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CLINICIAN'S PRIMER ON MULTIPLE SCLEROSIS

An In-Depth Overview

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ACTIVITY INFORMATION

TARGET AUDIENCE

This activity has been designed to meet the educational needs of neurologists, primary care physicians, MS nurses, fellows, residents, and other health care professionals actively involved in the care of patients with multiple sclerosis.

ACTIVITY DESCRIPTION

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system. Characterized by inflammation and demyelination of axons, MS presents in a variety of forms usually beginning with a relapsing-remitting disease pattern. Disease progression leads to neurologic damage, deterioration in physical and cognitive function, and permanent disability.

Over 400,000 people in the United States currently are living with MS, and 10,000 new cases are diagnosed each year. With a 1:600-800 lifetime risk of developing the disease, MS is the most common cause of neurologic disability in young adults between 18 and 45 years of age. This demographic represents the majority of the adult workforce in the United States; therefore, the direct and indirect costs of health care for this population currently are estimated at \$12 billion annually, including lost wages and reduced productivity. Clinician goals for effective MS management must include prompt treatment of an acute relapse, ongoing symptomatic management, and quality of life maintenance, as well as disease modification and long-term disability prevention.

The exact cause of MS remains unknown, but recent advances have improved understanding of the immunopathology and neuropathology of the disease. In order to successfully provide up-to-date, comprehensive health care and improved treatment outcomes for patients with MS, clinicians must understand clearly the current data on epidemiology, pathophysiology, diagnosis, treatment, and long-term monitoring of this important neurologic illness.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants should be able to:

- Evaluate new evidence and information on the pathophysiology and neuropathology of MS
- Recognize the major diagnostic criteria and clinical subtypes of MS
- Recognize clinical symptoms of MS, determine how these affect quality of life for patients, and understand effective symptom management therapies
- Identify the role of laboratory and imaging investigations in the diagnosis and monitoring of patients with MS
- Review disease-modifying therapy options for MS, including treatment goals, mechanisms of action of disease-modifying therapies, and possible side effects
- Evaluate treatment outcomes for MS
- Analyze disease progression and disability in patients with MS and the monitoring of these using disability scales

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ACCREDITATION STATEMENT

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FEE INFORMATION

There is no fee for this educational activity.

METHOD OF PARTICIPATION

There are no fees for participating in and receiving CME credit for this activity. During the period March 2011 through March 2012, participants must 1) read the learning objectives and faculty disclosures, 2) study the educational activity, 3) complete the posttest by recording the best answer to each question in the answer key on the evaluation form, 4) complete the evaluation form, and 5) mail or fax the evaluation form with answer key to Medical Education Resources.

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1 INTRODUCTION

Multiple sclerosis (MS), an inflammatory disorder of the central nervous system (CNS), is a chronic and progressive illness affecting approximately 400,000 people in the United States and 2.5 million people worldwide. As the leading cause of progressive neurologic impairment in young adults, MS typically affects those 20-40 years of age with a male-to-female ratio ranging from 1:2 to almost 1:4 in most populations.¹⁻⁴ Historically, Caucasians of northern European descent and those living in temperate geographical areas have shown increased prevalence of MS; however, MS can affect any ethnic group. In fact, recent data indicate the globalization of MS in the last decade.⁵⁻¹⁰ The economic burden of MS is massive, with total annual costs between \$6.8 and \$13.6 billion and a lifetime cost of at least \$2 million per patient in the United States.¹¹⁻¹⁴

Although the exact pathogenesis of MS remains unknown, research shows that interactions between environmental and genetic factors trigger an immune-mediated cascade. These abnormal immune responses cause acute inflammation against myelin, an important component of normal CNS axonal insulation and nerve impulse transmission. As myelin progressively is damaged by autoimmune processes, focal areas of demyelination along CNS neuronal axons develop (peripheral nerve myelin is not affected), causing axonal injury, axonal transection, neurodegeneration, and subsequent scar or plaque formation that can be seen as lesions on magnetic resonance imaging (MRI). Cumulatively, this process causes irreversible and progressive physical and cognitive disabilities.

Demyelination, axonal injury, and neurodegenerative processes occurring in the brain, spinal cord, and optic nerve of the CNS produce neurologic deficits and symptoms typical of MS. A clinical diagnosis of MS is based on medical history and examination findings, the exclusion of other possible diseases, and imaging and laboratory findings.

Clinically, most patients with MS present with an acute episode of neurologic dysfunction consistent with demyelination called a clinically isolated syndrome (CIS). Typical

CIS presentations include optic neuritis, spinal cord syndromes, and brainstem-cerebellar syndromes.¹⁵ Symptoms of these vary widely among individual patients; however, typical presenting complaints of a CIS are visual loss in 1 eye, fatigue, pain, muscle spasticity, diplopia, imbalance, lower body numbness, and weakness. Imaging studies reveal that underlying disease activity and CNS damage are present long before the first clinical manifestation of MS.^{16,17}

Following the initial CIS episode, the course of MS typically has a chronic pattern of acute neurologic exacerbations (relapses) followed by periods of clinical stability (remissions). The timing, progress, duration, severity, and specific symptoms of each acute relapse are variable and unpredictable. Evidence indicates that subclinical disease activity may be occurring during remissions.¹⁸ Disease activity, clinical manifestations, and long-term neurologic deficits of MS are highly variable and range from mild to severe, as is the case with most chronic medical disorders. Ultimately, MS is a progressive and neurodegenerative disease, and most patients will develop irreversible functional disability during its course.

MS is a dynamic, heterogeneous, and unpredictable disease in presentation and course; thus, clinicians historically have been hampered from making a reliable early diagnosis and initiating prompt, appropriate treatment. However, newer imaging techniques and improved understanding of the disease process now allow physicians to recognize and diagnose MS and initiate therapy earlier, which has been shown to prevent disease progression and delay permanent disability in the long term.¹⁹

With improved understanding of the immunopathology and natural history of the disease, new therapeutic targets, treatment options, and protocols are evolving for MS. Therapeutic options include first-line disease-modifying therapies (DMTs), including 3 interferon (IFN) beta products, glatiramer acetate (GA), and the newly approved oral agent fingolimod, all of which have been shown to reduce relapse rates and slow disease progression in MS.² Second-line DMTs include natalizumab and mitoxantrone. Multiple symptomatic therapies also are available and are important in effective short- and long-term MS management and in optimizing patient quality of life (QOL). Multiple new agents for MS

currently are under investigation or in late-stage development, including other oral agents and monoclonal antibodies.

Studies show that in order to achieve improved treatment and rehabilitation outcomes for patients with MS, a well-organized, comprehensive, and multidisciplinary health care team approach is needed, as well as ongoing support for both patients and families.²⁰ *The Clinician's Primer on Multiple Sclerosis* will serve as an information tool, providing clinicians with the latest data on MS history, epidemiology, neuropathology, diagnosis, imaging, treatment, and future directions.

2 HISTORY of MS

Multiple sclerosis was first noted in 1868 by Dr. Jean-Martin Charcot, a Parisian neurology professor, when he observed a tremor, slurred speech, and abnormal eye movements in a young female patient. Despite attempts to treat her symptoms with strychnine, electric stimulation therapy, and gold and silver injections, there was no improvement. After her death, Dr. Charcot performed a brain autopsy and described the plaques now known to be typical of MS.²¹

Later in the 19th century, clinicians in Europe and the United States noticed various clinical presentations of MS and epidemiologic factors, such as symptoms presenting more often in women and no evidence of the disease being directly inherited.²¹ Many patients were admitted to neurologic wards in the early 20th century due to MS,²² and in 1900, their resultant life expectancy was 5 years from diagnosis.²¹

In 1916, using advances in microscopy, scientists detected both damage to myelin and inflammation around blood vessels in pathology specimens from MS patients. By 1919, abnormalities of the cerebrospinal fluid (CSF) were discovered and thought to be significant but remained unexplained. Subsequently, electric nerve conduction tests, developed in 1925, enabled scientists to accurately describe neuronal and nervous system functions. With this greater understanding of nerve conduction mechanisms, the role of myelin in nerve transmission was defined, and the effects of demyelination in inhibiting conduction were identified.

In the 1930s, intense research efforts unsuccessfully focused on trying to identify an infective viral agent or toxin possibly triggering the inflammatory process noticed in MS. At that time, scientists also researched circulatory compromise as a possible cause for myelin damage. In addition, experimental MS therapies, such as antithrombotics, anticoagulants, and vasodilators, were studied to address this hypothesis related to the circulatory system.²¹ In 1935, scientists at the Rockefeller Institute in New York identified that an autoimmune process attacking myelin could produce the symptoms of MS.²¹ For research purposes, an autoimmune form of MS called experimental allergic encephalitis (EAE) was developed for use in laboratory animals. This became important for medical research by furthering the understanding of autoimmune processes in general and of MS in particular. Throughout the 1950s and 1960s, MS research was focused on understanding the EAE model in laboratory animals.

After World War II, further technological advances were made in the science and investigation of neurologic disorders. The National Multiple Sclerosis Society (NMSS) was founded in 1946 to garner funding for research and to promote awareness of MS in the medical and lay communities. In 1947, almost 30 years after abnormalities in the CSF were noticed, abnormal immunological proteins (oligoclonal bands) were identified in the CSF.

In the 1960s, the first clinical guidelines for the diagnosis of MS were developed by the NMSS, and the first treatment studies were conducted using adrenocorticotrophic hormone (ACTH) to stimulate adrenal production of corticosteroids in MS patients. Studies showed the anti-inflammatory effects of these steroids increased the rate of recovery from symptoms during an acute exacerbation of MS.²³ High-dose corticosteroids given intravenously were found to suppress the symptoms of acute relapse in MS patients; this remains the treatment of choice for acute exacerbations. In the late 1960s, myelin was identified as the specific target of an autoimmune attack in MS, and theories re-emerged about possible viral triggers for the disease. Despite advances in understanding the pathophysiology of MS at this time, the process of making a definitive diagnosis took an average of 7 years from first symptom presentation.

In the 1970s, the first valid clinical trials of therapy were conducted using ACTH.²¹ Computed tomography (CT)

scans and evoked potential testing first became available in the late 1970s, advancing both the diagnosis and monitoring of MS. In the early 1980s, new DMTs were tested; experimental treatments with IFN began on MS patients, and initial research was launched to develop synthetic polypeptide fragment therapy, later known as GA.

The 1980s were coined “the treatment decade” in MS, with many trials confirming the benefits of IFN beta and glatiramer acetate and addressing other treatments.²¹ Macrophages also were identified as key cells causing damage to myelin in MS. MRI first became available in England in the early 1980s and led to several important discoveries (Table 1). Sequential MRI scans of MS patients, with and without clinical symptoms, indicated the progressive nature of the disease and that CNS damage occurred not only during a symptomatic, acute relapse but also subclinically during periods of remission. In 1984, T2-weighted MRI scanning first became available and identified white matter lesions in the brains of patients with MS.

TABLE 1: Historical Milestones of MRI in MS

1982	First MRI used in patients
1984	MRI identifying clinically silent lesions
1988	MR spectroscopy (MRS)
1990	Gadolinium-enhancing lesion, T2 lesion volume
1992	T1 black hole lesion volume
1992-1994	MRS, MTI, and DWI
1995	Brain atrophy
1998	Functional MRI and position emission tomography
1999	DTI
2004	Perfusion and tractography
What's next?	Regional atrophy, cortical lesions, gray matter atrophy, and molecular imaging

Further technological development in MRI scanning during the 1990s produced magnetic resonance spectroscopy (MRS), diffusion weighted imaging (DWI), and magnetization transfer imaging (MTI). These new technologies enabled clinicians to more closely examine demyelination, axonal injury, and axonal loss in MS patients and clearly revealed scar or plaque formations in the brain and spinal cord. This MRI information became imperative to understand the progressive neurodegeneration of MS, even when patients experienced no clinical symptoms. Subsequent

diffusion tensor imaging (DTI) gave more detailed information on the neuropathology of MS and disease progression. Detailed MRS imaging showed that white matter abnormalities exist early in MS despite normal-appearing conventional MRIs and gadolinium (Gd)-enhanced scans.

The US Congress named the 1990s the “Decade of the Brain” to further research, funding, and efforts into the diagnosis and treatment of neurologic diseases. Volumetric imaging studies evolved, and information on the significance of chronic hypointense lesions or black holes, cortical atrophy on MRI scans, and cognitive decline became available. Later in the decade, brain parenchyma loss in early relapsing-remitting MS (RRMS) was linked with progressive disability and cognitive decline. Clinical trials focused on developing DMTs for MS. In 1993, IFN beta-1b became available, and in 1996, both IFN beta-1a and GA were introduced.

Reflecting a better understanding of the pathophysiology of MS, more accurate diagnosis techniques, and new treatments, the life expectancy of patients has gradually improved. In 1917, the survival expectancy of MS patients after diagnosis was around 12 years, by 1957 it was approximately 13 years, and by the 1980s it was 30 years.³ Currently, most people with MS have normal or near-normal (95%) life expectancy.²⁴ Due to this and the fact that the onset of MS typically occurs in young adulthood and is chronic, progressive, and incurable, the importance of effective DMTs to delay both disease progression and the development of functional disability is clear.

In 2007, the NMSS published a disease management consensus statement that recommended that patients with RRMS be treated with immunomodulating therapies immediately after diagnosis to prevent further relapses and neurologic damage.²⁵ Today, based on new evidence, the management goals for MS include:

- early recognition and reliable diagnosis of MS;
- early initiation of DMTs to prevent relapses, disease progression, and neurodegeneration and to delay disability;
- treatment of acute relapses to shorten the duration of the exacerbation, minimize its severity, and limit consequential neurologic damage; and
- effective treatment of MS symptoms, maintenance of functional ability, and optimization of patient health-related QOL (HRQOL).

3 THE COST *of MS*

The direct and indirect costs of MS in the United States are estimated at approximately \$12 billion annually. Direct medical expenditures include health care provider costs, physical therapy and rehabilitation costs, inpatient and outpatient expenses, as well as pharmaceutical costs. Indirect costs to the working, young-adult population (more susceptible to MS) include lost productivity, missed work days, reduced efficiency, and loss of individual earnings—accounting for approximately 20% of total costs.³ Some studies have revealed that 50%-80% of adults with MS are unemployed within 10 years of diagnosis,³ thereby increasing the financial burden of the disease. Health care expenses escalate with increasing disease severity and disability scale ratings.³ In addition to medical, professional, and economic detriments, MS causes wide-ranging personal, family, and social burdens.

4 EPIDEMIOLOGY

Approximately 10,000 new cases of MS are diagnosed annually in the United States.⁵ Worldwide, the disease affects up to 2.5 million people, but, for reasons not fully understood, the prevalence varies widely according to geographic areas.^{22,26,27} Historically, the highest prevalence of MS has occurred in Caucasians of northern European ancestry.²¹ Areas that were settled or visited by Vikings and other northern European tribes have the highest prevalence of MS throughout Europe, the Americas, South Africa, certain areas of the Mediterranean, Australia, and New Zealand and may be the result of “seeding” by these genetically susceptible individuals.^{28,29} Although MS is relatively rare in some ethnic groups such as African Americans, all ethnicities may be affected by MS. Recent data indicate that the prevalence of MS is increasing globally, including in India and Asia, although the exact reasons for this remain unclear.⁶⁻¹⁰

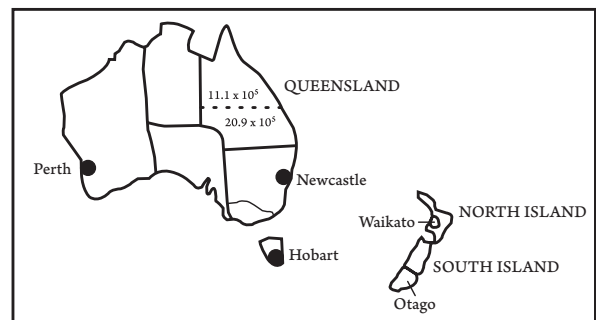
MS clearly favors temperate regions, as the incidence and prevalence increases farther from the equator.³⁰⁻³² The

incidence of MS is greatest at the extremes of latitude in the northern and southern hemispheres in susceptible populations, somewhat due to ethnic differences. For example, the United States has a higher concentration of African Americans (with a lower propensity for MS) in the south.³³ However, the differences are quite pronounced even in racially homogeneous countries such as Australia and New Zealand (**Figure 1**).³⁴ Previous explanations have focused on latitudinal variation and the risk of infection in more temperate climates. Another possible explanation is relatively low vitamin D levels at greater latitudes due to lower sunlight exposure. Although latitude remains the strongest risk factor after controlling for ethnicity, recent data indicate that the latitude effect has decreased over the last few years.³⁵

PATHOGENESIS

While the exact cause of MS still is unknown, research indicates the etiology is likely due to important interactions between genetics, infectious agents, and other environmental factors in susceptible individuals.³⁶ Currently, research indicates:

FIGURE 1: Comparison of Prevalence Rates for Australia and New Zealand³⁴



Australia	Prevalence per 10 ⁵
Queensland	18.3
Perth	29.9
Newcastle	36.5
Hobart	75.6
New Zealand	
North Island, Waikato	27.9
South Island, Otago	79.4

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- **Genetic factors** in predisposed individuals may allow an aberrant autoimmune response to target myelin proteins in the CNS in patients with MS.
- **Geographical factors** and **infectious agents** may represent environmental triggers initiating the abnormal immune response in genetically susceptible individuals.^{36,37}

Genetic Factors

Studies show genetics play a prominent role in susceptibility to MS, a complex, polygenic, inherited disease. Polygenic diseases are common within any population, and this pattern of genetic susceptibility is linked to the majority of chronic illnesses, including diabetes, hypertension, and heart disease, in developed societies.³⁷

Confirmation of genetic predisposition in MS comes from a variety of studies, including twins, siblings, parent-child, and other familial relationships (**Tables 2 and 3**).³⁸ The concordance rate for MS in monozygotic twins is 25%-30%, in contrast to the 2.5%-5% concordance rate between dizygotic twins, non-twin siblings, and a general population risk of 0.17%. Genetics, therefore, explains only part of the susceptibility to MS since monozygotic twins who share 100% of the same genetic information only both develop MS 30% of the time.

While other factors contributing to MS are almost certainly environmental, genetic susceptibility likely is the first step in the development of MS. Adopted family members living with someone with MS are at no higher risk of developing MS than the general population. Research identifying susceptibility/candidate genes in MS shows that human leukocyte antigen (HLA) types exert the most prominent genetic effect in MS. A confirmed gene demonstrating an increased risk for MS is the HLA DR2 allele (HLA-DRB1*1501), with different haplotypes occurring in populations of different geographic origins.^{39,40}

Studies indicate that approximately 60% of individuals with MS are HLA DR2 haplotype (DRB1*1501)-positive (compared with approximately 30% of healthy individuals). This indicates that HLA DR2 is associated with a cluster of alleles that have a 2-fold increased risk for developing MS.^{41,42} While HLA DR2 is associated with an increased risk for MS, genetics alone does not fully explain the risk of developing MS because DRB1*1501 is neither sufficient nor necessary for the development of MS.

