INTRODUCTION

Background

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). MS lesions, characterized by perivascular infiltration of monocytes and lymphocytes, appear as indurated areas in pathologic specimens; hence, the term "sclerosis in plaques."

MS is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability. For every 8-10 new lesions detected on magnetic resonance imaging (MRI), only one clinical manifestation typically can be demonstrated. Patients with relapsing remitting MS have an average of 5-10 new lesions per year and one or two clinical exacerbations.

With the advent of MRI, the ability to confirm the diagnosis of MS has improved dramatically. MRI characteristically shows lesions of high T2 signal intensity of variable location in the white matter of the brain, brain stem, optic nerves, or spinal cord. In typical cases, the lesions tend to occur in periventricular areas and may occur in the corpus callosum. Newer MRI techniques (eg, magnetization transfer, fluid attenuated inversion recovery [FLAIR], MR spectroscopy [MRS]) promise to yield important information regarding MS heterogeneity, prognosis, and treatment effects.

Despite intensive efforts at finding the source of the disease, no etiologic agent for MS has been identified. The disease presumably can be exacerbated by hormonal changes during the postpartum period. Some argue that MS could be a heterogeneous disorder triggered by several different environmental agents. In fact, only 1 of every 4 MS attacks is associated with an intercurrent infection.

The disease can present in different forms, such as primary progressive, relapsing remitting, relapsing progressive, and secondary progressive phenotypes. Genetic susceptibility factors may play a role, as the disease is more common in Caucasian populations living in northern latitudes. This susceptibility may be part of a complex and heterogeneous group of genetic and epigenetic factors that have an impact, along with environmental factors, on the initiation and maintenance of disease. In addition, migration to high-risk areas before age 15 years is known to increase the risk of developing MS, lending further support to the environmental factor hypothesis.

Pathophysiology

MS is characterized by perivenular infiltration of lymphocytes and macrophages in the parenchyma of the brain, brain stem, optic nerves, and spinal cord. Expression of adhesion molecules on the surface seems to underlie the ability of these inflammatory cells to penetrate the blood-brain barrier. The
elevated immunoglobulin G (IgG) level in the cerebrospinal fluid (CSF), which can be demonstrated by an oligoclonal band pattern on electrophoresis, suggests an important humoral (ie, B cell activation) component to MS. In fact, variable degrees of antibody-producing plasma cell infiltration have been demonstrated in MS lesions (depicted in Image 1).

Molecular studies of the white matter plaque tissue have shown that interleukin (IL)–12, a potent proinflammatory substance, is expressed at high levels in early-formed lesions. A molecule required to stimulate lymphocytes to release proinflammatory cytokines, B7-1, also is expressed at high levels in early MS plaques. Evidence exists of higher frequencies of activated myelin-reactive T-cell clones in the circulation of patients with relapsing remitting MS and higher IL-12 production in immune cells of patients with progressive MS, when compared with healthy controls.

The favorable clinical responses to the disease-modifying immunomodulatory agents (ie, interferon beta-1a and beta-1b, glatiramer acetate) suggest that these medications modify disease progression on the basis of their ability to counteract the proinflammatory phenotype of immune cells. Other disease-modifying treatments for MS include mitoxantrone (a DNA intercalator) and natalizumab (a monoclonal antibody against the adhesion molecule VLA-4).

MS is a complex and heterogeneous disease, and our understanding of the disease initiation mechanism and its wide clinical variability is limited.

**Frequency**

**United States**

MS has a prevalence of nearly 350,000 cases in the United States alone and more than 2.5 million worldwide. Every year, approximately 10,000 persons are newly diagnosed with MS.

**International**

More than 1 million worldwide are affected.

**Mortality/Morbidity**

MS causes considerable disability in the working age group. People with MS usually die of complications rather than of MS itself, including recurrent infections (especially in bedridden patients). Patients with MS are thought to have an average life expectancy 7 years shorter than that of the general population, but this issue remains controversial.

**Race**

MS presents more often in populations of northern European ancestry. Whether disease severity also may be accounted for by racial differences is controversial. The concordance rate for MS is 20-40% among monozygotic twins, suggesting the presence of predisposing genetic factors of non-Mendelian inheritance.

**Sex**

MS affects females more than males (1.6-2:1), but the basis for this difference is unknown. This ratio is even higher (3:1) among patients in whom onset of MS is before age 15 years or after age 50 years, suggesting a hormonal component to the disease process. Males have a greater tendency to develop primary progressive MS, while females tend to experience more relapses.
Age

MS most commonly afflicts people between the ages of 18 and 50 years, but any age group can be affected.

CLINICAL HISTORY

Attacks or exacerbations of MS are characterized by new symptoms that reflect CNS involvement. These symptoms typically are separated in time (eg, by months or years) and in anatomical location (eg, weakness of one or more limbs, optic neuritis, sensory symptoms). Recognizing that physical and cognitive disability progression in MS may occur in the absence of clinical exacerbations is important.

- Patients who improve after acute attacks have relapsing remitting MS (RRMS). However, during the natural course of RRMS, approximately 75-85% of patients enter a stage referred to as secondary progressive MS (SPMS).
- Patients with primary progressive MS (PPMS) tend to accumulate disability without interruption (ie, without remissions) from the time of disease onset. Some of these patients first present with weakness of only one limb, which gradually progresses to involve other limbs and may culminate in total paralysis. Patients with PPMS typically respond poorly to the current therapeutic options for MS, accumulate disability faster than other patients, and tend to have more weakness of the legs as well as incontinence (a reflection of greater spinal cord involvement).
- Patients who have RRMS but accumulate disability between and during attacks can be defined as having relapsing progressive disease (RPMS).
- Although most patients have a wide range of symptoms from lesions in different areas of the brain and spinal cord, others may present with predominantly visual, cognitive, or cerebellar symptoms.
- Patients with MS are now thought to reach a clinical threshold (itself a reflection of immune system dysfunction and axonal involvement), after which deterioration occurs in a continuous course and ominous MRI signs become more apparent (eg, T1 hypointensities, brain atrophy). These T1 "holes" and signs of brain or spinal cord atrophy are indicative of a neurodegenerative process, indicating that MS is not only an inflammatory disease. The clinical history will reflect these processes, as patients often report short-term memory problems, difficulty executing sequential tasks, or visuospatial disturbances.
- Use of the term "benign MS" should be discouraged, since practically all patients have relentless progression of the disease, even in the absence of clinical attacks. Not uncommonly, detailed examination of a patient with so-called "benign MS" encounters clear evidence of short-term memory difficulties, cognitive dysfunction, or brain atrophy on MRI of the head. In the author's view, the use of the term "benign MS" should be reserved for retrospective assessments of clinical course. The prospective use of the term "benign MS" leads to false expectations of disease outcome by the patients and their relatives, improper counseling, and inappropriate delay of treatment with disease-modifying drugs.
- Patients with MS tend to experience variable degrees of fatigue. This symptom typically is described as either physical exhaustion or mental/cognitive slowing. It must be differentiated from depression (which may, however, coexist), lack of sleep, and exertional exhaustion due to disability. Patients may feel particularly fatigued after taking a hot shower or after strenuous activity in heated environments. Heat exposure also may lead to episodes of optic nerve dysfunction (ie, Uhthoff phenomenon), the mechanisms of which remain poorly understood.
- MS may present in an acute and clinically fulminant form (termed Marburg variant of MS) or may present with concomitant optic nerve involvement and necrotizing myelopathy (ie, neuromyelitis optica [NMO] or Devic disease, considered by some to be an MS variant). However, MS must be
distinguished from other neuroinflammatory disorders, including acute disseminated encephalomyelitis (ADEM), Schilder disease, and Baló concentric sclerosis.

- ADEM is considered an isolated postinfectious or postvaccinial autoimmune attack on the CNS that leads to diffuse demyelination. It is often devastating, and occasionally has a fulminant hemorrhagic component (in which case it is termed acute hemorrhagic encephalomyelitis or leukoencephalitis of Weston Hurst).
- Schilder disease is characterized in children and young adolescents by massive demyelination, presenting often as asymmetrical foci (often the size of an entire lobe) in the white matter by MRI, and presenting with a malignant course (ie, deterioration over months or a few years with cortical blindness, hemiplegia, or paraplegia). Some patients, however, may respond to steroids and immunosuppressive therapy.
- Baló concentric sclerosis is considered by some authors to be a variant of Schilder disease, with MRI lesions showing a characteristic alternating pattern of spared and damaged white matter that suggests progression of the disease process from the ventricles outward. Baló disease often is associated with a more inflammatory CSF and a more fulminant progression than typical MS.

