Multiple Sclerosis: An Update

Kathryn Faguy, MA, ELS

Multiple sclerosis (MS) is the most common disabling neurologic condition in young adults and imposes high financial and quality of life costs on patients, their families, and society. Yet, developments in the battle against MS include new treatments to slow its progression and updated diagnostic criteria that can accelerate diagnosis and effective treatment. This article offers a review and update on the disease, focusing on risk factors and possible causes, symptoms, forms of MS, diagnostic criteria and tools, and the expanding array of approved treatments. It also reports on the skyrocketing cost of MS drugs, misdiagnosis, and special patient populations with MS.

Multiple sclerosis (MS) remains an enigmatic disease. Investigators have identified many risk factors for MS, but the precise cause still is unknown. Clinicians cannot accurately predict how the disease will affect individual patients over time. Although numerous treatments are available to help relieve MS symptoms and slow the disease’s progression in some cases, there still is no cure.

Disease Overview

MS is a chronic, disabling condition of the central nervous system (CNS). It is presumed to be an autoimmune process and causes multifocal inflammation and destruction of the myelin sheath that surrounds, supports, and protects nerve fibers (see Figure 1). These areas of inflammation and destruction are called plaques or lesions. The term sclerosis means hardening, a reference to the CNS plaques characteristic of MS. Ultimately, MS leads to loss of axons in the brain and spinal cord. The disease can progress at various rates and causes a wide variety of neurologic signs and symptoms. Symptoms can be mild, moderate, or severe; continuous or relapsing and remitting; and progressive or non-progressive. For many patients, however, the disease causes significant disability over time including mobility challenges, pain, and cognitive difficulties.

Prevalence, Incidence, and Demographics

An estimated 2.5 million people worldwide have MS, but distribution of the disease varies significantly among geographic regions. The prevalence of MS increases as distance from the equator increases and is several times higher in temperate climates than in tropical ones. Inhabitants of the northern United States, Canada, Europe, New Zealand, and southeastern Australia are particularly affected.
MS is comparatively rare in Africa and East Asia, where the prevalence of the disease is fewer than 5 per 100 000 people. In the highest-risk areas, prevalence is greater than 100 per 100 000 people. In some parts of Canada, for example, the rate is as high as 385 per 100 000 people. However, there are exceptions to this geographic pattern of susceptibility. For example, the Inuit people of Canada and Alaska rarely develop MS.

The geographic risk of developing MS appears to be set early in life and does not change after early adolescence. For example, if a person lives in a low-risk geographic region before age 15 years and then moves to a high-risk region, he or she retains the lower risk associated with the childhood residence, and vice versa.

The estimated prevalence of MS within the United States varies significantly, from 58 to 95 individuals per 100 000. As many as 570 000 Americans are thought to have MS, approximately 0.21% of the population. Whites are more affected than people of other races and ethnicities. Approximately 12 000 new diagnoses are made annually in the United States.

Initial symptoms of MS usually appear when patients are aged 20 to 40 years, and people in this age group account for 70% of new diagnoses. It is rare for symptoms to develop after age 60 or before 15 years old, but children and elderly people can develop the disease. Women are approximately 3 times as likely as men to develop MS; however, when the disease strikes later in life, the sex ratio is more even. For women, the average age at MS diagnosis is 29 years; for men, it is 31 years.

Causes, Associations, and Disease Mechanism
A leading hypothesis regarding the cause of MS is that it occurs in people who are genetically susceptible to the disease and who have experienced some type of environmental assault such as exposure to a particular virus or toxin. For example, the Epstein-Barr virus, which causes infectious mononucleosis, has been linked to MS. Compared with people who have not been infected with the virus, the risk of developing MS is 15 times higher for people infected with Epstein-Barr virus during childhood and 30 times higher for people infected in adolescence or adulthood. Also, MS plaques express high levels of Epstein-Barr virus antigens. The nature of this association is not yet understood, however, and many people with antibodies for the virus do not have MS.