TABLE 2: Crude & Age-Adjusted Empiric Risks for Male Index Cases³⁸

Relationship to Index Case	Proportion Affected	Crude Risk (%) ($\pm 95\%$ Intervals)	Age-Adjusted Risk (%) ($\pm 95\%$ Confidence Intervals)
Mother	7/184	3.80 \pm 1.41	3.84 \pm 1.42
Father	1/128	0.78 \pm 0.78	0.79 \pm 0.79
Parent	8/312	2.56 \pm 0.90	2.59 \pm 0.90
Daughter	2/223	0.90 \pm 0.63	5.13 \pm 3.53
Son	0/248	—	0.00 \pm 1.49
Child	2/471	0.43 \pm 0.30	2.47 \pm 1.72
Sister	9/340	2.65 \pm 0.87	3.46 \pm 1.14
Brother	10/326	3.07 \pm 0.96	4.15 \pm 1.28
Sibling	19/666	2.85 \pm 0.65	3.81 \pm 0.86
Aunt	10/310	3.23 \pm 1.00	3.28 \pm 1.02
Uncle	5/250	2.00 \pm 0.89	2.05 \pm 0.91
Aunt/Uncle	15/560	2.68 \pm 0.68	2.68 \pm 0.68
Niece	3/514	0.62 \pm 0.36	3.06 \pm 1.74
Nephew	0/486	—	—
Niece/Nephew	3/1000	0.30 \pm 0.17	1.47 \pm 0.84
Maternal first cousin	2/377	0.53 \pm 0.37	0.89 \pm 0.63
Paternal first cousin	5/418	1.20 \pm 0.53	2.14 \pm 0.95
First cousin	7/795	0.88 \pm 0.33	1.53 \pm 0.57

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TABLE 3: Crude & Age-Adjusted Empiric Risks for Female Index Cases³⁸

Relationship to Index Case	Proportion Affected	Crude Risk (%) ($\pm 95\%$ Intervals)	Age-Adjusted Risk (%) ($\pm 95\%$ Confidence Intervals)
Mother	14/383	3.66 \pm 0.96	3.71 \pm 0.97
Father	6/303	1.98 \pm 0.80	2.00 \pm 0.81
Parent	20/686	2.92 \pm 0.64	2.95 \pm 0.65
Daughter	5/386	1.29 \pm 0.57	4.96 \pm 2.17
Son	0/411	—	0.00 \pm 0.90
Child	5/797	0.63 \pm 0.28	2.58 \pm 1.14
Sister	25/608	4.11 \pm 0.81	5.65 \pm 1.10
Brother	10/612	1.63 \pm 0.51	2.27 \pm 0.71
Sibling	35/1220	2.87 \pm 0.48	3.97 \pm 0.66
Aunt	15/674	1.84 \pm 0.47	1.88 \pm 0.48
Uncle	8/817	1.19 \pm 0.42	1.22 \pm 0.43
Aunt/Uncle	23/1491	1.54 \pm 0.32	1.59 \pm 0.33
Niece	5/875	0.57 \pm 0.26	2.70 \pm 1.19
Nephew	2/914	0.22 \pm 0.16	1.02 \pm 0.71
Niece/Nephew	7/1789	0.39 \pm 0.15	1.83 \pm 0.69
Maternal first cousin	15/1339	1.12 \pm 0.29	1.93 \pm 0.49
Paternal first cousin	19/1008	1.89 \pm 0.43	2.89 \pm 0.65
First cousin	34/2347	1.45 \pm 0.25	2.37 \pm 0.40

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Several HLA haplotypes now have been associated with both MS susceptibility and protection and may play a key role in the geographic and demographic distribution of the disease. Genome wide and replication studies show the involvement of other genes in the risk of developing MS, including interleukin (IL) receptor genes IL-2Ra and IL-7Ra, tumor necrosis factor receptor superfamily member 1A (TNFRSF1A), interferon regulatory factor 8 (IRF8), CD58, and CD6.^{35,43}

Migration studies also support a role for genetic factors in the development of MS.⁴⁴ African and Asian immigrants to North America generally retain their lower risk of MS²⁹; however, there may be some increased risk in this group due to a genetic mixture with Caucasians after 1 or 2 generations.

Genetic factors play a key role in not only the susceptibility to MS but also may be involved in disease progression. For example, there may be important genetic elements involved in an individual's ability to repair myelin, preserve axonal function, and adapt nervous system functions when areas of the CNS are permanently damaged.

Environmental Factors

Geography

Due to the widely varied prevalence of MS around the world, research suggests that environmental factors may be acting on genetically susceptible individuals.⁴⁵ Genetics alone fail to address the variation of MS risk observed among people who migrate to areas of high or low MS prevalence.^{46,47} Several studies also have suggested that some populations change their risk of developing MS, depending on their age at migration.⁴⁷⁻⁴⁹ Examples include African and West Indies immigrants to the United Kingdom having a higher risk of MS in the second generation.⁵⁰ Migrants from high- to low-risk areas retain the risk of their birth place if they are at least 15 years old when they move.⁴⁸ Those moving from low- to high-risk areas have a greater susceptibility to MS if they move between the ages of 11-45 years.⁴⁸ Recent interpretations of these observations suggest that individuals born in low-risk areas may benefit from a type of long-lasting protection not transmitted to their children.⁵¹

Investigators have explored both noninfectious (eg, sunlight, cigarette smoking) and infectious (eg, Epstein-Barr virus [EBV]) environmental factors to explain patterns of geographic variation in cases of MS.^{51,52}

Noninfectious Agents: Sunlight Exposure and Vitamin D Status

One of the strongest links between latitude and correlating MS risk is exposure to sunlight and vitamin D.⁵² A study among US veterans found that the average annual hours of sunshine and the average December daily solar radiation at their place of birth were strongly and inversely correlated with the presence of MS.⁵³ Similar results were obtained in Australia^{54,55} and among immigrants to Israel.⁵⁶ A link between sunlight radiation and reduced MS risk was supported further by an inverse correlation in Switzerland⁵⁷ between MS prevalence and altitude, which also is a marker of sunlight intensity. Studies now indicate that vitamin D is the mediator of the sunlight effect in MS risk.³⁵ Research has demonstrated a reduction in the risk of developing MS in subjects taking vitamin D supplementation or in those with high serum concentrations of 25-hydroxycholecalciferol.³⁵

Infectious Agents

Historically, researchers have studied the roles of various infectious agents, including bacteria and viruses,²¹ in triggering the onset of MS. Of these agents, EBV, which causes infectious mononucleosis, has attracted the most attention. Studies show the risk of developing MS is about 10 times greater among individuals who experienced an undiagnosed EBV infection in childhood than those who did not. This risk increases at least 20-fold among individuals who developed clinical mononucleosis. Although EBV is not present within MS lesions on a pathology exam, investigators propose several hypotheses about how EBV may initiate a mechanism that increases the risk of MS without actually attacking the CNS directly.^{51,58} These infectious agents may be ubiquitous, and the timing of infection, as well as underlying genetic susceptibility may result in a cascade of events ultimately leading to MS.

Gender

Studies demonstrate women are more susceptible to develop MS during puberty, which has led investigators to assume that female hormones play a role in the inflammatory, neurodegenerative, and neuroreparative cascade of MS.⁵⁹ Research also indicates hormonal changes (eg, during menstrual cycles and in the postpartum period) are linked to acute relapses in MS.

While some observations have suggested women have a better prognosis than men,⁶⁰⁻⁶² a more recent study found that,

although men may progress faster through the forms of MS, both genders ultimately had the same degree of disability at the same age. Therefore, gender is not associated with worsened disease outcome.⁶³

Age

Some studies suggest a younger age of onset is associated with better prognosis and an older age with a worse prognosis, although the reasons for this are unclear.^{60,64-67}

Race

Recent studies indicate an effect of race on MS disease severity⁶⁸ and rate of disease progression. Although MS occurs in all ethnic groups, it is rare in native Africans but not uncommon among African Americans. In MS patients with African ancestry, studies show earlier and more disabling symptoms with a higher risk of cane dependency, a shorter time to cane use, and a shorter duration from symptom onset to diagnosis. Other studies in African Americans with MS showed that both MRI indicators of disease (such as volume of T1 hypointense and T2 hyperintense lesions) and functional abilities (such as impaired hand function as well as gait, vision, and cognition) are more severe compared with Caucasian Americans.⁶⁸ The reasons for these racial differences currently are under investigation.

Month of Birth

Recent evidence suggests that the risk of developing MS may be related to the month of birth, and this appears to be related to ultraviolet (UV) exposure effect. In one study, the risk of developing MS in the northern hemisphere was increased in individuals born in May (9% higher than expected) compared with those born in November (8.5% lower than expected); other studies indicate that patients with MS carrying HLA DRB1*1501 had a higher number of April births.⁶⁹

Seasonality of Subclinical Disease Activity

New study data demonstrated a seasonal pattern in subclinical disease activity in MS patients, with more lesions appearing on MRI scans March through August compared with the rest of the year. This study also showed that warmer temperatures and solar radiation were linked to disease activity.⁷⁰

Smoking Status

Evidence is emerging that smoking tobacco is associated

with increased risk of developing MS and is dose dependent. Further, there now is strong evidence that smoking promotes both clinical and radiological MS disease progression.⁷¹ Smoking cessation may prove important in the future prevention of MS.³⁵

5 PATHOPHYSIOLOGY

MS TERMINOLOGY

The following terms are used throughout this primer; definitions are provided here as a reference.⁷²⁻⁷⁵

Central Nervous System: The nervous system is composed of the peripheral nervous system and the central nervous system. The CNS includes the brain and spinal cord.

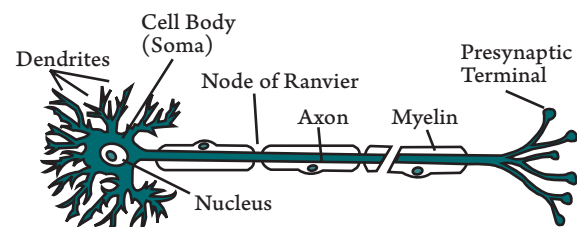
Neurons, the basic nerve cell unit of the CNS, are composed of a cell body and an elongated process called an axon (**Figure 2**). They interpret and transmit information.

Axons are long, branched processes of the neuronal cell body that conduct efferent nerve impulses away from the cell body.

Oligodendrocytes are myelin-producing neuroglia of the CNS.

Myelin is a white matter substance composed of phospholipid proteins forming a fatty sheath around the axons of CNS neurons (peripheral axons are not affected in MS). The sheath coats, protects, and insulates the neuronal axons. Acting as an electrical insulator in myelinated nerve fibers, the myelin sheath is divided into sections called internodes, which are separated from each other by Nodes of Ranvier (**Figure 2**).

FIGURE 2: A Neuron



Nodes of Ranvier are nodal spaces in the myelin sheath that play an important role in allowing rapid nerve impulse transmission along the axon by salutatory conduction within the CNS. The nodes are approximately 2 μm in length and are set at 1 mm intervals along the axonal shaft.

Action Potential Propagation (APP): The propagation of an action potential (nerve impulse) along a nerve fiber requires the activation of the sodium and potassium ion channels. Myelinated axons have voltage-gated sodium and potassium ion channels located only at the Nodes of Ranvier.

Saltatory Conduction: In the CNS, myelinated neurons transmit nerve impulses as follows:

- Action potentials (AP) jump from node to node. Studies show this stepwise conduction of the AP increases the velocity of nerve impulse transmission compared with nonmyelinated fibers. Removing or damaging the myelin sheath causes impulse transmission to slow down or even arrest, causing disability.⁷⁵

Demyelination: The proteins in myelin may be targeted and destroyed in acquired autoimmune diseases, such as MS, or in hereditary conditions, such as leukodystrophies. In demyelinating diseases, damaged myelin peels away from the nerve axons. The unprotected and uninsulated axonal fibers cannot conduct nerve impulses effectively, which results in distorted communications between the brain and body, producing neurologic symptoms.

Blood-Brain Barrier (BBB): The vascular endothelium lining the blood vessels of the brain forms a protective barrier between the systemic circulation and the brain parenchyma. This allows metabolic function while also helping to protect the brain from blood-borne infections, such as sepsis or meningitis, and immunological factors. Breaches of the BBB can result in serious injury to brain tissue.

Immunopathology and neuropathology are the 2 contributors to the pathophysiology of MS:

IMMUNOPATHOLOGY OF MS

Although the exact cause of MS is unknown, researchers have proposed that activation of an autoimmune cascade initiates disease processes and leads to neurologic damage

and symptoms of MS. The immunopathological cascade is thought to be triggered by both:

1. Cell-mediated processes: T-cell functions
2. Humoral and antibody-mediated processes: B-cell functions

1. Cell-Mediated Immunity: T-Cell Functions

As clearly shown in animal models, auto-reactive T lymphocytes are important in the development of demyelinating lesions within the CNS. In MS, up-regulation of adhesion molecules on vascular endothelial cells of the BBB allows peripherally activated T cells to exit the systemic circulation, cross the BBB, and penetrate the brain parenchyma. In addition, T-cell penetration of the CNS is enhanced by increased activity of proteinases responsible for the breakdown of extracellular matrix material.

Within the CNS, activated T cells proliferate and secrete one of the following series of cytokines:

- **Proinflammatory cytokine repertoire** in which T helper (Th)1-type cells secrete tumor necrosis factor (TNF)- α , IFN gamma, IL-17, and IL-22. These substances enhance macrophage and microglial (CNS macrophage) activity that directly injures myelin and oligodendroglia cells. They also increase the permeability of the BBB, allowing other cells access to the CNS.⁷⁶
- **Anti-inflammatory cytokine repertoire** in which Th2 cells secrete transforming growth factor (TGF)- β , IL-4, IL-5, and IL-10. These substances may play an immunoregulatory role in the CNS and attenuate damage to myelin and axons.

In addition, activated myelin-specific cytotoxic (CD8+) T cells are believed to play an important role in MS pathogenesis by directly damaging oligodendrocytes and myelin and can lyse neurons in the presence of IFN gamma.

In MS patients, regulatory T cells (Tregs) appear to have reduced functionality, which allows the activation, proliferation, and function of CD4+ Th cells and cytotoxic CD8+ cells that enhances the inflammatory processes.⁷⁷

2. Humoral and Antibody-Mediated Immunity: B-Cell Functions

Research shows that clonally expanded B cells and lympho-

cytes that produce antibodies are present in MS lesions and in the CSF of MS patients. Data suggest that B cells may play an important role in the pathogenesis of MS through specific myelin autoantibody production that may cause demyelination and activate CNS macrophages and microglial cells. In most patients with MS, immunoglobulins synthesized intrathecally are detected in the CSF, and testing for these antibodies remains one of the most specific laboratory diagnostic tests for MS.⁷⁸

Within the CNS, B cells may be activated by T cells associated with an antigenic substance. A theoretical mechanism for an antibody-mediated immunological process is that opsonization of an autoimmune target (such as myelin fragments or peptides secreted by infectious agents) causes damage to the target, promoting macrophage-mediated phagocytosis and activating the complement membrane. This process opens pores in myelin membranes, enhancing the susceptibility of the myelin sheath to the autoimmune process. Studies suggest that targeting antibody production may be an effective means of treating relapsing as well as progressing MS patients.

NEUROPATHOLOGY OF MS

For nearly 150 years, MS has been described as an episodic disorder with discrete areas of inflammatory damage to the myelin within the CNS. More recent evidence suggests that MS is a widespread, even global, disorder of myelin not only within the white matter but also within the gray matter; in addition, axonal damage is ongoing from the earliest stages of illness.

The pathophysiologic hallmarks of MS are demyelination, axonal injury, transection, microscopic abnormalities on the pathology exam in normal-appearing brain tissue, MS lesions on the pathology exam, and plaques in the white and gray matter of the brain tissue on MRI.

Demyelination occurs when the phospholipid sheath surrounding CNS axons is damaged and stripped away, resulting in slow, disordered, or arrested nerve conduction and subsequent neurologic dysfunction.

Axonal Injury: Although MS predominantly targets CNS myelin, attention recently has focused on axonal pathology. New data confirm axonal damage occurs and may be more widespread than previously thought.³⁷ Axonal loss now is thought to be a major determinant of progressive, long-

term, and permanent disability in MS.³⁷ New microscopic techniques used in examining pathology specimens of MS lesions demonstrate that axons are not only damaged in early demyelination but also may be transected.⁷⁹

Studies from 2002 and 2003 showed recovery from MS relapses is related to the ability of the nervous system to adapt and recruit neuronal networks to restore neurologic function.⁸⁰ However, researchers suggested that the ability for the CNS to recuperate function in this manner is finite, and repeated relapses with increased axonal damage over time will diminish this adaptive mechanism, leading to accumulated disability.⁸⁰

Research using new scanning technologies has identified biomarkers, such as N-acetyl aspartate (NAA), for neuronal integrity and function. Low or abnormal levels of NAA detected on MRS or MTI scanning indicate axonal pathology and have been detected in patients with MS, even at early stages of disease.⁸¹ As a reduction in NAA appears to be an indication of axonal loss, since the vast majority of NAA lies within neurons, this and other choline-containing compounds are being investigated as clinical tools for monitoring MS.

New research using the above techniques in MS patients shows abnormalities exist within both inflammatory demyelinating lesions and normal-appearing white matter. This indicates that diffuse axonal loss may occur separately from discrete pathological lesions,⁸² and this has triggered current research in clinically silent axonal loss.

Microscopic Abnormalities of Normal-Appearing White Matter: In some patients with MS, conventional MRI techniques, which can demonstrate typical lesions, may fail to show abnormalities in normal-appearing white matter. However, further imaging using newer technologies, such as MRS and MTI scanning, reveals that abnormalities exist in normal-appearing white matter.⁸³

MS Lesions: Lucchinetti and colleagues described 4 distinct pathological patterns of MS lesions based on their large series of biopsy and autopsy specimens.⁸⁴ All 4 patterns are characterized by T-cell- and macrophage-mediated inflammation:

- **Pattern I** is characterized by predominant T lymphocyte infiltration and macrophage-mediated demyelination.
- **Pattern II** resembles Pattern I but is distinguished by

a prominent humoral component with deposition of complement and immunoglobulin G (IgG). In both patterns I and II, lesions appear to have potential for remyelination, as seen in thinly remyelinated old lesions.

- **Pattern III** is characterized by a severe loss of oligodendrocytes by apoptosis and a selective loss of myelin-associated glycoprotein with preservation of other myelin proteins.
- **Pattern IV** demonstrates oligodendroglia death and is quite rare.

Due to the selective nature of MS patients who undergo autopsy and biopsy of lesions, these patterns may not be representative of all MS patients.

Imaging shows that both acute and chronic lesions are seen within the same patient many years after initial disease presentation, demonstrating the dynamic nature of the illness. Over time, lesions have less inflammation and more evidence of axonal loss and gliotic scarring. Currently, no therapy is available that will reverse these degenerative processes.

MS Plaques: Characteristic MS plaques on MRI represent areas of scarring and CNS damage. They are formed by the following processes²²:

- Immune engagement
- Acute inflammation injury of axons and glia
- Recovery of function and structural repair
- Post-inflammatory gliosis and neurodegeneration

Due to the wide clinical variations in MS, researchers consider it possible that distinct pathological subtypes exist and that MS is not homogenous in pathology but, instead, is a heterogeneous disease.¹⁹

6 CLINICAL Courses

The natural history of MS typically involves relapse (acute neurologic events consistent with demyelination) and remission (at least a partial recovery from the acute episode). Over time, with progressive disease and repeated relapses, neurologic damage accumulates and leads to permanent irreversible physical and cognitive disability. In 1989, Weinshenker et al published a long-term natural history study of patients with MS followed from 1972 to 1984. They found that frequent relapses early in the course of disease were associated with increased long-term disability.¹⁹

CLINICALLY ISOLATED SYNDROME

A CIS is an acute clinical and neurologic event indicative of MS, not accompanied by any other symptoms, lasting ≥ 24 hours, and caused by inflammation/demyelination in 1 (monofocal) or more (multifocal) sites in the CNS.⁸⁵ It often is associated with silent lesions on MRI. A CIS may present in a variety of ways; optic neuritis, brainstem dysfunction, or spinal cord syndrome are the most common signs.^{32,86,87} Up to 90% of patients with MS initially present with a CIS.⁸⁸ Patients presenting with a CIS suggestive of MS who also have lesions on baseline MRI are at a high risk of developing MS. These patients usually develop RRMS and then secondary progressive MS (SPMS).^{32,86,89}

Studies demonstrate that approximately two-thirds of CIS patients at presentation have multiple, clinically silent brain lesions on baseline MRI typical of those seen in patients with MS, confirming that subclinical disease activity predates the initial clinical event. CIS patients with baseline MRI lesions have a 50%-98% risk of being diagnosed with MS in the future compared with a $< 25\%$ risk in those with no detectable baseline lesions.⁹⁰⁻⁹³

However, the occurrence of a CIS does not necessarily mean the patient has or will develop MS but indicates an increased risk for subsequent development of MS in the future. A definite diagnosis of MS is established based on clinical criteria, almost always in combination with MRI findings.