- MS may present in various forms. Some patients have a predominance of cognitive changes, while others present with prominent ataxia, hemiparesis or paraparesis, depression, or visual symptoms. Bipolar disorder and frank dementia may appear late in the disease course, but sometimes are found at the time of initial diagnosis. Symptoms can be exacerbated by intercurrent illness, including viral or bacterial upper respiratory or urinary tract infections. Trauma has no impact on disease exacerbation. The impact of emotional stress on exacerbations is probably minimal and remains controversial.

- Optic neuritis presents clinically as orbital pain, at rest or during eye movement, and loss of vision. Patients may complain of "patchy loss of vision," and upon examination, a cecocentral scotoma and an afferent pupillary defect may be found. Patients may experience color desaturation even with normal visual acuity, usually manifested as the perception of red color as different shades of orange or gray.

- Patients with MS may present with facial palsies or trigeminal neuralgia. In fact, the presence of bilateral facial weakness or trigeminal neuralgia strongly suggests the diagnosis of MS. Facial myokymia also may be a presenting symptom. Nystagmus (direction-changing) and internuclear ophthalmoplegia signs are other manifestations.

- Painful limb syndromes are important to recognize. Commonly, patients complain of numbness or tingling in one or more limbs, variable weakness, or sensory level-related symptoms. Some have difficulty describing weakness or numbness, as these symptoms are obscured by incapacitating fatigue.

- Episodes of central (as opposed to peripheral) vertigo are not uncommon. The nystagmus accompanying central vertigo has a rapid onset, does not fatigue easily, and changes with direction of gaze. CNS vertigo usually is accompanied by other complaints that can be directly attributed to brainstem or cerebellar pathway involvement (eg, diplopia, dysarthria).

- An often overlooked manifestation of MS is the pseudobulbar affect, whereby patients have difficulty controlling their emotions (laughing, crying) and are perceived to act inappropriately by coworkers or friends.

  - Behavioral/cognitive symptoms also may include social disinhibition, dementia, or depression.
  - A greater tendency for attempting and committing suicide in MS is not related exclusively to a reactive depression, since this tendency is higher than that of patients with other devastating neurological disorders such as chronic inflammatory demyelinating polyradiculopathy (CIDP).
• The neurologist should be aware that patients with conversion reactions and inappropriate affect, such as "la belle indifference," may on occasion have an underlying organic illness such as MS.
• Urinary retention and incontinence are common. Bowel habit changes may occur, but bowel incontinence is less frequent.
• Sexual dysfunction affects the great majority of patients with MS and includes symptoms such as lack of desire, erectile dysfunction, impaired sexual responsiveness, premature ejaculation, impaired genital sensation, or inability to physically interact with the partner due to painful leg adductor muscle spasms.

**Physical**

The Kurtzke Expanded Disability Status Scale (EDSS) is used as a measure of disease progression by assigning a severity score (0-10) to the patient’s clinical status. Although the scale does not correspond linearly to common progression points for many patients, its widespread use and ease of implementation allow its utilization as a standardization measure for clinical trials.¹⁴

- 0 - Normal neurologic examination (all grade 0 in functional systems [FS]; cerebral grade 1 acceptable)
- 1 - No disability, minimal signs in one FS (ie, one grade 1 excluding cerebral grade 1)
- 1.5 - No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1)
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1)
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three or four FS grade 2, others 0 or 1)
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3 and one or two FS grade 2) or two FS grade 3, others 0 or 1, or five FS grade 2, others 0 or 1
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters (0.3 miles)
- 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for some 300 meters (975 ft)
- 5.0 - Ambulatory without aid or rest for about 200 meters (650 feet); disability severe enough to impair full daily activities (eg, to work a full day without special provisions); usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0
- 5.5 - Ambulatory without aid or rest for about 100 meters (325 ft); disability severe enough to impair full daily activities; usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4.0
- 6.0 - Intermittent or constant unilateral assistance (cane, crutch, brace) required to walk about 100 meters (325 ft) with or without resting; usual FS equivalents are combinations with more than two FS grade 3+
- 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters (65 ft); usual FS equivalents are combinations with more than two FS grade 3+
- 7.0 - Unable to walk beyond about 5 meters (16 ft) even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair a full day and transfers alone; up and about in wheelchair some 12 hours a day; usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone
• 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfers, wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; usual FS equivalents are combinations with more than one FS grade 4+
• 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair; but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms; usual FS equivalents are combinations, generally grade 4+ in several systems
• 8.5 - Essentially restricted to bed for much of the day; has some effective use of arm(s); retains some self-care functions; usual FS equivalents are combinations, generally grade 4+ in several systems
• 9.0 - Helpless bed patient; can communicate and eat; usual FS equivalents are combinations, mostly grade 4
• 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; usual FS equivalents are combinations, almost all grade 4+
• 10 - Death due to MS

Causes

The cause of MS is unknown.

• An environmental agent (eg, virus, bacteria, chemicals) has been hypothesized to act in concert with a specific genetic predisposition (ie, a set of genes or polymorphisms) to result in immune dysfunction. For instance, different variants of genes normally found in the general population, commonly referred to as polymorphisms, may lead to different gradations of cellular expression of those genes and, thus, of the proteins that they encode. Therefore, an individual with a polymorphism within the promoter region of a gene that is involved in immune reactivity may generate an exaggerated response (eg, elevated gene expression of a proinflammatory gene) to a given antigen, leading to uncontrolled immune cell proliferation and autoimmunity.
• Research on cytokine gene polymorphisms in MS is just beginning but promises to yield important clues about the pathogenesis of this disease. Genes encoding antigen presentation molecules such as the human leukocyte (HLA) antigens are highly polymorphic and have been shown to play a role in mediating MS susceptibility. For instance, MS has been associated, although not exclusively, with the HLA-DR2 allele, and linkage of MS to genetic regions where the HLA genes lie also suggests a component of genetic predisposition.
• Other molecules involved in activation of T and B cells have been implicated in MS. For instance, the co-stimulatory molecule B7-1, necessary for activation of T cells as a second signal to antigen presentation, has been found to be elevated in early MS lesions, suggesting a triggering role for inflammation within the CNS. Other factors elevated in MS brain tissues include the proinflammatory interferon gamma and the prodemyelinative tumor necrosis factor alpha molecule. In addition, interactions between molecules on the surface of B and T cells, such as CD40 and CD40 ligand, may mediate elevated levels of IL-12 (a proinflammatory cytokine) in the circulation of patients with MS.
• The molecular mimicry hypothesis refers to the possibility that peripheral blood T cells may become activated to attack a foreign antigen, then erroneously direct their attack toward brain proteins that share similar protein epitopes.
• Others support the hypothesis that a virus may infect the immune system, activating self-reactive T cells (myelin reactive) that would otherwise remain quiescent.
DIFFERENTIALS

Acute Disseminated Encephalomyelitis
Brainstem Gliomas
Central Pontine Myelinolysis
Essential Tremor
Hemifacial Spasm
HIV-1 Associated CNS Complications (Overview)
HIV-1 Associated Opportunistic Infections: PML
HIV-1 Associated Opportunistic Neoplasms: CNS Lymphoma
HIV-1 Associated Vacuolar Myelopathy
HIV-1 Encephalopathy and AIDS Dementia Complex
Inherited Metabolic Disorders
Lyme Disease
Lysosomal Storage Disease
Metabolic Disease & Stroke: MELAS
Myokymia
Paraneoplastic Encephalomyelitis
Persistent Idiopathic Facial Pain
Primary Lateral Sclerosis
Spinal Cord Infarction
Sudden Visual Loss

Other Problems to be Considered

Neuromyelitis optica (Devic disease)
Diffuse cerebral sclerosis of Schilder (encephalitis periaxialis diffusa)
Concentric sclerosis of Balo

WORKUP

Lab Studies

- Cerebrospinal fluid examination
  - Oligoclonal bands are distinct electrophoretic patterns that reflect substantial elevation of IgG produced by a restricted set of plasma cells and are demonstrated in CSF samples of approximately 85% of patients with MS.
  - Glucose level is usually normal. Protein level can be normal or slightly elevated. WBC count can be slightly to moderately elevated (6-40 x 10^9/L) but is usually <5 (predominantly mononuclear cells).
  - IgG index usually is elevated. This index is derived from the following formula: IgG Index = [IgG_{CSF}/albumin_{CSF}]/[IgG_{serum}/albumin_{serum}]
    Although the sensitivity of measurements may vary among various laboratories, a typically normal CSF IgG is <4.7 mg/dL (less than 12% of serum protein), and the normal IgG index is <0.77. Most patients with MS have a clearly elevated IgG index (>1.7).
Myelin basic protein (MBP) is a major component of myelin and may be elevated in the CSF of patients with MS. However, its clinical utility as a marker of disease activity or progression is limited (not recommended).

