acetate, Pregnancy Category B, is considered the safest ABCR drug in pregnant and/or lactating women. Although pregnancy may be considered a "honeymoon" period for patients with MS, the postpartum period is usually the complete opposite. An estimated 70% of patients relapse during the postpartum period. Most patients experience these relapses only during the first 3 months after delivery while other patients experience relapses for up to 9 months. Data suggest that the use of intravenous immunoglobulin in the immediate postpartum period (within 3 days of delivery) and repeated monthly for 6 months decreases relapses during the postpartum period.

Patient Counseling Challenges and Opportunities

About 50% of patients with MS suffer from cognitive dysfunction as a result of their illness. Just as the physical symptoms of MS can vary considerably from person to person, cognitive changes can vary as well. Memory impairment ranks as the most commonly experienced cognitive problem. Cognitive rehabilitation is generally the preferred treatment for MS-related cognitive dysfunction. Numerous studies have recently examined pharmacological treatments for MS-related cognitive dysfunction; thus far, donepezil hydrochloride appears to be the most effective pharmacological treatment for MS-related cognitive dysfunction. Because cognitive impairments can negatively affect patient compliance, pharmacists should make all attempts to simplify drug regimens to make things easier for patients (e.g., suggest drugs that can be given once per day rather than multiple times per day, recommend monotherapy options instead of multidrug ones).

Convincing patients who have MS of the importance of adhering to prescribed drug regimens can be a daunting task. Although the ABCR drugs have revolutionized the treatment of MS, these products must be administered parenterally. Drug treatment regimens can be extremely difficult and intimidating for many patients. Table 1-6 lists practical tips for decreasing the pain and discomfort associated with ABCR drugs. In addition, the various pharmaceutical manufacturers have free programs available to assist patients with administering the ABCR drugs. Table 1-7 lists the various programs and their toll-free access numbers. Patients should be regularly reminded about the importance of these parental medications, with adherence to therapy being emphasized.

With regard to treating symptomatic problems, pharmacists should make every attempt to simplify drug regimens. When possible, drugs should be prescribed that have dual purposes (e.g., using fluoxetine to treat both fatigue and depression) rather than prescribing a drug to treat each condition. Such drug regimens are easier for patients to follow and are associated with fewer adverse effects.

Table 1-6. Counseling Tips for Administering the ABCR Drugs

Use the auto-injector provided by the manufacturer (when available)
Make sure the drug is at room or body temperature before injecting
Ice the injection site before and after injecting the drug
Never shake the medication vials
Rotate injection sites
Never inject the drug into an area that has a lump or knot

ABCR = Avonex, Betaseron, Copaxone, and Rebif.

Table 1-7. Contact Information for the ABCR Drugs

Product	Program Name	Access Number
Avonex	Avonex Services	800-456-2255
Betaseron	MS Pathways	800-788-1467
Rebif	MS LifeLines	877-447-3243
Glatiramer acetate	Shared Solution	800-887-8100

ABCR = Avonex, Betaseron, Copaxone, and Rebif.

Conclusion

Treatment options for MS have dramatically changed since 1993, the year that the first DMD was approved for use in the United States. Although the DMDs are not a cure for MS, they can alter the disease course by decreasing the number and severity of relapses, by slowing the progression, and by reducing the accumulation of new lesions. Despite therapy with the DMDs, many patients continue to experience a variety of symptomatic problems that can negatively affect their lives. Clinical trials are currently under way that examine the safety and efficacy of other DMDs in the hopes of identifying new therapies that can significantly improve the quality of life of patients with MS.

Annotated Bibliography

1. Disease Management Consensus Statement. Expert Opinion Paper from the Medical Advisory Board of the National Multiple Sclerosis Society 2005. Available at *www.nationalmssociety.org/docs/HOM/consensus_summary.pdf*. Accessed May 15, 2007.

   The National Multiple Sclerosis Society Consensus Statements are educational and advocacy tools designed to promote increased access to approved DMDs through legislative, judicial, and regulatory means. The National Multiple Sclerosis Consensus Statements are ever evolving as new DMDs are approved, and new Consensus Statements are created and approved by the National MS Society Medical Advisory Board's Executive Committee. The most recent Consensus Statement, the 2005 Consensus Statement,

addresses the use of interferon-β productions (Avonex, Betaseron, glatiramer acetate, and Rebif), glatiramer acetate, and mitoxantrone. An updated Consensus Statement, examining the role of natalizumab, is expected to be released in the near future.

The goal of the 2005 Consensus Statement is to ensure that all patients who are appropriate candidates for approved DMDs have access to them as early in the disease process as possible. The 2005 Consensus Statement is comprehensive in nature (see Table 1-3 for a complete list of recommendations). One limitation to the 2005 Consensus Statement is that it only minimally addresses the topic of neutralizing antibodies, noting "that sufficient data do not yet exist to base clinical decisions exclusively on the results of neutralizing antibodies."