CIS patients with the following characteristics have a higher risk for developing MS:

- a. Patients under the age of 30
- b. Presence of high-activity monofocal lesions on MRI
- c. History of steroid treatment at the onset of symptoms
- d. Production of intrathecal immunoglobulin and presence of oligoclonal bands on CSF analysis^{94,95}

The lesion load on T2-weighted baseline MRI is a particularly strong predictor of conversion to MS.⁹⁶ In 85%-90% of MS patients, a CIS represents the initial attack of the disease; in up to 80% of these patients with a CIS, MRI lesions provide evidence of prior clinically silent disease activity. Two or more lesions appearing on an MRI in a patient with a CIS predicts an 85% rate of subsequent attacks and development of MS.

DEFINITE MS

Several sets of diagnostic criteria for MS have been proposed over the last decade; however, the most widely used and validated are the McDonald 2005 diagnostic criteria. According to the McDonald 2005 criteria, a diagnosis of RRMS requires at least 1 episode of neurologic dysfunction consistent with inflammation and demyelination lasting ≥ 24 hours that occurs in the absence of fever or infection and is accompanied by objective evidence of CNS lesions disseminated in space (DIS) and time (DIT). DIS may be demonstrated by 2 anatomically distinct CNS lesions consistent with demyelination or a focal lesion plus various combinations of MRI, CSF, and evoked potential findings. In the absence of 2 clinical attacks separated by more than 30 days, DIT may be demonstrated by subclinical disease evolution on MRI.⁹⁷

MS CLINICAL SUBTYPES

Multiple sclerosis is classified according to the frequency and severity of neurologic symptoms, the ability of the CNS to recover, and the accumulation of damage. There are 4 main subtypes of MS: relapsing-remitting, secondary progressive, primary progressive (PPMS), and progressive relapsing (PRMS).⁹⁸

Relapsing-Remitting MS

RRMS is the most common form of MS, accounting for up to 85% of patients at the time of initial diagnosis. Typically, patients with RRMS have clearly defined acute attacks (relapses) of neurologic symptoms followed by periods

of symptomatic quiescence (remissions), with a stable course between relapses. During episodes of relapse, acute symptoms typically develop over several days, peak after 1 to 2 weeks, and then gradually subside over the next several weeks or months, although some symptoms may persist indefinitely. Studies show that recovery from acute relapses is variable and may be incomplete with persistent disease activity on MRI even during remission phases.¹⁸

In more than 50% of patients with RRMS, the steadily progressive clinical deterioration persists for approximately 10 to 15 years.³¹ Natural-history studies have indicated that after 10 years, 50% of untreated RRMS patients will have developed SPMS, and after 25 years, approximately 90% will have developed SPMS.³¹

Secondary Progressive MS

SPMS is the second phase in the natural evolution from RRMS and represents the progressive course of neurodegenerative disease. After years of nerve and muscle deterioration caused by earlier acute relapses followed by remissions and plateaus, the intermittent remissions become less frequent and usually are replaced by a steady decline of neurologic function over months or years. Most of these individuals will develop diminished mobility and require a walking aid or wheelchair. Clinical relapses still can occur during SPMS, usually during the early transitioning period from RRMS to SPMS.^{98,99} Treatment of MS at the SPMS stage of the disease has been found to be less effective than treatment initiated during the relapsing stage of disease.

Primary Progressive MS

Approximately 10%-15% of patients with MS present with PPMS, which is characterized by disease progression and accumulating disability from the time of disease onset without clearly defined relapses or remissions. Occasionally, PPMS disease activity plateaus, and minor improvement is possible. Some PPMS patients may plateau or stabilize for an extended period of time.¹⁰⁰ Patients with PPMS tend to be older than the average MS patient at the time of diagnosis, and a higher proportion are men.¹⁰¹

Progressive Relapsing MS

PRMS, the rarest form of MS, is characterized by a steady decline of neurologic function from the onset interspersed with brief periods of acute exacerbations of symptoms.⁹⁸

MS VARIANTS

Other rare CNS disorders sometimes classified as MS variants include:

Neuromyelitis optica (NMO)– a necrotizing, inflammatory, demyelinating disorder targeting the spinal cord and optic nerves that involves a humoral immune attack against aquaporin 4, a BBB antigen.

Distinct pathology findings, MRI, and CSF appearance distinguishes NMO from typical MS. The common presentation of NMO includes:

- Recurrent optic neuritis and acute myelitis
- Spinal cord MRI showing contiguous lesions extending over at least 3 or more vertebral segments
- Cranial MRI usually showing lesions in the hypothalamic and periventricular regions
- Anti-aquaporin 4 IgG is detectable on laboratory testing (76% sensitivity, 94% specificity)
- CSF findings showing increased protein, often greater than 100 mg/dL, with pleocytosis and neutrophil predominance, but it is unusual to see oligoclonal bands

Clinical features include a monophasic acute presentation in 20% of patients and relapsing attacks in 80% of patients. The clinical outcome often is poor, with respiratory failure and ventilator dependency.¹⁰² Sixty-one percent of patients have onset after age 35, and there is racial predilection for non-Caucasians.

Acute disseminated encephalomyelitis (ADEM) is an acute, postinfectious autoimmune attack involving the CNS that can lead to diffuse demyelination, usually affecting children and young adults. Clinical signs include encephalopathy with multifocal neurologic signs and large MRI lesions, mainly involving the white matter. There can be repeated attacks in 10%-20% of cases. Prognosis for recovery is usually good unless a hemorrhagic component is present.¹⁰³

7 MS Symptoms

The symptoms of MS are highly variable and reflect disruption of myelinated axons within the CNS. The initial symptoms often are forgotten or go unrecognized as neurologic in origin. Recall and selection bias makes it difficult to know exactly which symptoms initially present most often and reappear. They can be experienced either as isolated features or in combination with another. Symptoms often present in a subacute fashion over days to weeks, but some experience acute presentations and others have such insidious, subtle, and mild features that no medical evaluation is sought for months or even years. Most acute symptoms last an average of 6 to 12 weeks, and 90% of patients will improve substantially within that time frame.

Although highly variable from patient to patient, and from relapse to relapse, the typical symptoms of MS are fatigue, depression, cognitive dysfunction, spasticity, pain, bladder dysfunction, bowel dysfunction, erectile dysfunction, and visual symptoms, such as unilateral visual loss and double vision. Other symptoms include tremor, ataxia, vertigo, weakness in one or more limbs, paroxysmal symptoms (cortical signs, seizures, aphasia, early dementia), extrapyramidal signs, sensory changes, movement disorders such as chorea, and gait disturbances.

Over time, many patients will experience features of MS believed to be more chronic, including bladder and bowel dysfunction, sexual problems, a diurnal pattern of fatigue, heat sensitivity (Uhthoff's phenomenon), and cognitive decline, although these symptoms also can occur in the acute phase of the disease. Some patients will present with fatigue or Uhthoff's phenomenon weeks to months before their first relapse. Uhthoff's phenomenon is a paroxysmal decrease in vision usually brought on by an increase in temperature or exercise that also can be associated with dysarthria and hypophonia. It occurs when there is a decrease in axonal conduction in partially demyelinated nerve fibers.¹⁰⁴ Younger patients may have symptoms seen almost exclusively in MS, including Lhermitte's sign (an electrical sensation down the spinal column and/or into the limbs typically with neck flexion), trigeminal neuralgia,

TABLE 4: Distribution of Patients (%) by Initial Symptoms According to Age at Onset of Multiple Sclerosis Among 1096 Patients³¹

	Age at Onset of Multiple Sclerosis (years)				
	<20	20-29	30-39	40-49	≥50
Optic neuritis	23	23	13	9	6
Diplopia/vertigo	18	12	11	17	13
Acute motor	6	7	7	3	4
Insidious motor	4	6	14	31	47
Balance/limb ataxia	14	11	15	13	11
Sensory	46	52	44	33	32

facial myokymia, and other paroxysmal symptoms, including tonic spasms (Tables 4³¹ and 5¹⁰⁵).

Neurologic symptoms often are episodic and followed, in many cases, by progressive deficits and gradual increased disability.^{22,102} The development of neurologic impairment occurs in a step-wise fashion and is quite different in its temporal course compared with the more typical scenario of patients becoming disabled decades after their initial presentation. One exception to this typical presentation is blindness due to MS. Patients who become permanently visually impaired often have had previous episodes of optic neuritis with poor recovery. Only a small percentage of patients develop progressive visual loss over time. Consensus guidelines from the American Academy of Neurology (AAN) and the NMSS advocate starting DMT as soon as a diagnosis of MS has been made to help prevent disease progression and delay the development of disability.²

Clinical manifestations and long-term neurologic damage may range from mild to severe in different individuals. However, the typical disease course involves cumulative and progressive disability over time. Statistics show that in most patients with MS, the mean duration of symptoms (eg, fatigue or pain) is 15 years, and approximately 30% of all patients with MS will need to use a wheelchair at some time in their disease course.³ In natural history studies, 50% of patients who had MS longer than 15 years progressed to a Kurtzke Expanded Disability Status Scale (EDSS) score of 6 (needing a cane, crutch, or brace to walk 100 meters with or without resting¹⁰⁶) or greater.²⁷

TABLE 5: Frequency of Symptoms in 301 Prevalent Patients in South Glamorgan Who Were Interviewed (%)¹⁰⁵

Symptoms	Ever?	At Onset?	At Prevalence?
Weakness	269 (89)	66 (22)	241 (80)
Sensory symptoms	263 (87)	103 (34)	219 (73)
Ataxia	248 (82)	32 (11)	218 (72)
Bladder symptoms	213 (71)	3 (1)	188 (62)
Fatigue	171 (57)	5 (2)	144 (48)
Cramps	156 (52)	2 (0.6)	133 (44)
Diplopia	155 (51)	25 (8)	77 (26)
Visual symptoms	148 (49)	38 (13)	98 (33)
Bowel symptoms	126 (44)	0 (0)	112 (37)
Dysarthria	110 (37)	2 (0.6)	74 (25)
Vertigo	107 (36)	13 (4.3)	57 (19)
Facial pain	106 (35)	5 (2)	42 (14)
Poor memory	96 (32)	1 (0.3)	91 (27)
Headache	90 (30)	6 (2)	51 (17)
Mental symptoms	68 (23)	1 (0.3)	49 (16)
Deafness	51 (17)	2 (0.6)	38 (13)
Facial weakness	48 (16)	4 (1)	15 (5)
Dysphagia	40 (13)	1 (0.3)	29 (10)
Sores	36 (12)	0 (0)	21 (7)
Blackout	32 (11)	2 (0.6)	12 (4)
Ageusia	17 (6)	1 (0.3)	5 (2)
Other	31 (10)	3 (1)	24 (8)

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MEASURING DISABILITY

Disability resulting from MS is measured using disability scales, such as the EDSS and the MS Functional Composite (MSFC), and these often are used as outcome measures in clinical trials. Using an ordinal scale of 1-10, the EDSS measures various functional system scores and ability to walk, with a high score indicating greater disability. Patients with an EDSS score of 8.5 or greater usually are unable to move their arms or legs. Although criticized for being an incomplete measure of disability in MS, at present the EDSS remains the most commonly used scale for researchers to gauge functional disability.³

The MSFC measures cognition, ambulation, and hand/arm function; a single composite score is derived from results of these 3 measures. Results are standardized with

the use of a reference population. A score of +1 is indicative of improvement by 1 standard deviation compared with the reference population. The MSFC has been demonstrated superior to the EDSS with regard to sensitivity, reliability, and statistical validity.^{89,107} Regardless, the EDSS remains the most commonly used disability assessment tool in MS patients.⁸⁰ Potential contributors to inaccurate results when using disability scales include variation in the frequency of clinical assessments and fluctuations in patients' disabilities due to relapse, illness, medication side effects, fatigue, depression, and cognitive function. Studies have demonstrated that increasing the time of follow-up and using clearly defined criteria in disability assessment measurements is important to obtain accurate information on treatment success or failure.⁸⁰

8 DIAGNOSING MS

Although MRI has greatly improved our ability to diagnose multiple sclerosis earlier, the initial diagnosis mainly remains clinical. There are several common presenting symptoms that increase the likelihood of having MS (**Table 6**). These symptoms usually are episodic, begin gradually, and slowly improve. However, the hallmark of diagnosis remains the demonstration of multiple lesions within different areas of the CNS, occurring at different times.

DIAGNOSTIC CRITERIA FOR MS

Several different research groups have proposed diagnostic criteria for MS, including those led by Poser, McDonald, and Swanton. The Poser criteria, one of the earliest formal criteria developed by Poser et al, were first published in 1983 and

TABLE 6: Common Presenting Symptoms of MS

- Loss of vision
- Diplopia
- Muscle weakness
- Bladder/bowel dysfunction and/or sexual difficulties
- Cognitive changes
- Fatigue
- Sensory symptoms, such as numbness or tingling
- Incomplete transverse myelitis
- Incoordination
- Gait difficulties
- Vertigo

required clinical evidence of 2 attacks disseminated in time and space.^{108,109}

More specific diagnostic criteria for MS were developed in 2001 by the International Panel on the Diagnosis of Multiple Sclerosis. Known as the 2001 McDonald criteria,⁹⁷ the initiative's goal was to facilitate a more reliable diagnosis of MS. Since then, the criteria have been shown to have good specificity and sensitivity and have been adopted by clinical neurologists worldwide. Most importantly, the 2001 criteria first incorporated MRI scanning into the scheme of detailed neurologic history, examination, and laboratory testing to assist in the diagnosis of MS.

In 2005, the panel reviewed new clinical evidence on MS and revised the McDonald criteria. The primary goals of the 2005 revised criteria were to establish the dissemination of lesions in time and space (**Table 7**⁹⁷), incorporate new imaging technology into the diagnosis of MS (**Table 8**⁹⁷), and assess the CSF for a diagnosis of PPMS.⁹⁷ Furthermore, the 2005 criteria classify signs and symptoms of MS as monofocal (a single lesion) or multifocal (more than one lesion).

According to the 2005 revised McDonald criteria, the essential requirements for a diagnosis of MS are:

- Objective clinical findings (**Table 9**⁹⁷, page 20)
- Evidence of dissemination of lesions in time and space

TABLE 7: Diagnosis of Multiple Sclerosis in Disease With Progression From Onset⁹⁷

Original McDonald Criteria	2005 Revisions
1. Positive CSF <i>and</i> 2. Dissemination in <i>space</i> by MRI evidence of ≥ 9 T2 brain lesions <i>or</i> • ≥ 2 cord lesions or 4-8 brain lesions and 1 cord lesion <i>or</i> • Positive VEP with 4-8 MRI lesions <i>or</i> • Positive VEP with < 4 brain lesions plus 1 cord lesion <i>and</i> 3. Dissemination in <i>time</i> by MRI <i>or</i> • Continued progression for 1 year	1. 1 year of disease progression (retrospectively or prospectively determined) 2. <i>Plus</i> 2 of the following: a. Positive brain MRI (9 T2 lesions or ≥ 4 T2 lesions with positive VEP) b. Positive spinal cord MRI (2 focal T2 lesions) c. Positive CSF ^a (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both)

^aMRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues and Tintore and coworkers.
 VEP=visual-evoked potential
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TABLE 8: Magnetic Resonance Imaging Criteria to Demonstrate Brain Abnormality and Demonstration of Dissemination in Space⁹⁷

Original McDonald Criteria	2005 Revisions
3 of the following:	3 of the following:
1. At least 1 Gd-enhancing lesion or 9 T2 hyperintense lesions if there is no Gd-enhancing lesion	1. At least 1 Gd-enhancing lesion or 9 T2 hyperintense lesions if there is no Gd-enhancing lesion
2. At least 1 infratentorial lesion	2. At least 1 infratentorial lesion
3. At least 1 juxtacortical lesion	3. At least 1 juxtacortical lesion
4. At least 3 periventricular lesions	4. At least 3 periventricular lesions
NOTE: 1 spinal cord lesion can substitute for 1 brain lesion	NOTE: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion; an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.

Based on data from Barkhof and colleagues and Tintore and coworkers.
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- Use of objective paraclinical laboratory findings, such as oligoclonal bands in the CSF
- Emphasis on specificity, rather than sensitivity, of testing
- Exclusion of other conditions and reliable differential diagnosis of MS

Note that in clinical situations where imaging, equipment, analysis, and interpretation of investigation results are not readily available or reliable, the criteria state that MS may still be reliably diagnosed on the basis of clinical findings.⁹⁷

Limitations of the McDonald Criteria

Studies showed that clinicians found the criteria to be a useful tool for diagnosing “classical” MS in a Caucasian adult of western European descent. However, the adequacy of diagnosing a CIS, or of accurately identifying early MS in subpopulations such as pediatric or non-Caucasian patients, is not covered by the criteria.

SWANTON CRITERIA

In 2006, Swanton et al proposed new MRI guidelines for the diagnosis of MS, and these criteria did not specify the requirement of a Gd-enhancing MRI lesion.¹¹⁰ In a study of CIS patients, the Swanton 2006 criteria demonstrated

higher sensitivity than the 2005 McDonald criteria (72% vs 60%) and similar specificity (about 90%). In 2009, MRI studies showed similar specificity of the revised 2005 McDonald criteria and Swanton criteria, with slightly greater (but non-significant) sensitivity and accuracy for the Swanton criteria.¹¹¹ Further studies are needed to assess the Swanton criteria more completely.

MAGNETIC IMAGING IN MS (MAGNIMS) CRITERIA

In 2007, MAGNIMS, a European multicenter collaborative research network specified DIS and DIT criteria and proposed a new diagnostic algorithm for MS based on MRI findings for CIS patients. The new MAGNIMS algorithm and criteria likely will have important implications in the clinical management of CIS patients in the future.¹¹²

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of MS is complex and involves the use of clinical, MRI, laboratory, and other paraclinical findings to exclude a wide range of other diseases and disorders that can mimic a clinical demyelinating event. The major differential diagnoses¹⁰² include:

- **Infectious diseases**, such as Lyme disease, syphilis, progressive multifocal leukoencephalopathy (PML), human T-lymphotrophic virus type 1 (HTLV1), or HIV
- **Inflammatory diseases**, such as systemic lupus erythematosus (SLE), Sjögren’s syndrome, vasculitis, sarcoidosis, or Behçet’s disease
- **Structural or anatomical disorders** including tumors
- **Psychiatric disorders** such as depression
- **Toxin exposure**
- **Vascular disorders** and events, such as cerebrovascular ischemic disease, arteriovenous malformations, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- **Metabolic disorders**, such as vitamin B12 deficiency, adrenoleukodystrophy, or mitochondrial disorders
- **Genetic disorders**, such as Friedreich’s ataxia, olivopontocerebellar atrophies, or hereditary spastic paraparesis
- **Neoplastic disease**
- **Other MS variants**

To differentiate MS from those diseases, the following laboratory tests are useful in clinical evaluation:

TABLE 9: 2005 Revisions to the McDonald Diagnostic Criteria for Multiple Sclerosis⁹⁷

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks ^a ; objective clinical evidence of ≥2 lesions	None ^b
≥2 attacks ^a ; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> • MRI^c <i>or</i> • ≥2 MRI-detected lesions consistent with MS plus positive CSF^d <i>or</i> • Await further clinical attack^a implicating a different site
1 attack ^a ; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: <ul style="list-style-type: none"> • MRI^c <i>or</i> • Second clinical attack^a
1 attack ^a ; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by: <ul style="list-style-type: none"> • MRI^c <i>or</i> • ≥2 MRI-detected lesions consistent with MS plus positive CSF^d <i>and</i> Dissemination in time, demonstrated by: <ul style="list-style-type: none"> • MRI^c <i>or</i> • Second clinical attack^a
Insidious neurological progression suggestive of MS	1 year of disease progression (retrospectively or prospectively determined) <i>and</i> 2 of the following: <ol style="list-style-type: none"> Positive brain MRI (9 T2 lesions or ≤4 T2 lesions with positive VEP)^f Positive spinal cord MRI (2 focal T2 lesions) Positive CSF^d

If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is "not MS."