- **Blood tests**
  - Patients with MS and atypical features initially should be tested for B-12 and folate levels or antinuclear antibody (ANA) titers. For instance, rapid cognitive deterioration or evidence of subacute combined degeneration of the spinal cord by clinical examination should prompt testing for folate and B-12 levels.
  - Other patients with atypical features suggesting disorders other than MS must be recognized. Investigation for the antiphospholipid antibody syndrome must be undertaken in patients with evidence of blood dyscrasia and in women with unexplained miscarriages or history of deep venous thrombosis. This syndrome is typically assessed with blood tests for the following: anticardiolipin, anti-beta2 glycoprotein I, and antiprothrombin antibodies.
  - An elevated erythrocyte sedimentation rate (ESR) and positive titers of rheumatoid factor (RF) should help identify the presence of a vasculitic disorder that may be mimicking MS.
  - If patients come from an endemic region for Lyme disease or have been exposed to tick bites, the physician should check Lyme titers. Evaluation by a rheumatologist should be sought if positive Lyme or ANA titer, elevated ESR, or evidence of vasculitis is uncovered.

- If clinical suspicion for a peripheral neuropathy arises, electrophysiological studies and blood tests for metabolic or toxic neuropathies should be done.

**Imaging Studies**

- MRI of head or spine, with and without gadolinium, should be performed according to clinical suspicion for lesion localization.
  - Typical MS lesions appear as T2 hyperintensities in the periventricular regions; they have an ovoid appearance with their largest axis oriented perpendicular to the ventricular surface; they typically involve only the white matter, and several arise from the corpus callosum (see Images 2-3). This characteristic configuration has been demonstrated in pathologic specimens and sometimes is referred to as "Dawson fingers" on the basis of neuropathologic work done in 1916 at the University of Edinburgh by James Dawson, who identified the perivascular distribution of inflammatory cells and the resulting fingerlike appearance of affected veins and venules in MS brain tissues.
  - The most common infratentorial locations for plaque formation are the surface of the pons, the cerebellar peduncles, and white matter regions adjacent to the fourth ventricle.
  - Lesions that enhance with gadolinium are thought to reflect active disease, as enhancement may correspond to breakdown of the blood-brain barrier from an ongoing subacute inflammatory process (few days to a few weeks). Usually a combination of enhancing and non-enhancing lesions is seen, reflecting the chronicity of the demyelinating process.
  - In a patient with a first clinical attack who presents with numerous (ie, >10) lesions by MRI, the presence of gadolinium enhancement in most or all the lesions should prompt a differential diagnosis of ADEM versus an aggressive first presentation of MS. A history of recent exposure to a vaccine or viral illness may be helpful in supporting the diagnosis of ADEM. However, note that exceptions occur and some patients with MS present with a fulminant and active demyelinating disease form from the onset.
  - Hypointensity of lesions in T1 images may reflect some degree of axonal damage or more chronic tissue damage resulting in gliosis. The clinician should attempt to correlate lesions with high T2 signal intensity with their corresponding T1 images to assess chronicity.
Although a lesion may appear old (low T1), it may exhibit a ringlike enhancement around the hypointense region after gadolinium, suggesting that even seemingly old lesions may have a component of active inflammation, especially at the advancing edge of lesion formation.

Additionally, a new lesion may present with T1 hypointensity, reflecting marked edema. Lesions range from a few millimeters to more than a centimeter in diameter with occasional large, rounded, tumorlike lesions. The latter are seen as areas of pronounced gliosis and demyelination on pathologic inspection.

The application of modern MRI techniques to detection and characterization of early lesions is changing rapidly. Recent MRI techniques such as FLAIR have increased the ability to detect demyelinating lesions due to MS. A disadvantage of FLAIR remains the less-than-optimal visualization of the posterior fossa. Other recent techniques such as fast FLAIR and fast spin-echo may increase the sensitivity of prediction for diagnostic and prognostic purposes. Magnetization transfer ratio (MTR) abnormalities may precede the appearance of T2-weighted and proton-density high-intensity lesions. Finally, MRS, which can identify neutral fat, helps identify the appearance of myelin breakdown products that result from the active inflammatory response. Neuronal or axonal loss or dysfunction is identified by the detection of reduced levels of N-acetylaspartate (NAA), a marker of neuronal integrity/metabolism, on MRS.

**Other Tests**

- Evoked potential testing (visual, auditory, or somatosensory) is especially helpful in 1) detecting clinically silent lesions, and 2) documenting an organic basis for vague complaints. The most sensitive are the visual evoked potentials (50-80% sensitivity), followed by the somatosensory potentials (50-70% sensitivity).

**Procedures**

- Lumbar puncture (see [Lab Studies](#))

**Histologic Findings**

Histopathologic examination reveals that MS lesions are caused by perivenular infiltration of lymphocytes (most of which are CD4+ T cells) and macrophages (see [Image 4](#)). Some lesions may have more infiltration by B cells. In fact, recent immunostaining reports by Lucchinetti et al show that MS lesions have considerable heterogeneity of microscopic appearance, with some lesions exhibiting oligodendrocyte apoptosis and others marked complement and antibody presence. Luxol fast blue stains (which stain myelin with an intense blue) reveal demyelinated areas as pale and confluent patches, with variable degrees of associated inflammation (see [Image 5](#)). Transected axons may be found in chronic and sometimes in acute MS lesions, as demonstrated by recent studies by Trapp and collaborators; these recent studies have helped refocus neurologists' attention to the issue of axonal loss in MS.

Expression of interferon gamma, IL-12, and B7 molecules is increased, especially in early MS lesions; this reflects the inflammatory nature of plaque formation.
TREATMENT

Medical Care

Patients with MS have multiple needs, and the neurologist should be receptive and cooperative and try to allay fears, facilitate access to rehabilitation and orthotic equipment and home evaluations, and solve transportation issues. Bone densitometry studies are indicated for patients with MS who have received long-term corticosteroid treatment or are at higher osteoporosis risk from menopause or chronic immobility.

- Patients with more advanced forms of the disease who have lost all family support, are separated from their spouses, require constant psychiatric and nursing assistance, and are unable to walk are not rare. These patients create a challenge for the physician who is not trained in handling these demanding (administrative or ancillary) aspects of medical care.

- The physician should not underestimate the impact of fatigue symptoms on the patient's daily activities. Treatment with amantadine (Symmetrel) or modafinil (Provigil) should be attempted if no contraindications exist. Pemoline should be used with caution for the treatment of fatigue because of reports of rare fatal liver damage events in patients taking this medication. The United States Food and Drug Administration (FDA) concluded that the overall risk of liver toxicity from pemoline outweighs the benefits. In May 2005, Abbott chose to stop sales and marketing of their brand of pemoline (Cylert) in the United States. In October 2005, all companies that produced generic versions of pemoline also agreed to stop sales and marketing of pemoline.

- Patients who have progressed beyond EDSS scores of 5.5-6 tend to respond poorly to the current treatments.
  
  - The impact of this disease on quality of life is reflected in the high suicide rate (7.5 times higher than in the general population). As already stated, however, reactive depression by itself does not fully account for this higher suicide incidence. Many believe that the accumulation of lesions in the brain eventually has an impact on mood.
  
  - Thus, preventing disease progression by using available medications is imperative in MS treatment, especially for patients who have been diagnosed early and probably will respond to treatment.