All clinicians who take care of patients with MS are encouraged to study and apply the principles of the 2005 Consensus Statement (and future Consensus Statements) to their practices, especially because the Multiple Sclerosis Consensus Statements are the only such available consensus or guideline available.

2. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al; Independent Comparison of Interferon (INCOMIN) Trial Study Group. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359:1453–60.

   The landmark Independent Comparison of Interferon (INCOMIN) study, which was funded by the Italian government and the Italian MS Society, compared the low-dose interferon-β product, Avonex, with the high-dose interferon-β product, Betaseron. Patients in this 2-year study received either Avonex 30 mcg intramuscularly once weekly or Betaseron 0.25 mg subcutaneously every other day. The authors found that the patients who received Betaseron were more likely to be relapse free (51% vs. 36%; p=0.035), have less Expanded Disability Status Score worsening (14% vs. 30%; p=0.04), and have decreased T2 lesion activity based on brain MRI (26% vs. 55%; p=0.0003) than the patients who received Avonex. According to the study authors, the results suggest that dose frequency and concentration, possibly acting together, can affect disease activity and progression in patients with relapsing-remitting MS.

   The results of this study, in conjunction with the results from EVIDENCE (discussed below), have clarified the differences in efficacy between the low-dose and high-dose interferon-β products. Consequently, all clinicians involved with the treatment of MS should understand and be able to apply these study results to their clinical practices.

3. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Conner P, et al; EVIDENCE Study Group. EVidence of Interferon Dose-response: European North American Compartative Efficacy; University of British Columbia MS/MRI Research Group. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002;59:1496–506.

   The landmark Evidence for Interferon Dose-respose: European-North American Comparative Efficacy (EVIDENCE) study examined the two interferon-β1a products, Avonex and Rebif. A total of 677 patients were enrolled in this 48-week study. At both 24 weeks and 48 weeks, patients who received the high-dose interferon-β product, Rebif, were more likely to be relapse free, have decreased MRI activity, and have fewer active MRI scans than the patients who received the low-dose interferon-β product, Avonex. Of note, the results of the EVIDENCE trial provided the basis for approval of Rebif for use in the United States. Before this, Rebif had only been available in Europe.

   Clinicians interested in better understanding the differences between the low-dose and high-dose interferon-β products are encouraged to examine the cumulative results of this study along with the INCOMIN study (discussed above). In combination, these two studies clearly demonstrate that the high-dose interferon-β products (Betaseron and Rebif) are more efficacious than the low-dose product (Avonex).

4. Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfield R, Sandberg-Wollheim M, et al; European IFN beta-1a (Avonex) Dose-Comparison Study Investigators. A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. Neurology 2002;59:1507–17.

   This double-blinded, parallel-group, dose-comparison study examined whether the approved strength of Avonex (30 mcg intramuscularly once weekly) was more effective than the double-dose strength of Avonex (60 mcg intramuscularly once weekly) in reducing disability progression in relapsing-remitting MS. A total of 802 patients from 38 European centers were randomized to receive either standard-dose or double-dose Avonex. The primary end point of the study was increasing Expanded Disability Status Scores; secondary end points included MRI findings, safety, immunogenicity, and subgroup analyses of disability progression. There was no difference between standard-dose Avonex and double-dosed Avonex in the rate of accumulation of physical disability in patients with relapsing-remitting MS.

   Because both EVIDENCE and INCOMIN found that high-dose interferon-β products (Betaseron and Rebif) were more effective than the low-dose interferon-β product (Avonex), many questioned whether the dose or the dosing interval was the more important factor. Because double-dosed Avonex did not prove to be more efficacious than standard-dose Avonex, it appears that the dosing interval may be more important than the dosing amount. This finding is consistent with data demonstrating that a sustained level of interferon-β (with a greater area under the curve drug concentration) is better than brief periods of interferon-β exposure.

5. Johnson KP, Ford CC, Lisak RP, Wolinsky JS. Neurologic consequence of delaying glatiramer acetate therapy for multiple sclerosis: 8-year data. Acta Neurol Scand 2005;111:42–7.

   This study, which assessed the long-term effectiveness of glatiramer acetate in the treatment of relapsing-remitting MS, represents the longest published duration of therapy for any DMD. This open-label extension of an earlier randomized, placebo-controlled, double-blind study lasted about 30 months. Patients previously randomized to glatiramer acetate continued receiving active drug, and those originally randomized to placebo were switched to glatiramer acetate. Of the 251 patients originally randomized to glatiramer acetate, 142 (56.6%) remained in the study after 8 years. With therapy, annual relapse rate for both groups declined to about 1 relapse every 5 years. Of the two groups, a significantly larger proportion of patients who had previously been randomized to receive glatiramer acetate, had stable or improved Expanded Disability Status Scores compared with patients who had only received active drug for about 30 months (65.3% vs. 50.4%, respectively; p=0.0263).

   This article not only reiterates the importance of the early initiation of glatiramer acetate, but also the significance of the

1998, 2002, and 2005 Consensus Statements. Clinicians desiring to better understand the basis of these Consensus Statements are encouraged to evaluate the trial results. Clinicians should also be encouraged to share the trial results with patients, especially noncompliant patients and patients questioning the efficacy of glatiramer acetate.

6. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924–33.

Natalizumab distribution was suddenly halted in February 2005 after three patients in the drug's clinical trials developed progressive multifocal leukoencephalopathy. Consequently, an evaluation was conducted to determine whether progressive multifocal leukoencephalopathy had developed in any other patients treated with natalizumab. Of the 3417 patients with MS, Crohn's disease, or rheumatoid arthritis who had received natalizumab while participating in clinical trials, 3116 (91%) who had been exposed to a mean of 17.9 monthly doses were evaluated for progressive multifocal leukoencephalopathy. Of these patients, 44 were referred to the expert panel because of clinical findings of possible progressive multifocal leukoencephalopathy, abnormalities on MRI, or a high plasma viral load of JC virus. PML was ruled out in 43 of the 44 patients. The authors concluded that the risk of PML is roughly 1 in 1000 patients treated with natalizumab for a mean of 17.9 months. However, the authors noted that the risk associated with longer treatment is not known.

This study is considered significant because its findings, in part, led to natalizumab being re-released in the United States, some 15 months after its distribution was abruptly halted. Clinicians who prescribe or monitor patients receiving natalizumab are encouraged to read this article so that they can properly educate their patients about risks of progressive multifocal leukoencephalopathy.

7. Fox FJ, Bethoux F, Goldman MD, Cohen JA. Multiple sclerosis: Advances in understanding, diagnosing, and treating the underlying disease. Cleve Clin J Med 2006;73:91–102.

This concise review article, which evaluated advances in the pathophysiology, diagnosis, imaging, and treatment of MS, is well written and easy to read. Much emphasis was placed on the various treatments of MS, including treatment of relapses, symptom management, and long-term prevention of tissue injury. The authors explored in detail the clinical monitoring of MS, with an emphasis on the MS Functional Composite scoring system and how MRI scans can aid in the diagnosis and management of MS. This article is a benefit to experienced MS clinicians as well as those unfamiliar with the disease state.

8. Goldman MD, Cohen JA, Fox RJ, Bethoux FA. Multiple sclerosis: Treating symptoms, and other general medical issues. Cleve Clin J Med 2006;73:177–86.

This review article discusses the incidence and treatment of various common symptomatic problems associated with MS (including spasticity, bladder dysfunction, bowel dysfunction, fatigue, pain syndromes, ataxia, tremors, vertigo, cognitive impairment, and mood disorders). Emphasis is placed on exploring both pharmacological and nonpharmacological treatments. The authors remind clinicians that they can positively impact their patients' overall health, quality of life, and daily functioning by participating in open dialogue, providing patient specific treatment plans, and anticipating patients' general medical needs. Many times in the article, the authors explain the importance of seeking referrals to treat complex, specific issues. The authors end by discussing general medical issues common to patients with MS, including pregnancy and fertility, vaccinations, and osteoporosis.

Patients with MS commonly have questions regarding the safety of vaccines and the effect vaccines could have on their disease. Table 4 of this article addressed all of these issues and listed the various recommendations from the Centers for Disease Control and Prevention. The vaccinations discussed in the table included age-appropriate vaccinations (e.g., tetanus or pneumonia vaccine), live-attenuated vaccinations, influenza vaccinations, and smallpox vaccinations.

9. Henze T. Managing specific symptoms in people with multiple sclerosis. Int MS J 2005;12:60–8.

This well-written and easy-to-read review article examines the management of many of the disabling symptoms of MS, including MS-related spasticity, fatigue, pain, and neurogenic bladder dysfunction, that often impair quality of life and social participation in people with MS. The authors note that the goal of therapy should be the elimination and reduction of symptoms. This article also reviews many recommendations for treating MS-related spasticity, fatigue, pain, and neurogenic bladder dysfunction from the MS Consensus Group of the German MS Society. Those clinicians interested in how to treat the various symptomatic problems associated with MS are encouraged to read this article.

10. Chabas D, Green AJ, Waubant E. Pediatric multiple sclerosis. NeuroRx 2006;(3):264–75.

This recently published review article examines the topic of pediatric MS, noting that childhood MS represents up to 10% of all MS cases. The authors explored the challenges of making a diagnosis of MS in pediatric patients, explaining that children often have different presenting symptoms (e.g., seizures, and brainstem and cerebellar symptoms) than adults (who most frequently experience acute episodes of optic neuritis). The authors also note that MS appears to affect adolescent girls to greater extent than adolescent boys (with a ratio approaching 3:1). The authors examine the limited available pediatric data regarding the various DMDs and stress the need for controlled, clinical trials in pediatric patients, but acknowledge that it is unlikely that such trials will ever take place. Finally, it is noted that the Multiple Sclerosis Society has initiated support for six regional pediatric MS centers across the United States, with the hope of better delineating disease course, underlying biological and epidemiological factors, and differences between pediatric-onset and adult-onset MS. Those clinicians interested in the field of pediatric MS are encouraged to study this concise review article.