^aAn attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hours.

^bNo additional tests are required; however, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.

^cMRI demonstration of space dissemination must fulfill the criteria derived by Barkhof and colleagues and Tintore and coworkers.

^dPositive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index.

^eMRI demonstration of time dissemination must fulfill the criteria.

^fAbnormal VEP of the type seen in MS.

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Infectious Differential Diagnosis of MS

- Lyme titers, Elisa, and Western blot are particularly important in endemic areas
- Syphilis testing using the venereal disease research laboratory (VDRL) test
- Human T-lymphotropic virus type 1 test does not need to be performed routinely but would be indicated if there is clinical history of travel or residence in a tropical region
- HIV testing is appropriate, particularly with history of intravenous (IV) drug use, blood transfusion, and other risk factors for HIV/AIDS
- Complete blood count (CBC) with differential helps to identify any underlying infection and/or hematological disorders

Inflammatory Differential Diagnosis of MS

- Antinuclear antibodies
- Antiphospholipid antibodies
- Prothrombin time/partial thromboplastin time tests,

- particularly in women with history of unexplained clotting problems, deep vein thromboses, history of repeated spontaneous abortion, or other blood disorders
- Erythrocyte sedimentation rate (ESR)
- Rheumatoid factor
- Lupus profile to rule out collagen vascular disease that can mimic MS symptoms, such as systemic Lupus erythematosus, Sjögren's syndrome, and Behçet's disease
- Angiotensin converting enzyme if there is suspicion of neurosarcoidosis
- Anti-acetylcholine receptor antibodies should be obtained if the clinical picture is suggestive of myasthenia gravis
- Electrophysiologic testing may be helpful, particularly to rule out any radiculopathy or underlying peripheral neuropathy

Metabolic/Toxic Differential Diagnosis of MS

- Thyroid function profile
- Chemistry studies

- c. Vitamin B12 and folate searching for nutritional deficiencies should be obtained. Subacute combined degeneration can be seen. B12 deficiencies have been a concern with patients undergoing weight-reduction surgeries
- d. Vitamin D levels can be drawn to look for deficiency
- e. Very long chain fatty acid testing for adrenoleukodystrophy should be obtained, particularly in younger patients

Neuroimaging

Imaging of the spine and brain can rule out mass lesions in the brain, such as CNS lymphoma, and also can eliminate the presence of degenerative lesions in the spine, arteriovenous malformations, and spinocerebellar degeneration.

In 2008, Miller et al published proposed guidelines for the differential diagnosis of MS developed by the International Task Force.¹¹³ This useful clinical tool provides a clear definition of a CIS; categorizes clinical and paraclinical features of a CIS that are most typical of patients eventually diagnosed with MS as well as red flags (features compatible with MS but could occur in other diseases); provides specific consensus-based algorithms for the differential diagnosis of the 3 most common CIS presentations related to MS (optic neuritis, spinal cord, and brainstem-cerebellar syndromes); and offers a classification system and diagnostic criteria for idiopathic disorders of the CNS.¹¹³

DIAGNOSTIC TESTS FORMS

The following tests can be used to support a diagnosis of MS:

Cerebrospinal Fluid Analysis

The analysis of CSF is helpful in patients with atypical clinical presentations, vague clinical symptoms, and normal or nonspecific MRIs; it also can establish a diagnosis of PPMS. In patients with a CIS, CSF analysis in conjunction with MRI findings can improve the predictive accuracy for the development of MS.^{31,114-116} The CSF of an MS patient typically shows a lymphocytic pleocytosis, mild elevation in total protein, normal glucose, increased IgG index, and oligoclonal bands (OCB), indicating the activity of plasma cell clones secreting immunoglobulin. Two or more OCBs detected in the CSF that are not present in the serum drawn at the same time are considered abnormal; this is the most specific spinal fluid test for MS. The IgG index, which measures intrathecal production of IgG, is elevated in 70%-90% of patients with MS, although studies show it is a less sensi-

tive and specific test for MS than OCB detection.¹¹⁴ CSF abnormalities increase over time; therefore, generally the longer a patient has had the disease, the greater the sensitivity. However, OCBs and elevated IgG index are not specific to MS and may be seen in numerous other inflammatory and neurological disorders.¹¹⁴

Evoked Potential Testing

Evoked potential testing records low amplitude electrical signals from neurologic tissues in response to a stimulus. Evoked potential includes somatosensory evoked potentials, particularly of the lower extremities, visual evoked potentials, and brainstem auditory evoked potentials. These tests are helpful to document lesions disseminated in space and can provide objective evidence of demyelination. Latency prolongation suggests demyelination.¹¹⁷

Magnetic Resonance Imaging

MRI and other advanced imaging techniques can reveal progressive changes marked by active lesions, plaque formations, black holes, and cortical atrophy in the brain and spinal cord occurring in MS patients before, during, after, and between symptomatic episodes. Clinically asymptomatic episodes of neural damage can result in significant disability over time.¹⁹

MRI uses natural magnetic properties of the human body with radiofrequency waves and strong external magnetic fields (measured in tesla units) to produce detailed, noninvasive anatomical cross-sectional images of soft tissues in the human body.

The nuclei of hydrogen protons in human body fluids and fat tissue behave as small bar magnets revolving on a north-south axis and randomly aligning. When the human body is in a strong magnetic field, such as an MRI scanner, the hydrogen proton axis aligns uniformly and creates a magnetic vector oriented along the axis of the MRI scanner.¹¹⁸ Short bursts of radio waves are used to momentarily disorientate the protons from their alignment. As they return to their original alignment, they resonate and emit a radio signal creating images.

The intensity of the proton emission correlates with the number of hydrogen protons in a particular tissue. Tissues are examined in cross-sectional slices; because each tissue contains differing proportions of fat and water (and therefore

hydrogen protons), unique signal emissions on MRIs are produced, distinguishing tissue types.

Clinical MRI scanners contain magnets of different strengths, typically ranging from 0.5 to 3.0 tesla. A higher tesla range induces a stronger magnetic field producing increased detail on images. Research MRI scanners may have a tesla of 7.0 or even higher.

MRI techniques widely available in the United States include Gd-enhanced T1-weighted images, T2-weighted images, including fluid-attenuated inversion recovery (FLAIR), and noncontrast T1-weighted images. These MRI techniques are highly sensitive in detecting typical MS lesions, may provide an assessment of inflammatory activity and lesion load, and are valuable tools in the diagnosis of MS as well as in the monitoring of disease activity, progression, and treatment response.

MRI detects and characterizes the location, size, volume, and morphology of brain and spinal cord lesions in CIS and MS patients. Typical findings include enhancing lesions on Gd-enhanced T1-weighted imaging, hyperintense lesions on T2-weighted imaging, and hypointense lesions including chronic hypointense lesions (black holes) on noncontrast, T1-weighted imaging.^{91,119}

Conventional MRI has limited specificity for pathological findings of MS (including edema, demyelination, axonal loss, and remyelination) and may be unable to detect and quantify the extent of damage in MS lesions and surrounding tissues. Studies in patients with RRMS show that inflammatory lesions in the CNS evolve continuously, with ongoing axonal damage/loss and tissue damage.¹²⁰ This is supported by the accumulation of T2 hyperintense lesions, T1 hypointense lesions, and brain atrophy as seen on MRI even during prolonged periods of clinical stability between relapses.

Advanced MRI techniques such as MRS, magnetization transfer ratio (MTR), and functional MRI (fMRI) may further elucidate ongoing axonal injury occurring early in the course of the disease, even in areas of normal-appearing white matter.^{83,121}

Significant advances in imaging technology in the last 20 years have enhanced clinicians' understanding of MS

pathology, diagnosis, progress, and prognosis.^{83,121} However, clinical changes in MS are not consistently related to MRI changes, and this is considered a limitation of cMRI.

ROLE OF MRI IN DIAGNOSTICS AND MONITORING

“MRI is the most important paraclinical measure for assessing and monitoring the pathologic changes implicated at the onset and progression of MS.”^{91,122} In conjunction with clinical evaluation, conventional MRI now is incorporated into diagnostic strategy for MS due to its unique sensitivity to demonstrate demyelinating lesion dissemination in space and time within the CNS.¹²³ However, MRI findings alone cannot be used to diagnose MS, and normal MRI findings do not necessarily exclude a diagnosis of MS.^{97,124}

The following conventional MRI imaging techniques are used in the diagnosis and monitoring of MS:

Noncontrast T1-Weighted MRI

Developed in the early 1990s, T1-weighted scanning was the first quantitative, volumetric imaging study used in MS. T1 images show acute MS lesions as hypointense (dark) areas due to edema of the damaged brain tissue in CNS white matter. Up to 70% of new T1 hypointense lesions resolve and become isointense over 6-12 months, with up to 80% of all lesions developing an isointense appearance. This may be a result of resolution of edema and possibly remyelination.¹²⁵⁻¹²⁹ Chronic MS lesions appear even darker and represent increased tissue destruction. Later in the disease, severe irreversibly destroyed areas of CNS tissue are seen as very dark sections on T1 imaging and are known as black holes.^{121,122}

Black Holes

In MS patients, black holes correlate with gliosis, demyelination, and axonal injury on pathology exams^{93,129,130} and are better predictors of progressive disability than inflammatory lesion measurement.¹³¹ Approximately 40% of all MS lesions evolve into black holes.¹³² Some studies indicate that in MS patients on DMTs, new or expanding black holes on T1-weighted imaging may represent a suboptimal treatment response and a need for change in therapy. Morgan et al demonstrated that patients with RRMS who had one or more Gd-enhancing lesions after a year of therapy showed an increase in the volume of black holes in the following 2 years. However,

patients who did not have new Gd-enhancing lesions did not have an increase in black hole volume,¹³³ and this may have implications for disease and treatment monitoring in MS.

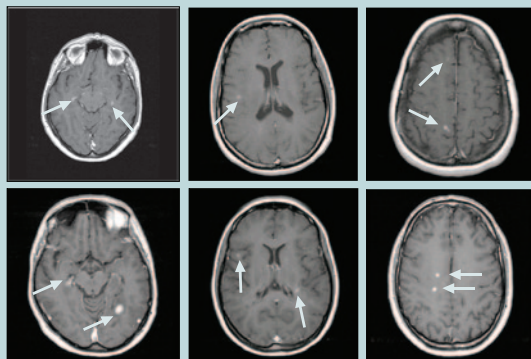
T1-Weighted Gd-Enhanced Imaging

Injecting MS patients with gadolinium, an IV contrast agent, at the time of imaging enhances areas of active inflammation and demyelination in the CNS. Lesions are enhanced when contrast leaks through disrupted junctions of vascular endothelium and subsequently accumulates in CNS tissues.

Initially, Gd-enhancing lesions usually are uniformly bright white small homogenous nodules on MRI, and these may progress to present as a ring-shaped enhancement lesions indicating more severe tissue damage (**Figure 3**).^{125,128} Gd-enhancing lesions provide a measure of CNS inflammation in currently or recently active lesions and may be used to distinguish active lesions from inactive ones. However, Gd enhancement does not provide information on tissue damage or the extent or severity of inflammatory activity and may correlate poorly with concurrent clinical disease activity.

Active enhancing lesions on MRI represent areas of disruption in the BBB, which on a pathology exam consist of CNS infiltrates of lymphocytes, macrophages, axonal injury, transection, and demyelination.^{86,89,107,131} Tissue edema appears as areas of hypointense, dark lesions on Gd-enhanced imaging. Other findings include brain atrophy, which increases as MS progresses. Gd imaging is a useful indication of new or expanding lesions, lesion load, brain atrophy, and neurologic disability.^{107,131}

FIGURE 3: Gadolinium-Enhancing Lesions



T2-Weighted MRI

On T2 scanning, MS patients demonstrate hyperintense bright lesions representing demyelination, edema, gliosis, or matrix destruction. Determining the presence and number of these lesions is the most frequently used imaging method to assess disease burden, known as the T2 lesion load.^{89,131,134}

FLAIR

FLAIR images demonstrate greater contrast between CSF and MS lesions. This technique is useful especially to identify periventricular lesions, which can be difficult to distinguish due to the brightness of CSF on scans.²⁶ FLAIR imaging with T2-weighted MRI demonstrates up to 3 times more lesions in periventricular neural tissue in and adjacent to the CSF fluid spaces than conventional T2 imaging.⁸⁹

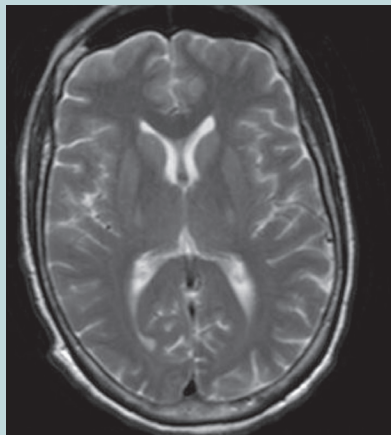
T2-Weighted Lesion Load

Brain MRI typically reveals T2 hyperintense lesions in the periventricular white matter, corpus callosum, centrum semiovale, juxtacortical regions, pons, floor of the fourth ventricle, cerebellar peduncles, or cerebellar hemispheres. In addition to the symptomatic lesion(s), brain MRI detects clinically silent lesions in 50%-80% of CIS patients. T2 hyperintense lesions usually are 3-15 mm in diameter, round or ovoid in shape, and clearly delineated.^{126,135,136} However, T2 hyperintense lesions are nonspecific and may represent edema, demyelination, axonal damage, matrix destruction, gliosis, and/or remyelination.^{126,127,137}

MS lesions vary in shape, size, and location. Demyelinating lesions typically are ovoid in shape, ranging from a few millimeters to greater than 1 centimeter in diameter. Lesions commonly are seen most in the periventricular tissue perpendicular to the lateral ventricles of the brain, known as Dawson's fingers (**Figure 4**, page 24).¹³⁸ Lesions also may be located in the corpus callosum, centrum ovale, or white matter tracts, such as the optic chiasm. Peripheral brain lesions are found in the cerebellum and cerebellar peduncle.^{109,138,139}

Disease activity and patients' response to treatments may be monitored using T2-weighted MRI scanning. Serial MRI scanning has been used to identify early inflammatory changes in MS and subsequently has played an important role in the development of the DMTs IFN beta and GA.

FIGURE 4: Dawson's Fingers



The lesion load recorded early in MS correlates with neurologic disability in the long term; however, as the disease progresses, the lesion load parameter becomes less accurate in prognostics due to a natural tendency for MS patients to produce fewer lesions later in the disease course.¹³¹ All patients with MS will continue to produce CNS lesions, regardless of DMT. After several years of therapy with IFN beta or GA, the lesion load will be reduced as compared with pretherapy.¹³¹ MS patients on first-line DMT who continue to have increasing lesion loads on T2-weighted MRI may have a suboptimal response to therapy or are experiencing treatment failure.^{131,140}

According to Cohen et al's 2004 study, patients on IFN beta therapy developed 2 new lesions a year compared with those on placebo who developed 4-5 new lesions per year. This data has been used to identify suboptimal treatment response or treatment failure. If patients on DMT develop 2 or fewer new lesions per year on therapy, they are considered treatment responsive. However, if patients develop more than 2 new lesions per year, they need treatment re-evaluation and optimization.¹³¹

ADVANCED IMAGING TECHNIQUES

Nonconventional (advanced) quantitative MRI techniques, including MTI, DTI, and MRS, may be more sensitive and specific for assessing and monitoring disease activity in MS and CIS patients compared with conventional MRI.^{123,125,137,141-152} Advanced MRI techniques may provide

detailed insight into the pathogenesis and the degenerative and reparative processes involved in MS in the future.¹²³

Proton MRS

MRS provides measurement of brain chemicals or biomarkers in vivo and may be useful in the long-term follow-up of patients with MS.^{2,26} MRS can detect markers of choline-containing compounds, such as creatine, phosphocreatine, lactate, NAA, and myoinositol, which indicate neuronal number and function.

Low levels of NAA on MRS scanning correlate with axonal injury¹⁵³ as well as reversible and irreversible axonal transection^{79,154}; it also can demonstrate demyelinating lesions and axonal damage not otherwise seen on conventional MRI scanning.^{26,155} Although preliminary studies show that the levels of NAA detected on MRS correlate with disability in MS, the use of these biomarkers still is under investigation.

DWI

DWI techniques involve the analysis of microstructural characteristics and direction of water diffusion in tissue and enables identification of early-stage lesions and neurologic damage.¹⁵⁶

fMRI

fMRI uses MRI to measure metabolic changes in active parts of the brain.

DTI

DTI determines the direction of water diffusion in cell structures, such as neuronal axons, and identifies changes in the structure of CNS white matter.

MTI and MTR

MTI/MTR measures macromolecular density, which demonstrates the capacity of molecules within brain tissue to exchange magnetization with water molecules, and reduction in this capacity reflects damage to myelin or axonal membranes.¹⁵⁷

Spinal Cord Imaging in MS

Spinal cord imaging is used to support a diagnosis of MS in patients with symptoms of spinal involvement, MS symptoms with normal cerebral MRI, or older patients with age-related changes in T2-weighted MRI. In MS patients with spinal involvement, spinal cord imaging may show focal atrophy, cord swelling, asymmetric or partial cord

thickness involvement, and involvement of short vertebral segments (Figure 5).¹⁰²

BRAIN ATROPHY ON IMAGING AND MS

For the first time in the 1990s, MRI revealed a loss of brain and spinal cord volume (parenchymal atrophy) occurring in patients with RRMS (Figure 6)¹⁵⁸ and progressing during clinically asymptomatic episodes. This parenchymal atrophy subsequently was found to be a key in predicting progressive decline of physical and cognitive function in patients with early RRMS.^{26,155} Cerebral atrophy now has become an important outcome measurement for clinical trials involving MS patients.

Brain atrophy represents a reliable predictor of neurologic dysfunction, physical disability, cognitive decline, and quality of life for patients with MS.^{89,154,159} However, because monitoring cerebral atrophy requires regular serial MRI scanning, which may not be possible in clinical practice, the current recommendation is that brain atrophy should be assessed along with clinical symptoms and measures of disability using appropriate scales.

NORMAL-APPEARING WHITE MATTER ON CNS IMAGING

Although conventional MRI may demonstrate normal-appearing white matter in the brains of patients with MS, newer imaging studies with MTI or MRS have shown changes in CNS tissue, indicating inflammation and damage even before Gd-enhanced MRI can detect a lesion.^{26,32,89,153} This evidence has become increasingly important in MS management, as research now calls for earlier diagnosis and treatment in order to prevent disease progression and delay long-term disability.

MRI PROTOCOLS

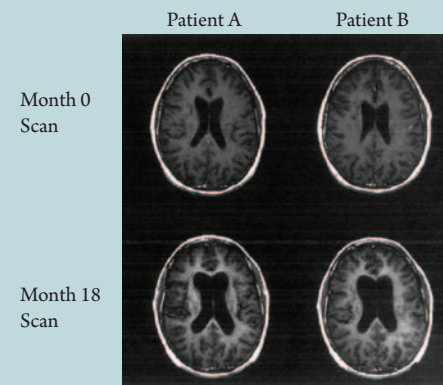
Standardized protocols for the use of cMRI in the diagnosis and follow-up of MS patients have been proposed by the Consortium of MS Centers (CMSC) and the International Panel of MS Experts,¹⁶⁰ and these include:

- A brain MRI with Gd is recommended for the follow-up of MS patients before starting or modifying therapy in order to evaluate an unexpected clinical worsening, reassess the original diagnosis, or assess subclinical disease activity.
- A surveillance brain MRI should be considered every 1-2 years, especially early in the course of the disease.