- Prevent relapses or disease progression by using the ABCR immunomodulatory drugs (ie, interferon beta-1a IM [Avonex], interferon beta-1b SC [Betaseron], glatiramer acetate SC [Copaxone], or interferon beta-1a SC [Rebif]). These 4 medications have been approved by the US FDA and are currently used in the United States as first-line therapies for MS. As a rule of thumb, the ABCR medications tend to decrease the rate of MS relapses by approximately one third, with the highest efficacy demonstrated in clinical trials for the high-dose, high-frequency interferons (ie, Betaseron [34%] and Rebif [33%]). Newer compounds approved by the FDA for use in MS include mitoxantrone (Novantrone) and natalizumab (Tysabri).
  
  - Interferon beta-1b (Betaseron) at 8 MIU SC every other day was shown in a 2-year, double-blind, placebo-controlled trial of 372 patients with RRMS to decrease the frequency of relapses from 1.27 per year to 0.84 per year, a 34% reduction in the relapse rate compared with placebo. Five-year follow-up data show that disease progression rate was 35% in the interferon beta-1b group and 46% in the placebo group. A 30% decrease in the yearly exacerbation rate in the treated group over 5 years also was demonstrated. While the placebo group had a median MRI lesion burden of 30.2% over 5 years, no significant increase (3.6%) was detected in the patients treated with interferon beta-1b. Interferon beta-1b is also of benefit in delaying disability in patients with SPMS who are experiencing relapses.
Interferon beta-1a (Avonex) was studied in a double-blind placebo-controlled study in 301 patients with RRMS receiving weekly intramuscular (IM) injections of 6 million units (30 mcg). Over 2 years, the annual exacerbation (ie, relapse) rate was 0.90 in the placebo group and 0.61 in the Avonex-treated group, a 29% reduction. At 2 years, the mean MRI lesion volume was 122.4 in the placebo group and 74.1 in the Avonex-treated group. The mean number of MRI enhancing lesions over 2 years was 1.65 in the placebo group and 0.80 in the Avonex-treated group. By the end of 104 weeks, the proportion of patients progressing was 34.9% in the placebo group and 21.9% in the Avonex group.

Interferon beta-1a (Rebif) was evaluated in a randomized, double-blind, placebo-controlled study in patients with MS for at least a year and EDSS scores ranging from 0 to 5. Patients received SC injections of placebo, Rebif 22 mcg, or Rebif 44 mcg 3 times per week (tiw) for 2 years. Rebif significantly reduced the number of clinical exacerbations (the primary endpoint). Rebif-treated patients had a significantly longer time to sustained disability progression than placebo-treated patients.

Interferon beta-1a was shown by the CHAMPS (for Avonex) and ETOMS (for Rebif) trials to delay the onset of disease (ie, recurrent attacks) if administered to patients after a clinically isolated syndrome (CIS). The BENEFIT trial (ongoing) will examine the efficacy of Betaseron in reducing conversion from CIS to clinically definite MS. Considerable controversy exists regarding whether the delay in onset of new attacks by these drugs ultimately has a long-term impact on neurodegeneration and disability; these issues need to be addressed in future trials.

Controversy has also existed regarding the eventual clinical impact (positive or negative) of raising the dose of these medications to maximally tolerated levels—studies (INCOMIN trial study group) that compared the effects of interferon beta-1b (Betaseron) administered subcutaneously and interferon beta-1a (Avonex) administered intramuscularly suggest that higher and more frequent doses delivered by Betaseron correlate with higher efficacy. The EVIDENCE trial, which compared interferon beta-1a SC (Rebif) to interferon beta-1a IM, also found that higher dosing and more frequent administration lead to more efficacy. Studies of combinations of interferons with drugs such as methotrexate and glatiramer acetate are also underway.

Glatiramer acetate (Copaxone) showed positive effects in a large randomized double-blind trial in 251 patients with RRMS. Patients on Copaxone had a 2-year relapse rate of 1.19, while patients on placebo had a rate of 1.68. The relapse rate reduction was 29% over 2 years for patients on Copaxone. Extension data show that over 140 weeks, 21.6% of patients treated with Copaxone worsened, while 41% of those on placebo worsened. Recent results of an 18-month study examining the impact of Copaxone on MRI outcome show a 35% reduction in the number of new T2 lesions.

Mitoxantrone (Novantrone) was evaluated in 2 multicenter, randomized clinical trials.

Study 1 was conducted in patients with SPMS or RPMS. These patients had experienced a mean deterioration of the EDSS of about 1.6 points over the 18 months prior to study entry. Patients on mitoxantrone had a mean change in the EDSS of -0.13 compared with placebo (0.23), an ambulation index mean change of 0.30 (placebo, 0.77), and a mean number of relapses requiring steroids of 0.40 (placebo, 1.20). The number of patients with new gadolinium-enhancing lesions on mitoxantrone was 0 out of 31, compared with placebo (5 [16%] of 32).

Study 2 lasted 6 months and evaluated mitoxantrone in combination with methylprednisolone in patients with SPMS or worsening RRMS. The average deterioration in EDSS was 2.2 points in the previous 12 months. Of patients who only received methylprednisolone in this study, 31% were without new gadolinium-enhancing lesions versus patients on mitoxantrone plus methylprednisolone (90%
without new gadolinium-enhancing lesions) (primary endpoint of the study). The annualized relapse rate was 3 for methylprednisolone patients and 0.7 for methylprednisolone plus mitoxantrone patients. The percentage of patients without relapses was 33% for the methylprednisolone group and 67% for the methylprednisolone-mitoxantrone combination.

- Two studies assessing the efficacy of natalizumab (Tysabri) have been conducted.
  - Study 1, Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM), was a randomized, placebo-controlled trial in RRMS patients. Patients were randomized to receive natalizumab \((n = 627)\) or placebo \((n = 315)\). The primary endpoints were the rate of clinical relapse at 1 year and the rate of sustained EDSS progression at 2 years. Natalizumab reduced the rate of clinical relapse at 1 year by 68%. The cumulative probability of progression was 17% in the natalizumab patient group versus 29% in the placebo group. Natalizumab also showed MRI efficacy, demonstrating a reduction in the accumulation of new or enlarging T2 lesions by 83% over 2 years and a 92% reduction in number of gadolinium-enhancing lesions in the natalizumab group at 1 and 2 years.
  - Study 2, Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL), evaluated patients on Avonex and placebo \((n = 582)\) vs. Avonex and Natalizumab \((n = 589)\). The primary endpoints were the rate of clinical relapse at 1 year and the cumulative probability of sustained EDSS progression at 2 years. The patient group on Avonex plus natalizumab had a 24% reduction in the relative risk of sustained EDSS progression and a lower annualized relapse rate \((0.34)\) versus Avonex plus placebo \((0.75)\). As shown in study 1, fewer new or enlarging T2 lesions developed in the Avonex plus natalizumab group \((0.9)\) than in the Avonex plus placebo group \((5.4)\).

- Acute exacerbations
  - No highly effective treatment is currently available to counteract MS attacks after their onset. The most widely used treatment is intravenous (IV) methylprednisolone, 1 g IV qd for 3-5 days. This medication may help expedite the timing of recovery but will not affect the actual degree of recovery.
  - High-dose IV steroids may work more effectively than oral steroids for the acute attack, and home IV therapy is recommended if the patient does not require hospitalization. Alternatively, high-dose oral methylprednisolone should be used, when feasible.

- Secondary progressive forms
  - These patients may be treated with Betaseron, especially when the clinical course reflects an early phase of progression (EDSS score <6). Betaseron is also effective for RRMS. The BENEFIT study will be the first trial to address the potential efficacy of a high-dose, high-frequency interferon preparation (Betaseron 8 million units SC eod) in reducing the conversion from CIS to clinically definite MS.
  - Mitoxantrone is approved in North America and Europe for use in patients with MS. Patients on mitoxantrone need to be monitored with echocardiograms prior to and during treatment, as the drug carries a risk of cardiomyopathy. Because of this risk, mitoxantrone is typically reserved for patients with aggressive clinical presentations of MS or in whom immunomodulatory drug therapy has failed.
  - Head-to-head studies are underway to compare the efficacy of mitoxantrone versus cyclophosphamide (Cytoxan) in large numbers of patients. When studied individually, mitoxantrone seems effective for all adults tested. The data on cyclophosphamide, in contrast, indicate that the benefits of this drug may be restricted to male patients younger than 40 years. Controversy exists whether patients with dramatic and rapid progression of disease (regardless of the type and timing of MS) should be treated earlier with immunosuppressive agents to try and arrest the ongoing inflammatory cascade.
Azathioprine and methotrexate also may be used as immunosuppressive treatments for MS, but these drugs should not substitute for ABCR drugs as first-line agents in newly diagnosed RRMS. They are considered less suppressive than mitoxantrone or cyclophosphamide and are being considered increasingly as combination partners for the ABCR drugs.

Surgical Care

Surgical procedures that relate to MS are directed primarily at alleviating symptoms such as dysphagia, significant limb spasticity or contractures, or severe neuropathic pain. Measures include gastrojejunal tube placement, adductor leg muscle tendon release, and rhizotomy, respectively. Intrathecal pumps for delivery of antispasticity medications (eg, baclofen) can be implanted surgically. Penile prostheses are an alternative for patients with erectile dysfunction that does not respond to medical management.

Consultations

Patients with MS may require multiple consultations to rule out other causes for their symptoms. For instance, patients with dysphonia may need an evaluation by an otolaryngologist (ie, ear, nose, and throat specialist) to rule out laryngeal lesions unrelated to MS. In addition, having MS does not exclude the possibility of concomitant peripheral neuropathy or other illnesses that may cause pain.

- Listed below are the most common consultant services involved in referrals from an MS clinic. Surgical consultation may be requested for gastric tube (G-tube) placement for feeding in persons with advanced MS. Urologic consultation might be warranted to help assess and treat incontinence. Neuropsychological evaluation, especially in patients with primary cognitive involvement, is advisable so that a baseline assessment for future reference can be obtained.
  - Otolaryngology
  - Neuropsychology
  - Ophthalmology
  - Physical therapy and rehabilitation
  - Psychiatry
  - Gastroenterology
  - Urology

Diet

No specific dietary restrictions apply to patients with MS; patients are encouraged to eat a balanced diet. Oral intake of calcium and multivitamin supplements is encouraged, as are adequate vitamin D sources. Although more studies are needed, recent observations suggest a role for vitamin D-related pathways in MS susceptibility.

Activity

- Patients are encouraged to exercise regularly. Strenuous exercise and excessive exposure to heat and or physical exhaustion probably should be avoided; however, no studies have addressed this issue comprehensively in patients with MS.
- Patients with MS should avoid exposure to hot showers or saunas, as increased body temperature has been associated with MS exacerbations.
- Sunlight by itself is not considered to be deleterious, but excessive exposure may mimic the effects seen with hot showers or high temperatures.
MEDICATION

In the past 5 years, neuroimmunology has witnessed an unprecedented expansion in treatment options for CNS autoimmunity. Multiple MS drug trials are ongoing throughout the world, with many disappointments but occasional positive results.

Drugs for MS discussed in this article have been evaluated in clinical trials that measure one or several of the following primary endpoints:

- Delay in progression to disability
- Reduction in relapse rate
- Increase in the number of relapse-free patients
- Increase in the time to first relapse
- Decreased MRI lesion burden, atrophy, and "T1 holes," or presence of new lesions

Patients should be educated and warned that these medications are preventive, not curative. Patients need to understand that mild sensory attacks may not warrant acute intervention with corticosteroids. Treatment of acute attacks should be reserved for functionally disabling symptoms and findings.

Therapeutic approaches such as combination therapy, intravenous immunoglobulin (IVIg), hormonal treatment, bone marrow transplantation, and plasmapheresis are not discussed here, as larger trials are needed for definitive recommendations. Combination therapy may be beneficial for some patients, however, and this practice may become commonplace within a few years. Treatments that can be used as combination partners include methotrexate, azathioprine, IVIg, and plasmapheresis. For reference about drug treatment of general neurological symptoms (eg, neuropathic pain, depression, tonic spasms, spasticity, sexual dysfunction), please refer to the appropriate articles in eMedicine.

Briefly, treatments of choice include the following:

- Depression - Fluoxetine (Prozac), sertraline (Zoloft), amitriptyline (Elavil)
- Spasticity - Baclofen, tizanidine, dantrolene, diazepam (Valium), intrathecal baclofen delivered via programmable pump
- Painful tonic spasms - Baclofen, carbamazepine (Tegretol), gabapentin (Neurontin), phenytoin
- Fatigue - Modafinil, amantadine, fluoxetine, methylphenidate (Ritalin), selegiline
- Urinary dysfunction - Propantheline bromide (Pro-Banthine), tolterodine tartrate, oxybutynin ( Ditropan), imipramine (Tofranil); intermittent self-catheterization
- Tremors/ataxia - Clonazepam (Klonopin), primidone (Mysoline), propranolol (Inderal), gabapentin; weighted bracelets
- Erectile dysfunction - Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), alprostadil (Muse), intracorporeal papaverine (not FDA approved), penile prostheses (Note that baclofen, fluoxetine, diazepam, and amitriptyline, listed above for therapy of other symptoms, may contribute to sexual dysfunction [eg, decreased libido, erectile dysfunction, abnormal ejaculation].)

Injection site reactions (ISR) seen with the ABCR drugs can be minimized by applying a topical steroid or cold packs at the intended site a few hours prior to administration of the drug or following the injection. These reactions include mild-to-severe erythema, skin induration or necrosis, and tissue loss or fibrosis, and may be complicated by superimposed bacterial infection.
Flulike symptoms (commonly experienced with Avonex, Betaseron, and Rebif) can be minimized by taking over-the-counter acetaminophen or ibuprofen 3-4 hours prior and 3-4 hours following the injection.

Interferon-related ISR and flulike symptoms drastically decline with time as patients adjust and learn to use preventive techniques.

Acute exacerbations that lead to constant pain or to physical impairment may be treated with IV methylprednisolone. If available, alternative high-dose oral methylprednisolone treatment may circumvent the need for hospitalization.

**Drug Category: Immunomodulators**

These agents reduce clinical attacks or the number of new MS lesions, and they may have an impact on disability progression.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a (Avonex)</td>
<td>Prescribed in USA as Avonex, administered by IM route (Biogen). Avonex is indicated for treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and to decrease the frequency of clinical exacerbations. Patients with MS in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with MS. Safety and efficacy in patients with chronic progressive MS have not been established. Believed to act via ability to counteract cell surface expression of proinflammatory or pro-adhesion molecules on immune cells, among other effects. More studies needed to fully understand mechanisms of action. Differs from interferon beta-1b (Betaseron, see below) only in that it has amino acid sequence identical to that of natural compound and is glycosylated. Presence of glycosylation is claimed to lead to structural stability and presumably to higher biological potency. Interferons act through common receptor that activates Jak/Stat pathway of signal transduction molecules, which, in turn, leads to activation of interferon-responsive genes. Interferon beta may decrease expression of B7-1 (a proinflammatory molecule) on surface of immune cells and increase levels of TGF-beta (anti-inflammatory molecule) in circulation of patients with MS. Interferon beta-1a is the only ABCR drug administered on a weekly schedule. Frequency of development of neutralizing antibodies against interferon is higher with interferon beta-1b than with interferon beta-1a, but clinical significance of neutralizing antibodies still unclear and controversial. May delay progression of disease in patients that...</td>
</tr>
</tbody>
</table>
have only manifested one clinical attack but have MRI
evidence of MS.