FIGURE 5: Spinal Cord MRI



FIGURE 6: Progressive Brain Atrophy Changes in Patients with RRMS¹⁵⁸



However, the exact frequency may vary depending on clinical course and other clinical features.¹⁶⁰

The International Panel of MS Experts recently accepted the appearance of a new lesion on MRI as a criterion that can be used to establish evidence of DIT after a CIS in lieu of a second clinical attack, allowing for an earlier, formal diagnosis of MS (providing that criteria for DIS also are met). These criteria are based on specific lesion number and location. At the time of a CIS, these lesion counts can be performed quickly and with good reproducibility.¹⁶⁰

9 TREATMENT *of MS*

At present, while there is no cure for MS, the immediate goal of DMT is to reduce CNS inflammation with long-term goals of:

- a. Reducing the frequency, severity, and duration of acute relapses
- b. Delaying and preventing clinical and radiological disease progression
- c. Effectively controlling and managing clinical symptoms
- d. Delaying the development of long-term disability
- e. Improving and maintaining HRQOL

The current treatment paradigm for acute relapses is IV methylprednisolone (MP) in order to speed recovery, although this has not been shown to improve long-term outcomes, risk of further acute relapses, or progression of disability. Long-term management of MS is achieved with DMTs and close patient monitoring of clinical and MRI indicators of disease activity, with therapeutic protocol changes as needed. MS symptoms are managed with pharmacologic, nonpharmacologic, and rehabilitative treatment strategies in order to improve and maintain patients' functional ability, minimize disability, and optimize HRQOL.

While great progress has been made in delaying or preventing disease progression in MS using DMTs, to date we have unable to prevent the development of disability in the long term. This, together with a highly variable disease presentation, course, and response to therapy in MS patients, creates a significant challenge for clinicians.

TREATMENT GUIDELINES

Current MS treatment guidelines issued by the NMSS in 2006 emphasize the following¹⁶¹:

- a. The importance of early, accurate diagnosis of initial MS symptoms
- b. Prompt, aggressive treatment using DMT as soon as MS is diagnosed
- c. Continuation of DMT indefinitely with re-evaluation if the patient demonstrates intolerance to the medication, a lack of improvement with a treatment, or a better therapy becomes available

This approach has been shown to reduce the frequency and severity of relapses and brain lesions on MRI and to delay long-term disability.

TREATMENT OF ACUTE RELAPSE IN MS

An MS relapse is defined by the McDonald criteria as “an episode of neurologic disturbance of the kind seen in MS when the clinopathological studies have established that the causative lesions are inflammatory and demyelinating.”¹⁰⁹ A relapse should last a minimum of 24 hours and reliably be distinguished from a pseudo-attack of symptoms (eg, experienced by MS patients with increased body temperature after a hot bath or during fever). Repeated attacks of paroxysmal symptoms, such as trigeminal neuralgia or tonic muscle spasm lasting longer than 24 hours also may be diagnosed as a relapse; however, a 30-day period of stability in between acute episodes generally is required in order to define it as a new exacerbation. A relapse, exacerbation, or attack of acute neurologic symptoms is the clinical hallmark of RRMS and also is seen in relapsing SPMS. Relapses have been described in some patients with PPMS.¹⁶² Most patients will make at least a partial recovery from relapses, but incomplete recovery from acute attacks is a key factor in developing permanent neurologic dysfunction and disability.¹⁶²

Studies show an increased number of relapse rates early in the course of MS are associated with increased long-term cumulative disability.⁸⁰ Studies suggest using a stable or static relapse rate to identify suboptimal treatment responders and an increasing relapse rate to indicate treatment failure in MS patients using DMT.^{80,94} However, in studies following the natural history of MS, relapses are common early in the disease but become less frequent as the disease advances. Therefore, measuring relapse rates in patients in a late disease stage is a less reliable indicator of treatment success.⁸⁰

Corticosteroids have been used to treat acute relapses since the 1940s and remain the current first-line treatment. Although the exact mechanism of action of corticosteroids in MS is unclear, they appear to decrease inflammation, reduce edema, and help to preserve the integrity of the BBB. Corticosteroid therapy often decreases the duration of a relapse and helps to speed recovery but does not affect long-term progression of disease activity.¹⁶³

As reflected in recent guidelines and consensus statements, the current standard of care in the United States for an acute MS relapse is intravenous MP 1 g daily for 3-5 days, which may be followed by an oral prednisone taper for 1-3 weeks.¹⁶²⁻¹⁶⁴ Some evidence exists to support the use of comparable doses of oral steroids in acute MS relapses, but definitive study data is lacking on this.¹⁶²

Chronic or regular steroid use in RRMS is not recommended, and evidence is lacking at this time on the value of pulse steroid therapy as an adjunct to DMT.¹⁶⁵

In 2005, a European Federation of Neurologic Sciences (EFNS) task force conducted a review of MS relapse treatment to determine whether therapy during acute exacerbations can increase the rate of recovery, influence long-term recovery, or impact long-term disease progression, as well as to determine whether these acute treatment regimens have significant side effects.¹⁶² The findings of this review included:

1. MP produced significantly faster recovery from acute MS relapse symptoms than placebo.^{89,162}
2. Evidence suggests that regular pulses of IV MP given in addition to standard doses during relapse may prevent or delay brain atrophy in patients with RRMS.¹⁵⁹
3. Patients who do not respond or respond suboptimally to MP therapy in the range of 1 g IV once daily for 3 days should be treated with higher doses of up to 2 g IV once daily for 5 days.¹⁶²
4. Up to one-third of patients with severe acute inflammatory demyelination who do not respond to higher-dose MP therapy may benefit from plasma exchange therapy.¹⁶²
5. To date, no studies have shown a difference between oral MP and placebo in the prevention of new exacerbations or improvement in the long-term disability of MS patients.¹⁶⁶
6. No studies conclusively have shown any differences in the efficacy or side effects of MP administered intravenously vs orally, but several studies show gastrointestinal (GI) and psychiatric adverse events were higher overall in the long-term oral MP group than in placebo.¹⁶³
7. Short-term MP therapy has not shown to be detrimental to bone mineralization and density, although pulsed MP treatment produces marked changes in bone metabolism. More research is needed on the effects on bone structure.¹⁶² Both men and women should be advised to supplement with oral calcium and vitamin D

while on steroid therapy, and those who have been on frequent steroid therapy should have bone density scans performed.

8. Currently, evidence is inconclusive on the glucocorticoid of choice, the optimal dose, and whether to taper after pulse therapy.
9. Intravenous immunoglobulin (IVIG) also has been used for the treatment of acute relapses; however, there is still some uncertainty as to the optimal treatment dose.¹⁶⁷
10. In 2006, a study by Craig et al¹⁶⁸ showed the value of using a planned comprehensive multidisciplinary team (MDT) in combination with steroid therapy for the treatment of acute MS attacks.¹⁶³ Studies are ongoing evaluating the use of high-dose oral prednisolone (1250 mg/day for 6 doses) vs intravenous therapy.

ADRENOCORTICOTROPIC HORMONE (ACTH)

ACTH is approved by the US Food and Drug Administration (FDA) for treating acute relapses in MS; studies show similar efficacy to IV MP.¹⁶² However, now ACTH largely has been replaced with IV MP, mainly due to the adverse event profile of ACTH. In the 2005 EFNS task force review, no definitive evidence was found showing major differences in the efficacy of IV MP over ACTH.¹⁶² Other studies show:

- ACTH also may increase the recovery speed of visual function in acute monosymptomatic optic neuritis.¹⁶⁹
- Significantly more side effects, such as weight gain and edema, may occur with ACTH compared with placebo.¹⁶³
- After treatment with ACTH, a higher—though not statistically significant—relapse rate may occur in the following months.

A Cochrane Review of 6 randomized placebo-controlled clinical trials of IV MP or ACTH showed a benefit using MP and concluded that the preferable treatment for relapse is IV MP over ACTH.¹⁶² Thus, ACTH treatment generally is reserved for patients with severe symptoms who do not respond to initial therapy with corticosteroids.

PLASMA EXCHANGE

Another therapy used for the treatment of acute relapses refractory to steroids includes the removal, treatment, and return of blood plasma from blood circulation. Studies utilizing plasma exchange (PLEX) as a treatment option for acute severe relapses refractory to steroid therapy

show that approximately 40% of patients had a functional improvement during plasma exchange compared with sham exchange. This improvement was sustained over 6 months following treatment.¹⁷⁰

TREATMENT OF A CIS

Based on study data, the current standard of care for treating clinically isolated syndromes uses treatment protocols similar to those for acute MS exacerbations that result in functional impairment (1 gram of IV MP per day for 3-5 days, with or without a brief oral steroid taper).¹⁶

Recent trial data clearly indicate that most CIS patients with lesions on baseline MRI progress to MS and are at risk of developing irreversible neurological disability. Therefore, the new standard of care is to initiate DMT in these CIS patients as early as possible to help prevent subclinical CNS damage and delay the onset of MS and disease progression (discussed further).¹⁷¹

DISEASE-MODIFYING THERAPIES

The goal of DMT is to prevent relapses, modify or prevent disease progression, and delay disability but not to treat specific symptoms or exacerbations. In MS, DMTs alter the immune cascade and response to pathogenetic triggers. The main types of DMT include immunosuppressives and immunomodulators.

DMTs CURRENTLY AVAILABLE FOR MS TREATMENT

Immunomodulating DMTs currently FDA approved for first-line treatment of relapsing MS are intramuscular (IM) interferon beta-1a, subcutaneous (SC) interferon beta-1a, SC interferon beta-1b, glatiramer acetate, and the first oral agent for MS, fingolimod, recently approved in 2010.

Mitoxantrone and natalizumab are approved agents for second-line use in relapsing MS. Mitoxantrone is an immunomodulator and an immunosuppressant administered by IV infusion and is FDA approved to slow progression of disability in SPMS, worsening RRMS, and PRMS. Natalizumab generally is used in patients who have not tolerated or responded to first-line agents. These agents are reviewed in **Table 10**.¹⁷²⁻¹⁷⁷

First-Line Agents to Treat MS

Interferon beta is a cytokine with immunomodulatory, antiviral, and antiproliferative properties. It currently is believed that the IFN beta agents transform the immune response in MS mainly via reduction of T-cell migration from the peripheral circulation into the CNS⁹⁴ by decreasing the production of adhesion molecules and proteases on the vascular endothelium of the BBB. Another key immunomodulating action of these drugs is to inhibit production of pro-inflammatory cytokines, such as gamma-type interferons, from Th cells.⁹⁴ Interferon beta products for the treatment of MS include:

SC Interferon beta-1b is FDA approved for use in RRMS, relapsing SPMS, and most recently, a CIS.⁹⁴ The usual dosing regimen is 0.25 mg SC every other day. The pivotal trial utilizing IFN beta-1b was a 2-year, double-blind, randomized, placebo-controlled trial of 372 patients with RRMS. Interferon beta-1b demonstrated a 34% reduction in relapse rates compared with placebo.¹⁷⁸ Five-year follow-up data were obtained from patients; the progression of disease activity was 35% in the IFN beta-1b group and 46% in the placebo group. Furthermore, the results of an SPMS study utilizing IFN beta-1b in Europe showed a benefit of delaying disability in relapsing SPMS patients.¹⁷⁹ A 16-year follow-up study of IFN beta-1b, started in 1990¹⁸⁰ using RRMS patients, showed that long-term treatment with this agent appears to be safe over a 16-year period and may reduce mortality due to MS in patients who take IFN beta-1b over the long term.^{181,182}

There have been comparison studies of higher-dose IFN beta therapies (SC IFN beta-1a and IFN beta-1b) vs IM IFN beta-1a that show improved relapse rate reduction with the higher-dose, higher-frequency medications.^{183,184} Whether this benefit will result in a sustained delay of long-term disability is unclear at this time.

It usually is recommended that IFN beta-1b be administered at night, with an initial dose titration and the use of nonsteroidal anti-inflammatory agents or an analgesic, in order to minimize the incidence of flu-like symptoms. Injection-site reactions, such as itching and redness, also can occur; injection site rotation can help to minimize these reactions. For all the IFN beta therapies, routine CBC with differential and liver function profile testing is

TABLE 10: FDA-Approved Disease-Modifying Agents¹⁷²⁻¹⁷⁷

Drug	Indication	Route and Usual Dose	Potential Mechanisms	Adverse Effects	Pregnancy Category
IFN Beta Agents					
IFN beta-1a	First line Relapsing MS and CIS	IM: 30 µg once weekly	<i>Class effects:</i> inhibition of T-cell migration, antigen presentation, T-cell matrix MMPs, ^a and leukocyte proliferation; may modulate cytokines	<i>For all:</i> Injection-site reactions, flu-like symptoms, liver enzyme elevations, lymphopenia, depression, NAb formation	<i>For all:</i> C (avoid if possible) ^b
IFN beta-1a	First line Relapsing MS	SC: 44 µg 3 times per week			
IFN beta-1b	First line Relapsing MS and CIS	SC: 250 µg every other day			
Glatiramer Acetate	First line Relapsing MS and CIS	SC: 20 mg/day	Increase regulatory T cells, suppress inflammatory cytokines, inhibit antigen presentation	Injection-site reactions, vasodilatation, chest pain, nausea, asthenia, anxiety, infections	B ^c
Fingolimod	Relapsing MS	PO: 0.5 mg/day	Active metabolite is a S1P receptor modulator, binds to S1P receptors on the surface of lymphocytes and thymocytes, blocks lymphocytes from leaving secondary lymphoid organs, and reduces the number of lymphocytes in peripheral blood. The MOA is thought to be related to reducing migration of lymphocytes into the CNS	First-dose bradycardia, lymphopenia, macular edema, pulmonary dysfunction, skin cancers, liver enzyme elevations, increased risk of bronchitis, and pneumonia. Herpes infections observed, and 2 deaths were reported from disseminated herpes zoster and herpes encephalitis. First dose of fingolimod requires specific monitoring. See text.	C
Natalizumab	Relapsing MS (as monotherapy; avoid immunosuppression)	Used only via prescribing program IV infusion: 300 mg every 4 weeks	Binds to alpha4/beta1 integrin on activated lymphocytes and monocytes, inhibits cell adhesion, inhibits leukocyte migration across the BBB	Rare: PML 1 in 1000 patients Other: hypersensitivity reactions, NAb, fatigue, headache, arthralgia, depression	C (avoid if possible) ^d
Mitoxantrone	Worsening RRMS; SPMS; PRMS	IV infusion: 12 mg/m ² every 3 months Lifetime: 8-12 doses total (max 140 mg/m ²)	Inhibits DNA synthesis, reduces lymphocytes, reduces Th1 cytokines	Rare: leukemias, cardiotoxicity Other: fatigue, nausea, infections, cytopenias, hair thinning, blue-green urine for 24 hrs post-dose	D avoid; pregnancy test before treatment ^e

^aMatrix metalloproteinase (MMPs) enable leukocyte migration across the BBB and contribute to myelin degradation

^bAnimal studies have shown an adverse effect and there are no adequate studies in pregnant women or no animal studies have been conducted and there are no adequate studies in pregnant women. If a woman becomes pregnant or plans to become pregnant while taking interferon beta, she should be informed about the potential hazards to the fetus and discontinuation of the interferon should be considered.

^cAnimal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies, which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

^dAnimal studies have shown an adverse effect and there are no adequate studies in pregnant women. Natalizumab should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

^eThere is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

recommended every 6 months.¹⁸⁵ Testing usually is performed every 3 months during the first year of use.

IM Interferon beta-1a is approved for use in RRMS and a CIS, with a usual dosing regimen of 30 µg by IM injection once per week. It was studied in a pivotal, double-blind, randomized, placebo-controlled trial in 301 patients with RRMS. Over 2 years, a 29% reduction in relapse rate compared with placebo was noted in these patients. The primary outcome measure in this study was time to sustained disability progression of at least 1.0 point on the EDSS. Results showed those in the IFN beta-1a treatment group had a significant delay in time to sustained EDSS progression ($P = 0.02$), had significantly fewer MS relapses ($P = 0.03$), a 29% reduction in annual relapse rate over 2 years (0.61 vs 0.90 in the placebo group), and a significantly lower number and volume of Gd-enhanced brain lesions on MRI.¹⁸⁶

SC interferon beta-1a also is approved for use in RRMS, with a usual dosing schedule of 22 µg or 44 µg by SC injection 3 times per week. SC IFN beta-1a was evaluated in a double-blind, randomized, placebo-controlled trial with 560 patients. Patients received either 22 µg or 44 µg of SC IFN beta-1a or placebo 3 times weekly for 2 years. There was a statistically significant difference seen in terms of relapses in the SC IFN beta-1a–treated patients compared with placebo, and a statistically longer time to sustained disability progression was noted in the SC IFN beta-1a–treated patients.¹⁸⁷

Glatiramer acetate is another immunomodulating agent approved for the treatment of RRMS and a CIS. The key mechanism of action of GA is to impair the immune cascade by interfering with antigen presentation. It does this by mimicking and competing with myelin basic protein (MBP) for binding to the major histocompatibility complex (MHC) on the antigen-presenting cell (APC). This GA-MHC complex competes with the MBP-MHC complex for the T-cell receptor sites on Th cells. This in turn reduces Th1-cell activity and upregulates the Th2-cell response, which ultimately increases production of anti-inflammatory cytokines. GA also has been shown to increase production of brain-derived neurotropic factor.

GA has a usual dosing schedule of 20 mg by SC injection once daily. It gained FDA approval following the result of a double-blind pivotal study of 251 patients showing a relapse rate

reduction of 29% over 2 years in the GA-treated patients vs placebo.^{188,189} Prospective, 10-year, long-term follow-up data have been obtained from original patients who continued on GA, and continued efficacy and tolerability were noted.¹⁹⁰

Side effects may include itching and redness at the site of injection, and 10% of patients may experience chest tightness, flushing, and palpitations transient to the injection that usually dissipate within 20 minutes. Lipoatrophy also may be seen rarely at the injection sites.¹⁹¹ Patients should be properly instructed on frequent injection site rotation.

Fingolimod was approved by the FDA in September 2010 as the first oral agent for relapsing forms of MS, representing an important milestone in the development of MS therapeutics. It is a DMT with a dose of 0.5 mg daily by mouth. Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that is indicated to decrease the frequency of clinical relapses and delay the accumulation of physical disability.¹⁷⁷

Fingolimod is metabolized to the active metabolite, fingolimod-phosphate, and binds with high affinity to S1P receptors on the surface of lymphocytes and thymocytes. This blocks lymphocytes from leaving the secondary lymphoid organs and reducing the number of lymphocytes in peripheral blood. The mechanism of action in MS is thought to be related to reducing migration of lymphocytes into the CNS.¹⁷⁷ It does not appear to cause generalized immunosuppression.

Pretreatment assessments include CBC and liver function tests (LFTs), baseline ophthalmologic exam, baseline electrocardiogram, contraception, and varicella-zoster virus (VZV) serology with a recommended vaccine if the VZV is negative. Contraception is required during treatment and 2 months after discontinuation due to risk of fetal anomalies. Patients who have been on injectable therapies may transfer directly to fingolimod; however, those who have been taking natalizumab should wait 6 months before starting fingolimod.

The first dose of fingolimod requires specific monitoring, including baseline pulse and blood pressure as well as observation of all patients for 6 hours. During treatment, patients are advised to report any symptoms, avoid live attenuated vaccines, have ophthalmological exams every 3-4 months, report any visual changes, undergo a spirometry if indicated,

and monitor LFTs. After treatment, patients should report symptoms of infection for up to 2 months.^{177,192}

Second-Line Agents to Treat MS

Mitoxantrone, an anti-neoplastic drug FDA approved for use in SPMS, PRMS, or worsening RRMS not responding to IFN beta or GA therapy, originally was designed and approved for treatment of acute myeloid leukemia in adults. Although the exact mechanism of action of this agent still is under investigation, it is thought to inhibit cell division and proliferation of T cells, B cells, and macrophages by cross-linking DNA in these cells (thus inhibiting DNA replication and RNA synthesis). Mitoxantrone also impairs antigen presentation by causing apoptosis of APCs and other cells associated with APCs.