**Adult Dose**
30 mcg IM weekly

**Pediatric Dose**
Not established

**Contraindications**
Documented hypersensitivity; liver dysfunction;
severe leukopenia; thrombocytopenia; lactation

**Interactions**
None reported

**Pregnancy**
X - Contraindicated; benefit does not outweigh risk

**Precautions**
Common adverse effect is flu-like reaction following
administration, usually lasting minutes or hours; 88%
of patients no longer experience this effect after
second month of treatment
Flu-like effects can be minimized by taking over-the-
counter acetaminophen or anti-inflammatory drugs
such as aspirin or ibuprofen a few hours prior to and a
few hours after injection; besides flu-like illness,
patients may experience injection-site skin reactions
which may range from mild (slight erythema) to
severe (skin necrosis).
Adverse effects may include hepatotoxicity (liver
enzyme elevation) and myelosuppression
(leukopenia); caution in preexisting seizure disorder;
cases of exacerbation of thyroid dysfunction have
been described—caution when using in patients with
uncontrolled thyroid dysfunction; interferons are
abortifacients; data on human teratogenicity are
limited; extreme caution in patients with severe
depression

**Drug Name**
Interferon beta-1b (Betaseron in US, Betaferon in
Europe)

**Description**
Indicated for treatment of relapsing forms of MS to
reduce the frequency of clinical exacerbations
(Europe indications include treatment of secondary
progressive MS with active disease). Acts via ability to
counteract cell surface expression of proinflammatory
or pro-adhesion molecules on immune cells, among
other effects. More studies needed to fully understand
mechanisms of action. May decrease expression of
B7-1 (proinflammatory molecule) on surface of
immune cells and increase levels of TGF-beta (anti-
inflammatory) in circulation of patients with MS.
Acts through common receptor that activates Jak/Stat
pathway of signal transduction molecules, which, in
turn, leads to activation of interferon-responsive
genes.
Frequency of development of neutralizing antibodies
against interferon is higher with interferon beta-1b
than with interferon beta-1a, but interferon beta-1b
nAbs disappear faster. The clinical significance of
nAbs is still unclear and controversial.
<table>
<thead>
<tr>
<th><strong>Adult Dose</strong></th>
<th>8 million U SC qod (high-dose, high-frequency interferon)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; liver dysfunction; severe leukopenia; thrombocytopenia; lactation</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>X - Contraindicated; benefit does not outweigh risk</td>
</tr>
</tbody>
</table>

**Precautions**

- Has adverse effect profile similar to Avonex (ie, flu-like reaction following administration tends to disappear after 2 mo on drug); flu-like effects can be minimized by taking over-the-counter acetaminophen or anti-inflammatory drugs such as aspirin or ibuprofen a few hours prior to and a few hours after injection; besides flu-like illness, patients may experience injection-site skin reactions.
- Adverse effects may include hepatotoxicity (liver enzyme elevation) and myelosuppression (leukopenia); cases of exacerbation of thyroid dysfunction have been described—caution when using in patients with uncontrolled thyroid dysfunction; interferons are abortifacients; data on human teratogenicity are limited; use with extreme caution in patients with severe depression.

**Drug Name**

Glatiramer acetate (Copaxone)

**Description**

- Mix of amino acids proposed to mimic myelin proteins when presented on surface of antigen-presenting cells. Copaxone is indicated for reduction of the frequency of relapses in patients with RRMS. In theory, lymphocytes reactive against CNS myelin would be diverted to bind to Copaxone in circulation, thus decreasing entry of immune cells across blood-brain barrier. Most mechanisms of action, however, remain unknown, and wider effect on immune system responsiveness may be at play. Has safest side effect profile of ABCRs.

**Adult Dose**

- 20 mg SC qd

**Pediatric Dose**

- Not established

**Contraindications**

- Documented hypersensitivity; pregnancy and lactation

**Interactions**

- None reported

**Pregnancy**

- B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

**Precautions**

- Common adverse effects are sensation of chest tightness or flushing following administration; no evidence of heart arrhythmias, angina, or pleuritic involvement.
- Other adverse effects include palpitations, shortness of breath, hypertonia, sweating, diarrhea, insomnia, nausea, injection-site skin reactions, and lipoatrophic
<table>
<thead>
<tr>
<th><strong>Drug Name</strong></th>
<th>Interferon beta-1a (Rebif)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Indicated for treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Believed to act via ability to counteract cell surface expression of proinflammatory or pro-adhesion molecules on immune cells, among other effects. More studies needed to fully understand mechanisms of action. Differs from interferon beta-1b (Betaseron, see above) only in that it has amino acid sequence identical to that of natural compound and is glycosylated. Presence of glycosylation is claimed to lead to structural stability and presumably to higher biological potency. Interferons act through common receptor that activates Jak/Stat pathway of signal transduction molecules, which, in turn, leads to activation of interferon-responsive genes. Interferon beta may decrease expression of B7-1 (a proinflammatory molecule) on surface of immune cells and increase levels of TGF-beta (anti-inflammatory) in circulation of patients with MS. Frequency of development of neutralizing antibodies against interferon is higher with interferon beta-1b than with interferon beta-1a, but clinical significance still unclear and controversial. For instance, neutralizing antibodies in patients taking interferon beta-1b disappear faster than those in patients taking interferon beta-1a. May delay progression of disease in patients that have only manifested one clinical attack but have MRI evidence of MS.</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>44 mcg/dose SC 3 times/wk (at least 48 h between each dose) (high-dose, high-frequency interferon)</td>
</tr>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; liver dysfunction; severe leukopenia; thrombocytopenia; lactation</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Common adverse effect is flu-like reaction following administration, usually lasting minutes or hours; 88% of patients no longer experience this effect after second mo of treatment. Flu-like effects can be minimized by taking over-the-counter acetaminophen or anti-inflammatory drugs such as aspirin or ibuprofen a few hours prior to and a</td>
</tr>
</tbody>
</table>
few hours after injection; besides flu-like illness, patients may experience injection-site skin reactions, which may range from mild (slight erythema or stinging sensations) to severe (skin necrosis). Adverse effects may include hepatotoxicity (liver enzyme elevation) and myelosuppression (leukopenia); caution in preexisting seizure disorder; cases of exacerbation of thyroid dysfunction have been described—caution when using in patients with uncontrolled thyroid dysfunction; interferons are abortifacients; data on teratogenicity are limited; extreme caution in patients with severe depression.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Natalizumab (Tysabri)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Three cases of progressive multifocal leukoencephalopathy (PML) associated with natalizumab use prompted temporary withdrawal from the market in 2005. Natalizumab was later reapproved in 2006 by the FDA for commercialization under a special restricted distribution program known as TOUCH. The drug now carries a package insert black box warning about potential risks of opportunistic infections. Patients, physicians, and pharmacists must be involved in the TOUCH program in order to receive, prescribe, or dispense (respectively) natalizumab. Indicated as monotherapy for MS, not to be used with other immune system-modifying drugs. Because of risks of PML, natalizumab is now generally recommended for patients who have had an inadequate response to, or are unable to tolerate alternate MS therapies. Recombinant humanized IgG4-1C monoclonal antibody produced in murine myeloma cells. Binds to alpha-4 subunits of alpha-4-beta-1 and alpha-4-beta-7 integrins expressed on leukocyte surface, which inhibits alpha-4-mediated leukocyte adhesion to their receptors. Clinical effect in MS may be secondary to blocking interaction of alpha-4-beta-1 expressed by inflammatory cells with VCAM-1 on vascular endothelial cells and with CS-1 and/or osteopontin expressed by parenchymal brain cells. Indicated for relapsing MS and to reduce symptom exacerbation frequency.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>300 mg IV q4wk; dilute in 100 mL 0.9% NaCl and infuse over 1 h</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, current infections, concomitant use of immunosuppressors</td>
</tr>
<tr>
<td>Interactions</td>
<td>Interferon beta-1a decreases clearance by 30%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Fetal risk revealed in studies in animals but not</td>
</tr>
</tbody>
</table>
**Drug Category: Corticosteroids**

These agents reduce acute inflammation and expedite recovery from acute exacerbations of MS. They may be used for "rescue" therapy as monthly boosters in patients who respond poorly to the ABC immunomodulators. Methylprednisolone, a glucocorticoid, has greater anti-inflammatory potency than prednisolone and even less tendency to induce water and sodium retention.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Methylprednisolone (Solu-Medrol, Depo-Medrol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>For treatment of inflammatory and autoimmune reactions. By reversing increased capillary permeability and suppressing PMN activity, may decrease inflammation. Also may alter expression of some proinflammatory cytokines.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>500-1000 mg IV (mix in 150-200 mL isotonic saline or D5 isotonic saline) infused over 1-2 h for 3-5 d without prednisone taper</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; systemic fungal infections; severe bone density loss; hip osteonecrosis; cataracts; psychosis</td>
</tr>
<tr>
<td>Interactions</td>
<td>Cyclosporine may induce seizures; phenytoin, phenobarbital, or rifampin may reduce levels because of their hepatic enzyme-inducing effects; ketoconazole may increase levels; may decrease levels of salicylates; may increase or decrease levels of anticoagulants; may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels; monitor patients for hypokalemia when taking with diuretics</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus</td>
</tr>
</tbody>
</table>
Precautions

Caution or discontinue in patients with early evidence of cataracts, bone density loss, hyperglycemia, psychosis, euphoria, emotional irritability, adrenal dysfunction, fluid retention, arrhythmias, or anaphylactoid reactions; monitor for decreased bone density in prolonged treatment; steroid-induced myopathy can occur, especially in underlying neuromuscular transmission disorders.

Drug Category: *Immunosuppressors*

These agents are used for their ability to suppress immune reactions.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mitoxantrone (Novantrone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Anthracenedione compound used for SPMS and RPMS. Induces DNA cross-links and strand breaks and leads to apoptosis. Mitoxantrone also interferes with RNA and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. Indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting MS (ie, patients whose neurologic status is significantly abnormal between relapses). Not indicated in the treatment of patients with primary progressive MS.</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>5 mg/m² and 12 mg/m² IV every 3 mo (clinical trial)</td>
</tr>
<tr>
<td><strong>Pediatric Dose</strong></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; heart disease; severe infections</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus</td>
</tr>
</tbody>
</table>

**Precautions**

Because of risk of severe myelosuppression and heart dysfunction, only clinicians experienced in chemotherapy should administer this medication. High risk of leading to long-term myocardial dysfunction; perform baseline and follow-up cardiac function tests (2D-echocardiography and ejection fraction measurements); increased risk of cardiotoxicity commonly seen after cumulative dose of 120-160 mg/m², as observed in oncology studies; hair thinning, alopecia, and nausea usually mild but common; may cause menstrual disorders or infertility; GI bleeding and mucositis/stomatitis may occur; increases chances of infections.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Cyclophosphamide (Cytoxan, Neosar)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Metabolized in liver by mixed-function microsomal</td>
</tr>
</tbody>
</table>
oxidase system. Mechanism of action believed to involve DNA cross-linking. Has been used off-label for secondary progressive MS, especially for patients with dramatic, rapid progression. Thought to be more effective if given in early stage of progression.

**Adult Dose**

Induction phase: 600 mg/m² IV qod for 5 d initial dose, accompanied by Solu-Medrol 1 g IV qd for 8 d

Monthly booster doses: adjust dose on basis of WBC counts on days 8, 11, and 14 after previous dose (to establish nadir) and WBC count before treatment; use following recommendations:

- Total WBC nadir 1500-2000/µL: 1-day booster dose of 800 mg/m²/mo, accompanied by Solu-Medrol 1000 mg IV
- Total WBC nadir <1500/µL, decrease dose by 100-200 mg/m²
- Total WBC nadir >2200/µL, increase dose by 200 mg/m²

Total WBC count before cyclophosphamide dose should be >4000/µL
- If 3000-4000/µL, 75% of dose
- If 2000-3000/µL, 50% of dose
- If <2000/µL, booster not given and WBC count checked in 1 wk

(Boosters should be given 1 day per mo for 12 mo, at which time effects of therapy should be reevaluated; if therapy working, give booster q6wk for another year, and then q2mo for a third year; authors do not advise administering cyclophosphamide for more than 3 consecutive years)

**Pediatric Dose**

Not established

**Contraindications**

Documented hypersensitivity; profound myelosuppression; active infections; hair thinning; alopecia; severe leukopenia; liver function abnormalities

**Interactions**

Long-term phenobarbital may increase metabolism of cyclophosphamide and ability to induce leukopenia; inhibits cholinesterases and thus potentiates effect of succinylcholine chloride

**Pregnancy**

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

**Precautions**

Causes infertility; increased risks of bladder hemorrhage or cancer or other secondary malignancies; increased risk of opportunistic infections; patients should be hydrated adequately while receiving cyclophosphamide

**Drug Name**

Azathioprine (Imuran)

**Description**

This immunosuppressive antimetabolite drug is an imidazolyl derivative of 6-mercaptopurine. Cleaved in
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Methotrexate (Rheumatrex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Immunosuppressive metabolite drug used for some neoplasias (including leukemia), psoriasis, and rheumatoid arthritis. Interferes with DNA synthesis, repair, and cellular replication. Inhibits dihydrofolate reductase, which participates in synthesis of thymidylate and purine nucleotides. Has been used off-label for MS.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>7.5-15 mg PO qwk</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Chloramphenicol interferes with intestinal absorption; NSAIDs and phenytoin elevate levels; probenecid impairs renal tubular transport of methotrexate</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus</td>
</tr>
<tr>
<td>Precautions</td>
<td>Use caution in patients with history of alcohol abuse, liver dysfunction, or renal dysfunction; may cause neurotoxicity (leukoencephalopathy), renal or liver damage, pulmonary fibrosis or pneumonitis (fully reversible), diarrhea, ulcerative stomatitis, hemorrhagic enteritis, seizures, anemia, leukopenia,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>6-thiouric acid (Mercaptopurine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>vivo to mercaptopurine and converted to 6-thiouric acid by xanthine oxidase. Generally used in treatment of transplant rejection or severe, active, erosive rheumatoid arthritis. Has been used off-label for MS.</td>
</tr>
</tbody>
</table>
| Adult Dose         | 1 mg/kg (50-100 mg)/d PO given bid or single-dose schedule  
Dose can be increased gradually (0.5 mg/kg increments); not to exceed 2.5 mg/kg/d |
| Pediatric Dose     | Not established                |
| Contraindications  | Documented hypersensitivity; pregnancy; previous treatment with alkylating agents such as chlorambucil, melphalan, or cyclophosphamide owing to possible increased risk of neoplasia |
| Interactions       | ACE inhibitors may induce anemia or leukopenia; may inhibit anticoagulant action of warfarin; allopurinol inhibits drug's detoxification pathway, thus reduce to one third to one quarter usual dose if used with allopurinol |
| Pregnancy          | D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus |
| Precautions        | Patients with serious hematologic or hepatic disorders should not use this medication; causes leukopenia or thrombocytopenia, nausea, vomiting, or diarrhea; <1% of patients may develop hepatotoxicity; instruct patients to contact their physician if they develop fever or any other evidence of infection |

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Allopurinol (Zymax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Purine antagonist; has been used off-label for MS.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>50-100 mg PO bid or 250-500 mg PO once daily</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Renal impairment, hyperuricemia, leukemia, lymphoma, active ulcerative colitis, gout, dialysis patients, myelosuppression</td>
</tr>
<tr>
<td>Interactions</td>
<td>Renal impairment; may lead to hyperuricemia; may cause myelosuppression</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus</td>
</tr>
<tr>
<td>Precautions</td>
<td>Use caution in patients with renal impairment, history of gout, or a history of lymphoma or leukemia; monitor patients for myelosuppression, hyperuricemia, or symptomatic gout</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Azathioprine (Imuran)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>xanthine oxidase inhibitor; used in the treatment of transplant rejection or severe, active, erosive rheumatoid arthritis. Has been used off-label for MS.</td>
</tr>
</tbody>
</table>
| Adult Dose         | 2.5 mg/kg/d PO given bid or single-dose schedule  
Dose can be increased gradually (0.5 mg/kg increments); not to exceed 2.5 mg/kg/d |
| Pediatric Dose     | Not established |
| Contraindications  | Documented hypersensitivity; pregnancy; previous treatment with alkylating agents such as chlorambucil, melphalan, or cyclophosphamide owing to possible increased risk of neoplasia |
| Interactions       | ACE inhibitors may induce anemia or leukopenia; may inhibit anticoagulant action of warfarin; allopurinol inhibits drug's detoxification pathway, thus reduce to one third to one quarter usual dose if used with allopurinol |
| Pregnancy          | D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus |
| Precautions        | Patients with serious hematologic or hepatic disorders should not use this medication; causes leukopenia or thrombocytopenia, nausea, vomiting, or diarrhea; <1% of patients may develop hepatotoxicity; instruct patients to contact their physician if they develop fever or any other evidence of infection |
or thrombocytopenia; may cause alopecia and photosensitivity, but these rarely occur at doses used for treating MS.