The usual dosing regimen for mitoxantrone is 12 mg/m² by IV injection every 3 months. During clinical trials, cardiotoxicity was noted with this agent, manifesting as reduced left ventricular ejection fraction (LVEF) in 13% of patients and fatal congestive heart failure (CHF) in 2 cases. Although CHF could not be directly linked to the drug, the FDA issued a black-box warning with a stipulated lifetime cumulative maximum dose of 140 mg/m².

A multiple gated acquisition (MUGA) scan or 2D echocardiography at both baseline and prior to each dose is required. The incidence of therapy-related acute leukemia reportedly occurs in 5 of 2336 treated MS patients (0.21%), and that risk apparently is not dose related. White blood cell count is required prior to each dose, as well as 2 weeks postinfusion.¹⁹³⁻¹⁹⁵ Studies evaluating the use of induction therapy with mitoxantrone in patients with aggressive MS disease activity have shown benefit.¹⁹⁶

Natalizumab is a recombinant monoclonal antibody currently approved for monotherapy in relapsing MS and generally is recommended for second-line use in patients who have had an inadequate response to or are unable to tolerate first-line agents.¹⁹⁷ It first was approved for use in RRMS by the FDA in November 2004. Directed against alpha 4 integrin adhesion molecules on activated immune cells, it prevents them from connecting to adhesion molecules on endothelial cells in the BBB, thereby blocking their transmigration across the BBB.⁹⁴ With reduced influx of T cells into the CNS, cytokine production is decreased, thus inhibiting the inflammatory response of MS.

Natalizumab was investigated in 2 phase III FDA clinical trials. One trial (AFFIRM) looked at the use of natalizumab alone vs placebo while the other trial (SENTINEL) compared the use of natalizumab combined with IFN beta-1a IM vs IFN beta-1a IM alone.¹⁹⁸ The IFN beta-1a IM plus natalizumab group experienced a 24% reduction in relative risk of sustained EDSS progression compared with placebo.¹⁹⁷ However, natalizumab now is approved for use only as a monotherapy. In the AFFIRM trial, natalizumab reduced the rate of relapses at 1 year by 68%. MRI efficacy also was noted with reduction in the accumulation of new or enlarging T2 lesions by 83% over 2 years and a 92% reduction in Gd-enhancing lesions at 1 and 2 years.

Natalizumab was approved in Europe and the United States for RRMS administered by monthly IV infusion.¹⁸⁰ After initial FDA approval in 2004, natalizumab was withdrawn from the market by the manufacturer in February 2005 due to 3 clinical trial patients developing PML, a rare but serious progressive viral infection of the brain. The viral agent in PML is the JC polyomavirus. PML is incurable and can cause irreversible neurologic dysfunction and death. Typical symptoms of PML include a subacute onset with a progression of symptoms, seizures, cognitive and/or behavioral changes, hemiparesis, and visual deficits. Some of these symptoms may be difficult to distinguish from MS symptoms.

The FDA put clinical trials on hold until March 2006 when the manufacturer was able to confirm that no further cases of PML had been diagnosed in patients. Subsequently, the FDA Advisory Committee on Drugs for the Peripheral and Central Nervous System recommended a mandatory risk-minimization program that included patient registration and follow-up for all patients on the drug. As the patients who developed PML also were receiving other DMTs, the committee also advised that natalizumab be used only as a monotherapy. The manufacturer responded by developing a prescribing program, which required that all potential natalizumab patients be counseled in detail by their physician on the risks and benefits and be required to agree to all instructions of the plan.¹⁹⁷

As of September 2010, 75,500 patients had received natalizumab, and as of January 2011, 85 cases of PML from around

the world had been reported, with 36 in the United States.^{199,200} Approximately 19% of patients with PML have died, and others experience varying degrees of disability.^{197,200,201}

Clinical diagnosis of PML typically is made by MRI and detection of JC virus in the CSF. It appears that previous therapy with immunosuppressants might increase the risk of developing PML. On February 5, 2010, the FDA alerted that the risk of developing PML increases with the number of natalizumab injections received.²⁰² Management of PML usually involves PLEX or immunoabsorption to increase clearance of natalizumab and shorten the period in which natalizumab remains active.²⁰³

A consequence to the management of PML is immune reconstitution inflammatory syndrome (IRIS), a deterioration in clinical status caused by recovery of the immune system, leading to serious neurological complications or death and typically occurring days to weeks after receiving PLEX.²⁰¹ IRIS has been reported in a majority of patients who develop PML, have natalizumab subsequently discontinued, and undergo PLEX.^{197,204} Clinicians should monitor patients at risk for the development of IRIS. High-dose corticosteroids have been used to manage IRIS.²⁰¹ Clinicians need to actively screen patients who may be at risk for JC virus prior to receiving natalizumab therapy; those who receive natalizumab require close monitoring of clinical status.

THE EFFICACY AND SAFETY OF DMTs IN MS

Treating established MS with IFN beta has proved beneficial in reducing the development of brain lesions, decreasing relapse rates, slowing development of long-term disability, and reducing brain atrophy.⁹⁵

In July 2007, Oregon Health & Science University conducted a drug-class review on MS DMTs to evaluate comparative efficacy and safety profiles of the agents currently available for MS. Most of the information on effectiveness and safety of DMTs approved for MS is found in indirect-comparison data from placebo-controlled trials and non-randomized studies. Four direct-comparison clinical trials have been conducted on the different types of IFN beta products.⁹⁴ The findings are summarized as follows:

Treatment of a CIS With DMT

Studies showed that in a CIS, early inflammatory processes, which subsequently cause demyelination and axonal injury, are likely to result in irreversible neurologic dysfunction and disease progression.¹⁹ These changes were seen in patients with active MS lesions and in normal-appearing white matter on MRI.¹⁹

These findings triggered research interest in the early treatment of MS. Several studies using different interferon betas and glatiramer acetate have shown that early treatment can beneficially impact the chance of a CIS progressing to MS. Additionally, more recent studies have demonstrated that early treatment can decrease the rate of disability progression in those patients who develop MS.

In 2000, Jacobs and colleagues conducted a randomized double-blind trial using IM IFN beta-1a 30 µg/week for patients with a CIS and evidence of prior silent neurologic damage on MRI. The patients were first treated with corticosteroids for the initial acute episode and then started on IM IFN beta-1a; they were followed for a period of 3 years post-treatment. Patients receiving IM IFN beta-1a had a significantly lower probability of developing clinically definite MS (CDMS) during the 3-year follow-up period when compared with the placebo group. Also, in the IFN treatment group, reduced volume of brain lesions on MRI, fewer new or enlarging lesions, and fewer Gd-enhancing lesions were seen. The authors concluded that initiating treatment with IM IFN beta-1a was beneficial at the first acute episode of demyelination.⁹⁵

Another study in 2001 used weekly subcutaneous IFN beta-1a injections for 2 years in patients with a CIS and neurologic damage on MRI. The treatment group had fewer new T2-weighted MRI lesions and lower lesion loads compared with patients receiving placebo.⁹⁶ Although these parameters for disease activity improved with SC IFN beta-1a, therapy did not stop disease progression. At the conclusion of the study, most patients in the treatment group had temporal dissemination of MRI lesions. Furthermore, both the treatment and placebo groups showed an increase in disability ratings on the EDSS, indicating that some level of irreversible neurologic damage occurred even at the earliest stage of the disease.⁹⁶ This suggests that MS in its early stages may be more responsive to DMT than advanced disease.⁹⁶

The PreCISe trial demonstrated that glatiramer acetate (20 mg/day) significantly increased the 25th percentile time to conversion of a CIS to CDMS by over 100% ($P = 0.005$) compared with placebo. In this same group of patients, glatiramer acetate reduced the conversion to CDMS ($P = 0.0005$) by 45% compared with placebo.²⁰⁵

In 2006, recommendations from the NMSS Medical Advisory Board advised that patients with a definite diagnosis of MS and active disease, as well as selected patients with a first attack or CIS symptoms who are at high risk for CDMS, should be started on immunomodulating therapy as soon as possible.

Evidence shows that patients with relapsing MS who are treated early in the course of disease (eg, at CIS presentation) have successfully delayed development of CDMS, fewer and less severe relapses, reduced lesion load on MRI, and, in the long term, less neurologic disability. With this growing body of evidence, many experts advocate early treatment of a CIS with DMT agents. However, some have countered this approach, emphasizing the fact that not all patients with a CIS will develop RRMS, and some may experience a persistently mild non-progressive disease course called benign MS. Retrospective studies show that some patients presenting with optic neuritis or sensory symptoms at their initial episode usually have a more benign course of MS with little disease progression compared with those who initially present with significant motor symptoms.

In a 2001 Mayo Clinic review, benign or mild MS was found in approximately 27% of patients with low disability scores at 10 years post-diagnosis.¹⁹ Indications of a mild course of MS were identified as:¹⁹

1. Early age at onset, usually before age 40
2. Optic neuritis at presentation
3. First remission lasting more than 1 year
4. Only 1 relapse in the first 5 years from diagnosis

Rationale for early treatment to reduce long-term permanent neurologic damage and disability comes from the findings of 4 placebo-controlled clinical trials (BENEFIT, CHAMPS, ETOMS, and PreCISe). These trials indicate that the 3 IFN beta agents and glatiramer acetate all are effective in reducing the probability of conversion from a

CIS to CDMS over a period of 2-5 years when compared with placebo.^{206,207} The BENEFIT (**B**etaferon/**B**etaseron **N**ewly **E**merging Multiple Sclerosis for **I**nitial **T**reatment) trial evaluated the potential impact of interferon beta-1b for patients with an initial clinical episode suggestive of MS. At 2 years, 28% of the interferon beta-1b group and 45% of the placebo group had progressed to CDMS as defined by the McDonald Criteria.²⁰⁸ The 3-year results from the study showed that the early treatment of patients with interferon beta-1b delayed disability progression by 40%.²⁰⁹ There also was a significant reduction in MRI disease activity in the IFN-treated group. IFN beta-1b recently was approved for treatment of a CIS in the United States, Europe, Iceland, Norway, and Canada.¹⁸⁰

Two large clinical trials were the CHAMPS and ETOMS studies. CHAMPS (**C**ontrolled **H**igh Risk **A**vonex **M**ultiple **S**clerosis Study) tested IM IFN beta-1a once weekly injections.⁹⁵ The ETOMS (**E**arly **T**reatment of **M**S) study tested SC IFN beta-1a 22 µg/week injections for up to 2 years.⁹⁶ Both demonstrated delayed conversion to CDMS in patients with a CIS. The BENEFIT trial found that patients with low-activity lesions benefited from early treatment more than those with highly active disease.^{208,209} In CHAMPS and ETOMS, the patients with high disease activity benefited most from early treatment.¹⁸⁰

There is no current evidence of benefit in patients with a CIS taking mitoxantrone or natalizumab.

TREATMENT OUTCOMES FOR RRMS⁹⁴ **Interferon Beta**

Rates of disease progression at 2 years and relapse rates in all IFN beta groups in controlled trials were less than with placebo groups.⁹⁴ Some evidence from 2 trials supports that SC IFN beta-1a produces better outcomes in relapse rates than IM IFN beta-1a, but there was no difference in terms of disease progression or the side effect profile.^{210,211} To date, there is no evidence of differences in outcomes between IFN beta-1b and IFN beta-1a products.

Glatiramer Acetate

Evidence from 3 trials shows GA is significantly better than placebo at reducing relapse rates. Additional data demonstrate improved EDSS scores compared with placebo. Recent randomized, assessor-blinded studies comparing

the efficacy of IFN beta-1a vs GA (the REGARD trial) and IFN beta-1b vs GA (BEYOND trial) suggests comparable effectiveness of IFN beta agents and GA in terms of disease progression.^{212,213}

Fingolimod

Evidence from the FREEDOMS trial, in which 1272 patients with RRMS were randomized to fingolimod 0.5 mg or 1.25 mg vs placebo, showed a significant reduction in the annualized relapse rate in both fingolimod groups compared with placebo (annualized relapse rates were 0.18 with 0.5 mg dose, 0.16 with the 1.25 mg dose, and 0.40 with placebo) as well as a reduction in MRI disease activity, including the number of new or enlarged lesions on T2-weighted images, Gd-enhancing lesions, and brain volume loss.²¹⁴ Further, patients in both fingolimod treatment groups showed a significant decrease in disability progression at 3 months and 6 months.²¹⁴

In the other key trial, TRANSFORMS, where 1292 patients were randomized to receive either fingolimod 0.5 mg or 1.25 mg vs IM IFN beta-1a 30 µg/week, demonstrated a significant relative risk reduction in relapse rates in both fingolimod treatment groups compared with the IFN group (annualized relapse rates were 0.20 in the 1.25 mg group and 0.16 in the 0.5 mg group compared with 0.33 in the interferon group; $P < 0.001$ for both comparisons). MRI findings supported the primary results; however, no significant differences were seen among the study groups with respect to progression of disability. Over 80% of patients in both fingolimod groups were relapse free at 12 months, with reduced MRI-disease activity.¹⁹²

Natalizumab

Data from 2 clinical studies showed reduced relapse rates and disease progression with natalizumab compared with placebo.⁹⁴ In one of these studies, IFN beta-1a combined with natalizumab for 2 years reduced the relative risk of sustained disability progression by 24% in patients who had been responding suboptimally to IFN beta-1a alone. The combination was significantly superior to IFN beta-1a alone in reducing annualized relapse rates and new or enlarging lesions on T2-weighted MRI.²¹⁵ Due to safety concerns, the current FDA-approved use of natalizumab is for monotherapy only.

Mitoxantrone

There is very little evidence on this agent regarding RRMS. In 1 phase III trial, a dose of 12 mg/m² every 3 months for 2 years vs placebo significantly reduced disease progression in patients with worsening MS.¹⁰⁷

TREATMENT OUTCOMES FOR SPMS Interferon Beta

Evidence shows all IFN beta products reduce relapse rates in patients with SPMS, and those with more active inflammatory disease benefit more than those with less inflammation in the CNS. In European phase 3 trials in SPMS patients, IFN beta-1b also significantly reduced progression in disability (EDSS scores) compared with placebo, with efficacy sustained for 8 years.^{107,179}

Mitoxantrone

Mitoxantrone has improved EDSS scores and reduced relapse rates, T2 lesions, and new Gd-enhancing lesions in relapsing forms of MS (patients with SPMS or worsening RRMS).²¹⁶

TREATMENT OUTCOMES OF MIXED POPULATION STUDIES WITH SPMS AND RRMS

Studies show an improved QOL in MS patients treated with SC IFN beta-1b compared with controls.⁹⁴ Limited studies show no statistical significance between natalizumab and placebo regarding improvement on the EDSS. One trial did show improved relapse rates with this agent. All studies in this population were relatively small and of shorter duration compared with RRMS studies.⁹⁴ Data from 4 trials showed mitoxantrone reduced relapse rates and disease progression compared with placebo.⁹⁴

TREATMENT OUTCOMES OF PPMS

There is no clear effective treatment available for PPMS. Studies with GA and IFN beta have not yielded significant benefit, except for an improvement in MSFC scores with IFN beta in one trial.¹⁰¹ The phase 3 PROMiSe trial with GA showed a non-significant trend toward slowing progression compared with placebo. In the same study, a post-hoc analysis showed a treatment effect in men with PPMS; GA significantly delayed time to sustained progression of accumulated disability compared with placebo ($P = 0.0193$).²¹⁷

TREATMENT OUTCOMES OF MIXED POPULATIONS WITH PPMS AND SPMS

Limited evidence suggests that in patients with chronic progressive MS, GA reduces disease progression and improves EDSS scores at 2 years compared with placebo.⁹⁴

TREATMENT OUTCOMES FOR PRMS

In PRMS, clinical data are limited. Mitoxantrone 5 mg/m² or 12 mg/m² IV every 3 months has shown some benefit in reducing relapses, improving disability (EDSS score), and reducing new Gd-enhancing lesions.²¹⁸

NEUTRALIZING ANTIBODIES⁹⁴

All IFN beta products can induce the formation of neutralizing antibodies (NABs) in patients during the first 2 years of treatment.¹⁸⁰ Increasing evidence suggests that higher persistent titers of NABs are associated with reduced clinical efficacy, and this negatively impacts relapse rates in short-term therapy (less than 2 years). NABs apparently play a less important role during long-term therapy over 2 years.¹⁸⁰ Current study data show both SC IFN beta-1b and SC IFN beta-1a produce NABs.

Evidence suggests that IM IFN beta-1a has the lowest immunogenicity of all the IFN products with SC IFN beta-1a following, and SC IFN beta-1b the most immunogenic. Of note, studies show that approximately 40%-50% of all MS patients treated with IFNs who develop NABs will revert to antibody-negative status over time. However, a small number of NAB-positive patients will remain positive.⁹⁴

At this time, the diagnostic value of NABs is still under investigation, and there is no evidence to support routine NAB measurement in IFN beta treatment regimens.¹⁸⁰ Some researchers believe that serial NAB measurement is appropriate in MS patients who respond suboptimally to treatment and who demonstrate consistently high NAB titers. In these cases, modification of treatment regimens usually is required.

Binding antibodies to GA have been observed. The role, if any, these antibodies may play in the course of treatment has not been determined. There is no evidence indicating that GA efficacy is affected.²¹⁹

THERAPEUTIC RESPONSE AND TREATMENT OPTIMIZATION

The European MS Treatment Consensus group recently updated treatment guidelines as follows:¹⁸⁰

1. IFN beta products or GA are the recommended standard initial therapy for RRMS.
2. Mitoxantrone or natalizumab are considered second-line agents for persistent ongoing MS disease activity in patients who are already on IFN beta or GA or in patients with very high initial disease activity.¹⁸⁰

Current clinical guidelines have not yet been updated to reflect the availability of fingolimod as a first-line option for relapsing MS, and this presents a challenge for clinicians in how to integrate a new agent into MS care.

SUBOPTIMAL RESPONSE TO THERAPY AND TREATMENT FAILURE

Patients with MS who are treated with DMTs demonstrate a wide variety of responses to therapy. In 2005, Zaffaroni et al⁸⁰ proposed guidelines for defining responders, suboptimal responders, and nonresponders to immunomodulating agents in order to optimize patient care. Suboptimal responders and nonresponders likely need a change of medication dose, regimen, or agent, or they need combination therapy.

Various research states the most common reasons for stopping or changing MS medications are perceived lack of efficacy, injection-site reactions, or other adverse effects; several studies show that patients have varying responses or tolerances to therapy.⁸⁰ The basis for establishing criteria for levels of response to DMTs, as suggested by Zaffaroni et al,⁸⁰ were the presence of multiple symptoms, disability progression, MRI findings, NABs, and absence of relapses.

Other Indicators

Immunological markers, such as TNF alpha and IFN gamma, need further investigation to validate predictive values in treatment decision making.

Genetic parameters, such as polymorphisms of the class 1 IFN receptor, are being studied in relation to the prediction of an individual patient's therapeutic response.

Identifying and Treating Suboptimal Responders

In 2004, a panel of US neurology experts proposed a process for identifying suboptimal treatment responders and for monitoring MS patients on DMTs.⁸⁰ International panels of experts also suggested protocols for monitoring relapses, disease progression, and MRI changes in patients on DMT.⁸⁰ This process uses a grading system from notable (low level of concern) to actionable (high level of concern) regarding treatment re-evaluation. These protocols are based on frequency of relapses, clinical disease progression, EDSS score, MRI changes, new Gd-enhancing lesions, new T2 lesion load, increasing size of T2 lesions, new T1 black holes, and enlarging black holes.

The International Working Group for Treatment Optimization in MS⁸⁰ found clinical disease progression to be the most important parameter and advised a change in treatment regimen if the grading is at a worrisome or mid-level concern. Currently, the question of appropriate MRI frequency in MS patients taking DMTs remains unanswered.⁸⁰ Patients on DMTs need constant monitoring to assess their response to therapy and optimize treatment. Proposed models of criteria for responders need to be researched further to establish valid guidelines for successful treatment.⁸⁰

Evidence indicates there may be benefits to utilizing one of several therapeutic strategies in suboptimal responders, including increasing the DMT dose, switching to an alternative first-line agent, switching from a first-line to second-line agent, initiating combination therapy, or using induction therapy and escalation protocols.^{80,220-223}

DMT SIDE EFFECTS

Adverse events and side effects have been reported with all DMTs. The most common of these are injection-site reactions, flu-like symptoms, fatigue, depression, fever, thyroid dysfunction, and elevated liver enzymes. Patients who are immunosuppressed should not receive therapy.

Interferon beta Side Effects

All 3 IFN beta agents produce adverse events⁹⁴ as listed above. However, the products vary in the type of side effects reported (Table 11).⁹⁴ Elevated liver enzymes are common in patients taking any IFN beta product. Severe hepatic injury, including cases of hepatic failure, is included as a

TABLE 11: Comparative Tolerability of Interferon Betas⁹⁴

Adverse Effect	Relative Frequencies Based on Pooled Trial Rates
Injection site reaction	IFN beta-1b SC>IFN beta-1a SC>IFN beta-1a IM
Flu-like syndrome	IFN beta-1a IM>IFN beta-1b SC>IFN beta-1a SC
Fatigue	IFN beta-1a SC>IFN beta-1b SC
Fever	IFN beta-1b SC>IFN beta-1a SC>IFN beta-1a IM
Depression	IFN beta-1b SC>IFN beta-1a IM>IFN beta-1a SC
Overall withdrawal	IFN beta-1b SC>IFN beta-1a SC>IFN beta-1a IM
Discontinuation due to AE	IFN beta-1b SC>IFN beta-1a SC>IFN beta-1a IM

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special precaution in the labeling of all 3 products as well as depression, suicide, and anaphylaxis. Injection site necrosis is identified as a potential adverse event with all 3 products. Thyroid dysfunction also can occur in patients using any IFN product, with slightly more thyroid anomalies found using SC IFN beta-1b.

Glatiramer Acetate Side Effects

Adverse events for GA may include injection-site reactions and postinjection systemic reactions, both usually of short duration. In a cohort of 76 patients receiving GA, 34 exhibited some evidence of lipoatrophy at the injection site. While most were mild, 5 cases were considered severe.²²⁴ Other events that may occur include vasodilation, tachycardia, chest pain, nausea, asthenia, or anxiety.

Fingolimod Side Effects

The adverse events associated with fingolimod have been reported as first-dose bradycardia, as well as first- and second-degree atrioventricular (AV) heart blocks, lymphopenia, macular edema, pulmonary dysfunction, skin cancers, liver enzyme elevations, increased risk of bronchitis, and pneumonia. Herpes infections were observed, and 2 deaths were reported from disseminated herpes zoster and herpes encephalitis.^{172,174-177}

Mitoxantrone Side Effects

Adverse events associated with mitoxantrone include

nausea, vomiting, fatigue, alopecia, urinary tract infections in both male and female patients, and amenorrhea in women. Although not shown to be of statistical significance currently, adverse cardiac events reported include increased risk of asymptomatic decreases in LVEF.

Natalizumab Side Effects

As discussed, cases of PML have been reported, and action was taken by the FDA and by the manufacturer. Natalizumab was reintroduced to the market in June 2006 with restrictions. Other adverse events include hypersensitivity reactions, NABs, fatigue, headache, arthralgias, depression, opportunistic infections, and liver injury.¹⁹⁷ Patients who become jaundice or experience liver toxicity, even after the first dose, should discontinue natalizumab immediately.

In summary, side effects associated with DMTs should be managed proactively with regular reassessment and therapy adjustment as needed.

EMERGING THERAPIES

Multiple novel agents are being investigated or are in late-stage development for disease modification in MS currently, including:

- Immunomodulator oral agents: cladribine, laquinimod, teriflunomide, and dimethyl fumarate
- Monoclonal antibodies: alemtuzumab, daclizumab, and rituximab

These new agents show promise as future first-line agents and may offer patients and clinicians important choices in terms of mechanism of action, efficacy, safety, tolerability, and routes of administration.²⁸⁷

Stem Cells

Autologous hematopoietic stem-cell transplantation (AH SCT) to “reset” the immune system is a rarely used alternative treatment for severe MS resistant to other therapies. Results of AH SCT from a European database indicate stabilization of EDSS scores occurred in about two-thirds of patients at 3 years post-AH SCT and that responses were better in those with EDSS \leq 6.0 and in those with malignant forms of MS.^{17,225-227} A recent phase I/II study reported benefits of AH SCT in RRMS patients responding suboptimally to DMTs (slowed or reversed EDSS progression).²²⁸

10 SYMPTOM *Management*

Comprehensive, thorough symptom management by clinicians is extremely important to patients' perceptions of their QOL. Considering the long term and progressive nature of the disease, symptom control is an especially significant piece of overall care for patients with MS.²²⁹

Primary symptoms in MS occur directly as a result of demyelination and include fatigue, altered mobility; spasticity; pain; cognitive problems; depression; bowel, bladder, and sexual dysfunction; visual disturbances; altered sensation; and insomnia. Secondary symptoms in MS occur as a result of the primary symptoms and include falls, infections, injuries, contractures, skin breakdown, and decreased ability to perform activities of daily living. Tertiary symptoms result from social, vocational, and psychological effects of primary and secondary symptoms and include job loss, loss of intimacy, relationship disruption, change in family roles, social isolation, dependency, and loss of self esteem.²³⁰

Symptoms of MS vary widely depending on the location of the areas of demyelination and damage within the CNS. Often symptoms are interrelated in MS patients, such as pain exacerbating spasticity or urinary dysfunction interrupting sleep and leading to fatigue. Most acute symptoms of MS become chronic and must be managed promptly, sensitively, and as completely as possible.²³¹ The goal of individualized symptom management in MS is to eliminate or reduce symptoms that impair functional abilities, to improve QOL, and to avoid secondary and tertiary complications.²³¹

FATIGUE

Fatigue is a common, recurrent, and sometimes persistent symptom for patients with MS,²³² presenting as a debilitating lack of energy not necessarily related to overexertion. Fatigue often is the first symptom noticed by patients and usually precedes other clinical presentations. Many factors, including fatigue with acute relapses, concomitant infections, and medication side effects, contribute to this exhaustion. Frequently, fatigue also is related to other MS symptoms, such as pain, spasticity, and bladder dysfunction,

all of which may cause disturbed sleep at night and can be exacerbated by physical or mental activity, humidity, acute infection, and food ingestion.²³³ Recently, fatigue has been defined as a reversible motor and cognitive impairment with reduced motivation and increased desire to rest.²³³ In attempts to quantify fatigue and measure treatment outcomes for fatigue,²³⁴ scales such as the Fatigue Impact Score have been developed.

In clinical settings, fatigue often is under-reported and under-recognized but (along with cognitive dysfunction) is a leading cause of workplace disability.²³³ To successfully manage daytime fatigue in MS patients, contributing factors that could be interfering with patients' sleep must be addressed first. Counseling in lifestyle modification and energy conservation techniques may be very helpful for patients suffering with chronic fatigue.

Medications, such as modafinil, fluoxetine, methylphenidate, and amantadine, have proved beneficial in the management of fatigue in MS patients; however, paradoxical agitation may be a side effect.^{235,236}

A study of the impact of GA vs IFN beta on fatigue was conducted on 218 patients (86% diagnosed with RRMS), using the Fatigue Impact Score.²³⁴ In 61% of patients receiving GA and 39% receiving IFN beta over 6 months, an improvement in fatigue was seen in 24.8% of the GA-treated patients compared with 12.9% of the IFN beta-treated patients ($P = 0.033$); thus, GA may improve fatigue in MS more effectively than IFN beta.

ALTERED MOBILITY

Walking impairment affects most patients with MS and is one of MS' most debilitating symptoms.²³⁷ The possible causes of this are multifactorial and include spasticity, weakness, impaired balance, peripheral neurological changes, sensory changes, and visual impairment. The risks of walking impairment include risks of falls, pain, immobility, isolation, and reduced QOL.²³⁸

In January 2010, a new product, dalfampridine, was approved by the FDA and indicated specifically to improve walking speed in patients with MS. Dalfampridine is a broad-spectrum potassium channel blocker that increases

the conduction of action potentials in demyelinated axons through inhibition of potassium channels.²³⁹ Studies show that dalfampridine does not prolong the QTc interval and did not have a clinically important effect on QRS duration.

Recent data show the efficacy of dalfampridine extended-release oral tablets at a maximum dose of 10 mg bid increases walking speed in MS patients with RRMS, SPMS, and PPMS. In 2 Phase III trials, dalfampridine increased walking speed on the timed 25-foot walk test an average of 25% compared with placebo and independent of DMTs.^{240,241} The definition of a responder to dalfampridine is a patient whose walking speed on at least 3 out of 4 on-drug visits is faster than the fastest speed during any off-drug visits.²⁴⁰

The most common adverse events in MS patients were urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.²⁴¹ Dalfampridine has been shown to cause seizures and is contraindicated in patients with a history of seizure or moderate or severe renal impairment.

The overall management of altered mobility and walking impairment in MS patients requires early recognition, involvement of physical and occupational therapy teams, and the appropriate use of mobility aids and environmental adaptations as indicated.²³⁸

DEPRESSION

Patients with MS are more likely to experience depression than the general population or other patients with chronic illnesses, with a lifetime occurrence in approximately 50% of patients.²³¹ Younger patients are more likely to be affected by depression than patients older than 45 years of age due to concerns related to QOL during career- and family-building years.^{242,243} Research shows that QOL for MS patients can be adversely affected more by depression than physical disability or other MS symptoms²⁴⁴ and can lead to an increased risk of suicide. Depression in MS often is associated with fatigue and cognitive difficulties, and it is important for clinicians to screen and question MS patients about depression. Selective serotonin reuptake inhibitor (SSRI) antidepressant medications, such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram; serotonin-norepinephrine reuptake inhibitor (SNRI), such as venlafaxine or duloxetine;

tricyclics, such as amitriptyline, imipramine, nortriptyline; or others such as bupropion²⁴⁵ may be helpful. However, the combination of counseling or psychotherapy with the use of antidepressants has been shown to be much more effective than either therapy alone.^{245,246}

PSEUDOBULBAR AFFECT DISORDERS (PBAs)

PBAs involve sudden, frequent episodes of uncontrolled laughing or crying and may affect MS patients. A new combination of oral therapeutic agents dextromethorphan hydrobromide and quinidine sulfate recently has been FDA approved for the first-line treatment of PBAs. This is anticipated to be available in 2011 and may be useful in the treatment of MS patients with these symptoms.^{247,248}

COGNITIVE DYSFUNCTION

Studies show that cognitive dysfunction may occur early in MS, and approximately half of all patients with MS suffer from cognitive dysfunction during the disease course.^{231,249} Cognitive dysfunction may not correlate with physical symptoms or disability in MS and may go unrecognized. Typical manifestations of cognitive dysfunction include declining memory; impaired information processing and problem solving; visuospatial impairments; and reduced attention, concentration, and verbal fluency.²⁵⁰ These have implications for impaired ability to care for oneself as well as reduced mental agility,¹⁹ which often leads to frustration and demoralization for the patient and family. Evaluation by a neuropsychologist; speech, physical, or occupational therapists; and a cognitive rehabilitation therapy program often is beneficial. Counseling and learning compensatory strategies, such as note taking, making lists, and improved organization, can be helpful. It is important for family members to be aware of any dysfunction so they can help the patient more effectively and decrease their own potential frustration.

Cognitive disorders may represent significant problems for the patient in the workplace, and studies advocate that MS should be disclosed to patients' employers as soon as possible so that duties may be renegotiated and eligibility for disability coverage assessed. Failure to disclose cognitive dysfunction in patients with MS can lead to termination for poor performance without an opportunity to remediate the symptoms or receive potential benefits.

Disease-modifying therapies may help slow cognitive dysfunction by reducing new lesion development.²⁵¹ Other medications used to alter cognitive function in dementia, such as donepezil and memantine, have been used with limited benefit in MS.^{251,252} It has been widely speculated and anecdotally reported that there may be some benefit with dalfampridine in improving cognitive dysfunction in MS, although this use is off-label.

Therapies under investigation for cognitive dysfunction in MS include the cholinesterase inhibitors donepezil, galanthamine, and rivastigmine. Counseling to specifically address issues of cognitive dysfunction may be beneficial for the patient and family.

PAIN AND PAROXYSMAL MOVEMENTS

Up to 80% of patients with MS suffer pain²⁵³⁻²⁵⁵; this is a common cause of disability and is often under-recognized and under-treated. Acute pain syndromes include neuralgias and optic neuritis; chronic pain syndromes include neurogenic pain, musculoskeletal pain, and spasticity/muscle spasms. Typically, burning pain and trigeminal neuralgia are the most common complaints. Anatomic areas most often affected by pain in MS include extremities, joints, back, head muscles, and neck.²⁵⁵

Medications such as gabapentin may be helpful to treat the chronic, burning pain many patients experience.²⁵⁶ Amitriptyline also is beneficial, particularly when pain prevents patients from sleeping, as it tends to be sedating.²⁴⁵ Other agents used to treat pain include topiramate and tiagabine. These agents also can cause somnolence and dizziness.²⁴⁵ Newer agents now available for the treatment of pain in MS include pregabalin and duloxetine, as well as botulinum toxin A, baclofen intrathecal pump, and lidocaine patches.

Trigeminal neuralgia in MS patients is characterized by sharp facial pain resulting from activities, such as chewing, smiling, and other simple facial movements. This pain may be severe and debilitating. Carbamazepine is helpful for the treatment of trigeminal neuralgia.²³¹

SPASTICITY AND MUSCLE SPASMS

Myalgias and spasms frequently occur in the antigravity muscles, such as the quadriceps and gastrocnemius muscles

of the leg and are common in patients with MS.¹⁰² Frequently, these spasms are exacerbated by acute relapse and concurrent illness.

Prevention and management of spasticity depends largely on physical therapy, daily exercise, and proper seating evaluation, along with pharmacologic therapies. Eliminating underlying problems that can worsen spasticity, such as infection or pain, is important for successful treatment.

Treatments for spasticity include non-steroidal anti-inflammatory drugs (NSAIDs), pain medication, and muscle relaxants. Typically baclofen, tizanidine, clonazepam, levetiracetam, gabapentin, carbamazepine, and diazepam have been used successfully. Medications such as ropinirole or levodopa can be helpful for treating night spasms associated with restless legs. Medication regimens for spasticity usually start at a low dose and titrate upwards to help minimize the drowsy side effects of the treatment.²⁵⁷ Combination therapies may be used in patient unresponsive to monotherapy, and intrathecal baclofen therapy is used for intractable spasticity despite the use of oral therapies.²³¹

In 2010, botulinum toxin type A (BoNT A) was approved by the FDA for the treatment of upper extremity spasticity and cervical dystonia. Studies show good results in MS patients for the treatment of focal spasticity in the extremities, as well as improved function and pain relief with good tolerability and safety data.²⁵⁸ Each injection applied directly to the affected muscles lasts approximately 3 months.²⁵⁸⁻²⁶¹ Technological and surgical interventions also have been used in patients with spasticity not responsive to the use of pharmacologic and regional agents.²³¹

BLADDER DYSFUNCTION

Patients with MS often complain of urinary urgency and frequency sometimes associated with incontinence. The goal of the initial work-up for bladder dysfunction is to determine if the incontinence is due to failure to store or to empty urine; urodynamic studies may help determine this. When patients fail to empty urine, there is a large volume in the bladder after urinating. Therefore, they usually have a high post-void residual (PVR) when measured on ultrasound. In patients with an overactive or spastic bladder, urine is emptied frequently, and the PVR is low volume. MS patients with urinary retention and a high PVR may need to intermit-

tently self-catheterize in order to fully empty the bladder and prevent urinary tract infections (UTIs). Sometimes, mixed bladder disturbances present with both retention and overactivity.

PVR is measured by an ultrasound after urination. If the residual is less than 150 cc, the diagnosis is an overactive or spastic bladder.²⁶² Medications that help to decrease bladder spasm, urinary urgency, and frequency include:

- Oxybutynin, both immediate release and extended release
- Tolterodine tartrate, both immediate and extended release forms
- Darifenacin, trospium CL, solifenacin, imipramine, and hyoscyamine

For patients with a PVR greater than 150 cc, the diagnosis is a flaccid bladder, and intermittent self-catheterization usually is recommended. Patients who have a flaccid bladder and urinary retention are prone to recurrent UTIs and will often need treatment for these and possible prophylactic antibiotic treatments. Patients with persistent UTIs and those who are unresponsive to therapy may need a urological referral.

Other treatments for bladder dysfunction in MS patients include:

- Botulinum toxin injections administered by a urologist to treat overactive bladder (usually need to be repeated every 3 months). The risk of this treatment is urinary retention²⁶³
- Pelvic nerve-stimulator devices²⁶⁴

BOWEL DYSFUNCTION

MS patients may experience bowel dysfunction in the form of constipation, diarrhea, or both.

Constipation is caused by several factors in MS:

- Stool may pass through the GI tract more slowly than normal
- Patients may deliberately restrict their fluid intake due to fear of urinary incontinence, which leads to hard stool formation
- Patients decrease their physical activity

To effectively manage constipation in MS, patients are encouraged to have a consistent daily bowel program, increase exercise, and increase fiber and fluids. Laxatives and stool softeners also may be necessary.

Diarrhea

Diarrhea in MS may be related to fecal impaction, medications, food intolerance, malabsorption, or infection. For loose stool in MS patients, bulk formers may be helpful; in severe diarrhea, drugs such as loperamide or opiates may be necessary. Monitoring of labs, weight, and diet is necessary in patients with persistent diarrhea, and some may need a gastroenterology referral for imaging or endoscopy to rule out underlying GI disease.

Involuntary bowel function also may occur in MS due to decreased sphincter control and hyperreflexive bowel. Pharmacologic measures and bowel retraining with timed evacuations may help.²³¹

SEXUAL DYSFUNCTION

Sexual dysfunction is common in both men and women with MS. A questionnaire determined that in the 45-59 year age group, approximately 50% of women and 75% of men feel that sex is important to QOL. Fulfilled sexuality plays a significant role in maintaining patients' personal relationships and QOL and yet often is an overlooked symptom in MS.²⁶⁵

Men with MS often experience problems involving erectile dysfunction (ED) (50%-75% incidence), decreased libido, and ejaculatory difficulties.^{266,267} Women also have problems with decreased libido, decreased lubrication, dyspareunia, and difficulty achieving orgasm. Sometimes pain and spasticity can cause problems with positioning during sexual intercourse. According to one survey, 67% of 5868 US men and women with MS identified significant sexual dysfunction (one or more symptoms that interfered with sexual function or satisfaction) over the previous 6-month period.²⁶⁷

Although not always effective, medications for ED, such as sildenafil,²⁶⁶ vardenafil, or tadalafil, may be helpful for men with MS. Managing other symptoms that interfere with sexual function, such as spasticity, fatigue, pain, paresthesia, and bladder and bowel dysfunction are important, and couples counseling to help cope with intimacy issues also are beneficial.^{231,268,269}

QUALITY OF LIFE

QOL is negatively impacted by many aspects of MS, including:

- Symptoms
- Incurability of the disease

- Disease unpredictability and progressive loss of independence
- Impaired mobility, often requiring walking aids or wheelchair use
- Decreasing ability to independently perform activities of daily living and self-care
- Chronic pain
- Intermittent relapses often requiring hospitalizations
- Impaired ability to work, often with loss of employment
- Financial hardship with high medical expenses
- Relationship difficulties due to illness, financial hardship, sexual dysfunction, and other aspects of the disease
- Restricted ability to participate in family, social, or community activities
- Declining ability to exercise

Crucial factors in preserving and improving MS patient perceptions of their QOL include:

1. A comprehensive, caring multidisciplinary health care team²⁰
2. Regular screening for unreported MS symptoms, including depression and cognitive dysfunction²⁰
3. A strong family-, social-, and community-support network
4. Healthy lifestyle including diet and exercise
5. Well-established routines for patient self-care
6. Regular preventive health care visits
7. Access to counseling services for patient and family

Exercise, yoga, and tai chi are all helpful for stretching, flexibility, and maintaining muscle tone. A study assessing the benefits of yoga found significant improvements in fatigue relative to a control group.²⁷⁰ Occupational therapy, physical therapy, aerobic exercise, and recreation can have positive impacts on quality of life, as well as on fatigue and depression.²⁷¹⁻²⁷³

Presently, no specific diet is recommended for MS patients. However, a well-balanced, low-fat diet is advised, including plenty of fresh fruits, vegetables, increased water and fluid intake, and avoidance of caffeine. Daily multivitamin use with calcium supplementation is recommended. To screen for osteoporosis, bone density scans should be performed in both men and women, particularly if there is a history of frequent steroid use for acute relapses. As in all women, female patients with MS have an increased risk of osteoporosis postmenopausally. Some data exist demonstrating that

hormonal changes during menstrual periods and menopause also can worsen MS symptoms.