**Drug Category: Antiviral, anti-Parkinson agent**

This agent is used for treatment of fatigue in MS.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Amantadine hydrochloride (Symmetrel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Mechanism of counteracting fatigue unclear. May have antiviral effects by inhibiting replication of some viruses, including influenza A.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>100 mg PO bid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Either triamterene or hydrochlorothiazide (or both) may increase plasma levels; thioridazine may worsen tremor in elderly patients with Parkinson disease</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus</td>
</tr>
<tr>
<td>Precautions</td>
<td>Patients with history of seizure should be observed carefully for signs of seizure recurrence; because of its anticholinergic effects, use caution by prescribing limited quantities to patients at risk of overdosing; may induce suicidal ideation in some patients, or may exacerbate existing mental disorders; use with caution in patients taking CNS stimulants; acute withdrawal should be avoided in patients with Parkinson disease, as acute parkinsonian crisis may ensue; because excreted in urine, reduce dose in patients with renal insufficiency or who are aged 65 years or older</td>
</tr>
</tbody>
</table>

**Drug Category: Central nervous system stimulants**

These agents are used for treatment of fatigue without interfering with normal sleep architecture. They promote wakefulness.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Modafinil (Provigil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Mechanism of action currently unknown. Listed in Schedule IV of the Controlled Substances Act. Patients should be observed for signs of use or abuse, as drug has psychoactive and euphoric effects similar to those seen with other scheduled CNS stimulants (eg, methylphenidate).</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>100-200 mg PO qd; some patients may require as much as 300 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Documented hypersensitivity; history of left ventricular hypertrophy, ischemic ECG changes, chest pain, or arrhythmias as response to CNS stimulants</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>Reversible inhibitor of drug-metabolizing enzyme CYP2C19, and therefore must be used with caution with other drugs metabolized by this enzyme, including diazepam, phenytoin, and propranolol; in individuals deficient in CYP2D6 (7-10% of Caucasian population), levels of CYP2D6 substrate drugs such as SSRIs and TCAs may be elevated, as these individuals may use CYP2C19 as ancillary elimination pathway</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Dose should be reduced in patients with severe hepatic impairment; most common adverse effects are headache and anxiety, but both occur in &lt;17% of patients; less common adverse effects are irritability, restless legs syndrome, epigastric discomfort, dizziness, infection, insomnia, and nausea; patients may be advised not to operate hazardous machinery or drive an automobile until reasonably clear that drug does not place them at risk because, in some patients, drug may affect judgment, motor skills, or thinking; used with caution in patients with recent myocardial infarction, unstable angina, or history of psychosis</td>
</tr>
</tbody>
</table>

**FOLLOW-UP**

**Deterrence/Prevention:**

- Patients must understand that the ABCR immunomodulatory drugs are preventive, not curative. Early treatment is thus essential.
- Patients should avoid exposure to extreme heat.
- The impact of stress on MS exacerbations is thought to be minimal or noncontributory, and trauma has no demonstrated impact on the disease course.

**Complications:**
Complications in patients with MS include the following:

- Adverse drug reactions
- Rare cases in which large, tumor-like demyelinating lesions necessitate brain biopsy to rule out malignancy

For bedridden patients, preventive measures regarding decubitus ulcers, atelectasis, pneumonia, and aspiration should be addressed.

Seizures are rare in MS but may occur at a higher rate than in the general population. Patients with seizures who work in conditions of high risk for self-injury (e.g., operating heavy machinery) should exercise caution, taking into account specific state laws. This also pertains to driving a motor vehicle.

Patients with ataxia and weakness are at increased risk of falls and personal injury; the physician should recognize these patients early and provide any needed assistance.

Prognosis:

- If untreated, more than 30% of patients with MS will develop significant physical disability within 20-25 years from onset. This prognosis is changing for these patients with the advent of new treatments.
- Male patients with PPMS have the worst prognosis, responding less favorably to treatment and rapidly accumulating disability. The higher incidence of spinal cord lesions in PPMS is also a factor in the rapid development of disability.
- Less than 5-10% of patients have a clinically milder MS phenotype, in which no significant physical disability accumulates despite several decades passing since onset (sometimes in spite of multiple new lesions by MRI). Detailed examination of these patients in many instances reveals some degree of cognitive deterioration.
- The physician should remind patients that early treatment with some agents may help counteract the progressive brain atrophy seen on MRI.

Patient Education:

- Patients may benefit from referral to comprehensive and professional organizations and web sites that are dedicated to MS.
- Among these, the National Multiple Sclerosis Society Web site is recommended highly for information on current hypotheses, ongoing research, general resources, and educational programs. Other highly recommended MS-related Web sites include MultipleSclerosis.com, msworld.com, Consortium of Multiple Sclerosis Centers.
- For excellent patient education resources, visit eMedicine's Brain and Nervous System, Muscle Disorders Center, and Erectile Dysfunction Center. Also, see eMedicine's patient education articles, Multiple Sclerosis and related articles Impotence/Erectile Dysfunction and Erectile Dysfunction FAQs.

MISCELLANEOUS

Medical/Legal Pitfalls

- Treatment of "presumed MS" is not indicated. The neurologist should have a fairly reasonable diagnosis based on history, clinical examination, and MRI findings. Treatment based on a suspected diagnosis can lead to unnecessary emotional and financial costs and should be avoided.
A common misconception is that any attack of demyelination means a diagnosis of acute MS and its implications for management. If a patient has the first attack of demyelination, the physician should not rush to diagnose MS. Postinfectious demyelination or other diseases that mimic MS should be considered carefully. Follow-up should be performed to ascertain whether the episode was self-limited. Although therapy for CIS with immunomodulatory medications has not yet become standard practice throughout the world, recent trials suggest that early intervention may be appropriate. The McDonald diagnostic criteria are helpful in the decision to treat patients early during the course of MS.

Clinicians who specialize in MS commonly see patients referred for multiple, ill-defined, vague complaints who had recent head or spine MRIs in which T2 hyperintense lesions have been demonstrated.

- Careful questioning reveals that symptoms have been stereotyped and vague or do not truly qualify as exacerbations (eg, scintillating scotomas in a patient who also admits to concomitant migraines; symptoms consistent with carpal tunnel syndrome).
- A history of meningoencephalitis during childhood occasionally emerges and an explanation for the lesions may become obvious.

A third common problem is the presence of small T2 hyperintensities, typically referred to as "unidentified bright objects" (UBOs) by neuroradiologists.

- These nonspecific lesions are relatively common in the general population, and clinical correlation (ie, a high degree of suspicion based on clinical evidence) becomes important in the diagnosis.
- The neurologist seeking to confirm MS should look for sites of involvement that are rare for UBOs but frequent for MS (eg, corpus callosum or throughout the spinal cord).

**Special Concerns**

- For the patient with MS who wants to become pregnant, ABCR drugs should be discontinued.
- If the patient becomes pregnant during treatment, the drug should be discontinued immediately.
- The treatment can be resumed a few weeks after delivery or after the patient finishes her period of lactation.

**MULTIMEDIA**

Media file 1: The mechanism of demyelination in multiple sclerosis may be activation of myelin-reactive T cells in the circulation, which then express adhesion molecules, allowing their entry through the blood-brain barrier (BBB). T cells are activated following antigen presentation by antigen-presenting cells such as macrophages and microglia, or B cells. Perivascular T cells can secrete proinflammatory cytokines, including interferon gamma and tumor necrosis factor alpha. Antibodies against myelin also may be generated in the periphery or intrathecally.

Ongoing inflammation leads to epitope spread and recruitment of other inflammatory cells (ie, bystander activation). The T cell receptor recognizes antigen in the context of human leukocyte antigen molecule presentation and also requires a second event (ie, co-stimulatory signal via the B7-CD28 pathway, not shown) for T cell activation to occur. Activated microglia may
release free radicals, nitric oxide, and proteases that may contribute to tissue damage.

Media file 2: MRI of the head of a 35-year-old man with relapsing remitting multiple sclerosis. MRI reveals multiple lesions with high T2 signal intensity and one large white matter lesion. These demyelinating lesions may sometimes mimic brain tumors because of the associated edema and inflammation.

Media file 3: MRI of the head of a 35-year-old man with relapsing remitting multiple sclerosis, also shown in Image 2. This MRI, performed 3 months after the one shown in Image 2, shows a dramatic decrease in the size of lesions.
Inflammation in multiple sclerosis. Hematoxylin and eosin (H&E) stain shows perivascular infiltration of inflammatory cells. These infiltrates are composed of activated T cells, B cells, and macrophages.

Demyelination in multiple sclerosis. Luxol fast blue (LFB)/periodic acid-Schiff (PAS) stain confers an intense blue to myelin. Loss of myelin is demonstrated in this chronic plaque. Note that absence of inflammation may be demonstrated at the edge of chronic lesions.

REFERENCES