Due to the link between sunlight radiation and reduced MS risk (MS less prevalent near the equator), studies also have looked at the preventive benefit of vitamin D.^{274,275}

Complementary and alternative therapies have been widely used in MS, with approximately 60% of patients using one or more alternative therapy, including acupuncture, meditation, massage, hypnotherapy, chiropractic medicine, and herbal therapies.²⁷⁶

In summary, optimal symptom management of MS is essential for improving and maintaining patient QOL and is key in providing a successful therapeutic strategy. Using a multidisciplinary team approach, pharmacologic and nonpharmacologic therapies together with frequent reassessment of symptoms and treatment adjustment can provide optimal symptom management.²⁷⁶

11 SPECIAL Considerations

MS AND PREGNANCY

Patients with MS typically are in the 20-40 year age group; for most females, this represents their childbearing years. Current evidence shows that MS does not affect the ability for women to conceive, and there is no increased risk of congenital malformations.²⁷⁷ However, a large study of 649 births by mothers with MS from Norway indicated that small-for-gestational-age neonates were more common in mothers with MS, and the deliveries were more complicated.²⁷⁷

A recent study of women with MS who conceived while taking IFN beta-1a therapy showed decreased birth weights, higher rates of miscarriage, stillbirth, and malformations (chromosome X abnormalities and Down's syndrome) in comparison with healthy controls who were not exposed to IFN beta. The study concludes that IFN beta therapy should be discontinued prior to conception or stopped as soon as pregnancy is identified.^{278,279}

None of the immunomodulating therapies are recommended for use during pregnancy. However, GA has a rating of Category B (no evidence of teratogenicity or other problems in animal studies, but human data are lacking). Patients considering pregnancy usually stop their immunomodulating therapy 1-2 months prior to trying to conceive but should discuss treatment options with their physicians. Additionally, patients who are taking natalizumab should wait 6 months to conceive after discontinuing treatment.

Fingolimod has a pregnancy category rating of C; there have been no adequate studies in pregnant women on this new oral drug; in animal studies, fetal abnormalities have occurred, and the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. The body takes approximately 2 months to eliminate fingolimod after discontinuation of treatment. Therefore, potential risks to the fetus may persist after treatment ends, and contraception is recommended for 2 months after treatment.¹⁷⁷

Clinical symptoms of MS, such as gait disturbances, fatigue, and urinary frequency may worsen during pregnancy. Although acute MS relapses tend to decrease during pregnancy, they may increase in the postpartum period. Relapses during pregnancy can be treated with steroids after the first trimester.^{162,280} Postpartum MS relapses have been treated successfully with IVIG and steroid therapy. Research shows that pregnancy in women with MS does not affect the long-term course of their disease.

Lactation and MS

All therapies should be avoided while breast feeding due to a lack of data regarding breast-milk excretion.²⁷⁷

MS IN CHILDREN

Five percent of all patients with MS develop the disease before the age of 18 and 1% before the age of 10 years. Although data are still limited for childhood MS, increasing evidence suggests that IFN beta and glatiramer acetate are safe, effective, and well-tolerated in the pediatric population.^{180,281,282}

INFECTIONS AND MS RELAPSE

Studies suggest that MS patients are more prone to acute relapses following infections, such as respiratory tract infections (RTI), colds, influenza, as well as enteric and hepatic

infections.²⁸³ In 2002, the Immunization Panel of the MS Council for Clinical Practice Guidelines (MSCCPG) met to review the risk of MS relapse after infections that potentially may be preventable with vaccination. The panel concluded that strong, consistent evidence exists demonstrating that infections increase the risk of MS exacerbations. However, the data were not clear on whether MS patients were at an increased risk of contracting infections.²⁸⁴

IMMUNIZATIONS AND MS

As many patients and clinicians are concerned that vaccinating MS patients will cause an acute relapse, the above panel for the MSCCPG reviewed data regarding this topic. They found that the influenza vaccine (the most commonly used vaccine), as well as the hepatitis B, varicella, tetanus, and Bacille Calmette-Guerin (BCG) vaccines are safe in MS patients and not associated with significant risk of exacerbation.²⁸⁴

12 FUTURE *of MS* *Treatment*

To further improve the understanding of the pathophysiology, diagnosis, and treatment of MS, intensive research efforts must be continued in the following areas:

1. Identify disease subtypes and subpopulations and the underlying epidemiologic, immunologic, and neurologic mechanisms for these differences.²⁸⁵ Identifying these areas may indicate if MS should be addressed differently in different subpopulations, with the goal of developing specific treatment regimens tailored to individual patients' needs.
2. Further research the effects of treatment initiated early in the course of MS and its impact on disease progression and long-term disability.⁹⁶
3. Develop improved MS disability scales to thoroughly measure not only the physical disabilities but also psychological, social, and cognitive dysfunction and impairment.⁹⁶
4. Identify better surrogate outcome measures and clinical measurements that correlate accurately to the clinical aspects of the patient's disease state.²⁸⁵
5. Research further into the use of biomarkers for monitoring disease activity and response to therapy.²⁸⁶
6. Further developments in genomic research for refining future individualized treatment options.
7. Develop new therapies that will help to promote axonal repair and neuroreparative processes as well as prevent neurodegeneration.
8. Perform longer-term treatment follow-up studies assessing secondary disease progression.²⁸⁵
9. Develop prophylactic therapies to delay or prevent the onset of MS in the at-risk population, most likely the first-degree relatives of those with MS.

13 CONCLUSION

Although much knowledge about MS has been gained in recent years, the disease continues to have a major impact on the quality of life of people with MS as well as their families. Available treatments offer the hope of symptom control as well as preventing disease progression and delaying disability, but further progress is needed. Increased efforts in understanding the mechanisms of neuroprotection may result in more effective treatments for progressive MS. Recent unprecedented advances in the development of new therapeutic targets and novel agents, including oral agents, for disease modification in MS indicate a new era in MS care that offers improved hope for disease control for patients and clinicians. Undoubtedly, advancing diagnostic technologies will provide not only earlier diagnosis but also more enhanced methods of monitoring disease progression and treatment response. This, as well as the establishment and validation of interim markers, will be instrumental in the design of clinical trials to more effectively evaluate the efficacy of current and future treatments.

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GLOSSARY OF TERMS

- Axon** – long, branched processes of the neuronal cell body that conduct efferent nerve impulses away from the cell body.
- B cell** – white blood cell manufactured in the bone marrow that makes antibodies.
- Balo's concentric sclerosis** – a demyelinating disease similar to MS but appears with concentric layers of demyelinated tissue on MRI.
- Benign MS** – persistently mild, non-progressive MS disease course.
- Black holes** – correlate with gliosis, demyelination, and axonal injury on pathology exams and are better predictors of progressive disability than inflammatory lesion measurement.
- Blood-brain barrier** – a semipermeable cell layer around blood vessels in the brain and spinal cord that prevents large molecules, immune cells, and potentially damaging substances and disease-causing organisms from passing out of the bloodstream into the CNS. A break in the BBB may underlie the disease process in MS.
- Clinically isolated syndrome** – an acute or subacute neurologic episode indicative of demyelination, not accompanied by any other symptoms, and often is associated with silent lesions on MRI.
- Demyelination** – occurs when the phospholipid sheath surrounding CNS axons is damaged and stripped away, resulting in slow, disordered, or arrested nerve conduction.
- Expanded disability status scale** – a disability scale using an ordinal scale of 1-10, measuring various functional system scores and ability to walk, with a high score indicating greater disability.
- Gadolinium** – a chemical compound that can be administered to a person during MRI to help distinguish between new and old lesions.
- Gadolinium-enhancing lesion** – a lesion appearing on MRI, following injection of gadolinium, that reveals a breakdown in the BBB. This breakdown indicates either a newly active lesion or the re-activation of an old one.
- MS functional composite** – a disability scale that measures cognition, ambulation, and hand/arm function. A single composite score is derived from the results of these 3 measures, and results are standardized with a reference population.
- Myelin** – a soft, white coating of nerve fibers in the CNS serving as insulation and an aid to efficient nerve fiber conduction.
- Myelin basic protein** – a protein group believed to play an important but undefined role in the process of the myelination within the brain and spinal cord.
- Neuromyelitis optica** – a necrotizing, inflammatory, demyelinating disorder targeting the spinal cord and optic nerves.
- Neuron** – the basic nerve cell unit of the CNS composed of a cell body and axon that interprets and transmits information.
- Nodes of Ranvier** – nodal spaces in the myelin sheath that allow rapid nerve impulse transmission along the axon by salutatory conduction within the CNS.
- Oligoclonal bands** – a diagnostic sign indicating abnormal immunological proteins in the cerebrospinal fluid; seen in approximately 90% of people with multiple sclerosis but not specific to MS.
- Oligodendrocyte** – myelin-producing neuroglia of the CNS.
- Optic neuritis** – inflammation or demyelination of the optic nerve with transient or permanent impairment of vision and occasionally pain.
- Plasmapheresis** – the removal, treatment, and return of blood plasma from blood circulation.
- Plaque** – an area of scarred or demyelinated CNS tissue appearing on MRI.
- Primary progressive MS** – a clinical course of MS characterized from the beginning by progressive disease, with no plateaus or remissions or an occasional plateau and very short-lived, minor improvements.
- Progressive relapsing MS** – a clinical course of MS that shows disease progression from the beginning, but with clear, acute relapses, with or without full recovery from those relapses along the way.
- Relapse** – acute neurologic events consistent with demyelination.
- Relapsing-remitting MS** – a clinical course of MS characterized by clearly defined, acute attacks with full or partial recovery and no disease progression between attacks.
- Secondary progressive MS** – a clinical course of MS that is initially relapsing-remitting and becomes progressive at a variable rate, possibly with an occasional relapse and minor remission.

Remission – a lessening in the severity of symptoms or their temporary disappearance during the course of the illness.

T cell – white blood cell that develops in the bone marrow, matures in the thymus, and works as part of the immune system in the body.

T1-weighted MRI – MR images show acute MS lesions as hypointense areas due to edema of the damaged brain tissue. It was the first quantitative, volumetric imaging study used in MS.

T2 lesion load – the changes in volume and number of lesions on T2-weighted MRI.

T2-weighted MRI – images show hyperintense bright lesions representing demyelination, edema, gliosis, or matrix destruction.

Trigeminal neuralgia – characterized by sharp facial pain resulting from activities such as chewing, smiling, and other simple facial movements.

Uhthoff's phenomenon – a paroxysmal decrease in vision usually brought on by an increase in temperature or exercise.

ABBREVIATIONS GUIDE

AAN	American Academy of Neurology	IFN	interferon
ACTH	adrenocorticotropic hormone	IgG	immunoglobulin G
ADEM	acute disseminated encephalomyelitis	IL	interleukin
AHSCT	autologous hematopoietic stem-cell transplantation	IVIG	intravenous immunoglobulin
APC	antigen presenting cell	LFT	liver function test
AP	action potential	LVEF	left ventricular ejection fraction
APP	action potential propagation	MBP	myelin basic protein
AV	atrioventricular	MDT	multidisciplinary team
BBB	blood-brain barrier	MHC	major histocompatibility complex
BCG	Bacille Calmette-Guerin	MP	methylprednisolone
BoNT A	botulinum toxin type A	MRI	magnetic resonance imaging
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	MRS	magnetic resonance spectroscopy
CBC	complete blood count	MSCCPG	MS Council for Clinical Practice Guidelines
CDMS	clinically definite MS	MSFC	multiple sclerosis functional composite
CHF	congestive heart failure	MTI	magnetization transfer imaging
CIS	clinically isolated syndrome	MTR	magnetization transfer ratio
CMSC	Consortium of Multiple Sclerosis Centers	MUGA	multiple gated acquisition
CNS	central nervous system	NAA	N-acetyl aspartate
CSF	cerebrospinal fluid	NAbs	neutralizing antibodies
CT	computed tomography	NMO	neuromyelitis optica
DIS	dissemination in space	NMSS	National Multiple Sclerosis Society
DIT	dissemination in time	NSAIDs	non-steroidal anti-inflammatory drugs
DMT	disease-modifying therapy	OCB	oligoclonal bands
DTI	diffusion tensor imaging	PBA	pseudobulbar affect disorder
DWI	diffusion weighted imaging	PLEX	plasma exchange
EAE	experimental allergic encephalitis	PML	progressive multifocal leukoencephalopathy
EBV	Epstein-Barr virus	PPMS	primary progressive MS
ED	erectile dysfunction	PRMS	progressive relapsing MS
EDSS	expanded disability status scale	PVR	post-void residual
ENFS	European Federation of Neurologic Sciences	QOL	quality of life
ESR	erythrocyte sedimentation rate	RRMS	relapsing-remitting MS
FLAIR	fluid attenuated inversion recovery	RTI	respiratory tract infections
fMRI	functional MRI	S1P	sphingosine-1-phosphate
GA	glatiramer acetate	SC	subcutaneous
Gd	gadolinium	SLE	systemic lupus erythematosus
GI	gastrointestinal	SPMS	secondary progressive MS
HLA	human leukocyte antigen		

TGF	transforming growth factor
Th	T helper cells
TNF	tumor necrosis factor
Tregs	regulatory T cells
UTI	urinary tract infection
VDRL	venereal disease research laboratory test
VZV	varicella-zoster virus

POSTTEST

- 1. Which of the following statements regarding axonal injury in MS is correct?**
 - a. It can only be detected reliably using high-powered microscopy techniques.
 - b. It is not related to progressive long-term disability in MS.
 - c. It occurs in normal-appearing white matter as well as in MS lesions.
 - d. It always produces neurological symptoms.
- 2. Which of the following is not an essential element for a diagnosis of MS according to the 2005 revised McDonald criteria?**
 - a. Elimination of other conditions by reliable differential diagnosis
 - b. Subjective report from the patient of their symptoms
 - c. Evidence of dissemination of lesions in time and space
 - d. Use of objective paraclinical laboratory findings
- 3. A 41-year-old Caucasian female patient had an acute neurological event (optic neuritis) consistent with demyelination without other symptoms approximately 2 years ago. She has been well since then but now presents to her neurologist with different neurological symptoms (brainstem dysfunction). In this patient, the most likely diagnosis is:**
 - a. CIS
 - b. Definite MS
 - c. RRMS
 - d. SPMS
 - e. PPMS
- 4. What percentage of patients with RRMS will develop SPMS after 10 years?**
 - a. 20%
 - b. 35%
 - c. 50%
 - d. 75%
 - e. 80%
- 5. Early and aggressive treatment of a CIS with disease-modifying therapies has been shown to consistently prevent MS.**
 - a. True
 - b. False
- 6. A black hole on MRI represents healing brain tissue following an acute exacerbation of MS.**
 - a. True
 - b. False
- 7. Influenza vaccine should not be given to MS patients due to a risk of precipitating an acute exacerbation of symptoms.**
 - a. True
 - b. False
- 8. A patient with known RRMS presents with symptoms of worsening acute neurological dysfunction. The most appropriate course of action would be to:**
 - a. monitor the patient in the outpatient primary care setting over the next few weeks until symptoms resolve.
 - b. have a specialist monitor the patient in an outpatient setting.
 - c. admit the patient for immediate treatment with an IFN beta or GA.
 - d. admit the patient for treatment with methylprednisolone intravenously.
 - e. admit the patient for lumbar puncture to rule out meningitis.

(Continue to page S4)

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- 9. Which of the following statements regarding neutralizing antibodies (NAbs) is correct?**
- a. NAbs are an experimental treatment for RRMS.
 - b. The presence of NAbs is associated with improved treatment response to DMTs in patients with MS.
 - c. NAbs may be produced in patients who are treated with a high-dose of methylprednisolone for acute MS relapse.
 - d. NAbs may be produced in patients taking any IFN beta product for MS.

- 10. First-line therapy for RRMS includes all of the following except:**
- a. IM IFN beta-1a
 - b. Natalizumab
 - c. Glatiramer acetate
 - d. SC IFN beta-1b
 - e. SC IFN beta-1a

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I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 3.0 credits.
 I participated in only part of the activity and claim _____ credits.

ACTIVITY POSTTEST

Please circle the appropriate answer:

1) a b c d	2) a b c d	3) a b c d e	4) a b c d e	5) a b
6) a b	7) a b	8) a b c d e	9) a b c d	10) a b c d e

Please answer the following questions by circling the appropriate rating.

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

	Outstanding	Good	Satisfactory	Fair	Poor
Evaluate new evidence and information on the pathophysiology and neuropathology of MS _____	5	4	3	2	1
Recognize the major diagnostic criteria and clinical subtypes of MS _____	5	4	3	2	1
Recognize clinical symptoms of MS, determine how these affect quality of life for patients, and understand effective symptom management therapies _____	5	4	3	2	1

CONT.

	Outstanding	Good	Satisfactory	Fair	Poor
Identify the role of laboratory and imaging investigations in the diagnosis and monitoring of patients with MS _____	5	4	3	2	1
Review disease-modifying therapy options for MS, including treatment goals, mechanisms of action of disease-modifying therapies, and possible side effects _____	5	4	3	2	1
Evaluate treatment outcomes for MS _____	5	4	3	2	1
Analyze disease progression and disability in patients with MS and the monitoring of these using disability scales _____	5	4	3	2	1

Please indicate if this activity was free from commercial bias. Yes No

If No, please indicate the topic(s) that were not free from commercial bias.

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity _____	5	4	3	2	1
Enhanced my current knowledge base _____	5	4	3	2	1
Will help me improve patient care _____	5	4	3	2	1
Provided new ideas or information I expect to use _____	5	4	3	2	1
Was timely and will influence my practice of medicine _____	5	4	3	2	1
Addressed my most pressing questions _____	5	4	3	2	1

Please indicate any changes you plan to make in your practice of medicine as a result of information you received from this activity.

Please rate your commitment level to making these changes _____ 5 4 3 2 1

In what time frame do you anticipate making these changes?

- Immediately 1-2 months 3-6 months At some point in the future

Based on my participation in this CME activity, I will now incorporate the following new clinical strategies:

(Check all that apply.)

- Utilize the most up-to-date information, skills, and tools to formulate an early, dependable clinical diagnosis of MS to prevent disease progression and preserve quality of life (QOL).
- Evaluate and select the most appropriate therapeutic options and apply this knowledge to MS patient care to optimize long-term disease management.
- Confidently initiate therapy with DMTs in a timely manner to prevent relapses, disease progression, neurodegeneration, and delay permanent disability in the long term.
- Assess technological advances and formulate individualized monitoring of MS symptoms to maintain functional ability and optimize patient health-related QOL.
- I already do all these things.

If this activity did not give you strategies to be better able to practice medicine, please list the factors acting as barriers.

This activity was designed to help the participant master the ABMS/ACGME core competency of patient care, medical knowledge, and practice-based learning and improvement. How well did this activity address this competency? _____ 5 4 3 2 1

Please provide general comments regarding this activity and suggest how it might be improved.

Please provide any other medical topics that would be of interest to you.