In addition, having another autoimmune disease, such as thyroid disease, type 1 diabetes, or inflammatory bowel disease, is known to slightly raise the likelihood of developing MS. Low levels of sun exposure and vitamin D have been suggested as possible contributing factors to MS development, as have cigarette smoking, obesity, and high levels of salt consumption. On the other hand, several previously suspected risk factors have been definitively ruled out (see Box 1).

To evaluate the roles of sun exposure and vitamin D status on the risk of developing MS, Lucas et al performed a case-control study in groups of Australian adults with and without a first demyelinating event. The researchers found that both factors might play a role in demyelination. Specifically, higher levels of...
sun-related skin damage and higher serum levels of vitamin D were independently associated with decreased risk of a first demyelinating event. \(^12\)

Although MS is not considered a genetic condition, family members of people with MS are at increased risk. \(^5,6\) First-degree relatives of a person with MS have a 7-times-greater chance of developing the disease than do those who have no close relatives with MS. \(^9\) For monozygotic twins, the concordance is 30%. \(^7\) So far, the only chromosomal locus consistently associated with susceptibility to MS is major histocompatibility complex, class II, DR beta 1 (\(HLA-\text{DRB1}\)), which is believed to account for approximately half of the disease’s genetic basis. \(^4,7,9\) Conversely, the \(HLA-C^*05\) allele is believed to protect against MS.

MS is considered an immune-mediated disease. It begins when various types of immune cells, such as T cells, are activated and penetrate the blood-brain barrier. These cells then secrete interleukins that allow additional immune cells to enter the CNS. \(^4\) The invading cells produce inflammatory cytokines, proteases, free radicals, glutamate, and nitric acid that damage the myelin, ultimately leading to destruction of the nerve fibers or axons. \(^4,13,14\)

**Multiple Sclerosis Clusters**

Several clusters or so-called epidemics of MS have been noted in the medical literature, and although explanations for these outbreaks have been suggested, none have been proven. \(^7\) One of the earliest and most well known of these clusters occurred in the Faroe Islands, which are located in the North Atlantic between Norway and Iceland. Before World War II, MS had not been documented among the inhabitants of the Faroe Islands, but beginning in 1943 several waves of MS diagnoses were reported. \(^15,16\)

British troops occupied the Faroe Islands for 5 years during World War II, and many of the occupying force came from the Scottish Highlands, where the prevalence of MS is high (90 cases per 100 000 people). One early investigator of the outbreaks, American neurologist John Kurtzke, speculated that the troops might have brought a virus with them that triggered a new susceptibility to MS in the native Faroe Island population. \(^15,16\) He suggested that infection with the virus probably is asymptomatic and typically occurs during adolescence or young adulthood. According to Kurtzke’s hypothesis, MS is a rare, late outcome of infection with the as-yet-unidentified virus. \(^17\) However, no specific cause for the Faroe Island clusters has ever been determined. \(^15,16\)

Additional MS clusters have been identified among residents of DePue, Illinois; Rochester, New York; and El Paso, Texas. These outbreaks tentatively were linked to high levels of exposure to zinc and other metals used in manufacturing facilities and metal smelters. \(^15\) However, no evidence definitively links any metal with MS. \(^15\)

**Symptoms**

Symptoms of MS are highly variable and can be attributed to other conditions (see **Box 2**). \(^4\) Symptoms can occur singly or in combination and can arise as sudden attacks or progress steadily. \(^7\)

Typical MS symptoms include\(^5,7,9,21\):

- Fatigue (occurs in 70% of cases).
- Unusual sensations such as paresthesia (tingling or “pins and needles”), often an early symptom.
- Muscle stiffness.
- Muscle spasms.
- Tremors.
- Numbness or weakness.
- Dizziness.
- Paralysis (usually in the legs) or gait disturbances.
- Bladder or bowel problems such as urinary urgency or retention.

**Box 1**

**Disproven Suspected Causes of Multiple Sclerosis**

Although the exact cause or causes of multiple sclerosis (MS) remain unknown, researchers have disproven a number of previously suspected causes including:

- Using Aspartame, the artificial sweetener used in soft drinks and foods.
- Having been exposed to heavy metals such as mercury, manganese, or lead.
- Having allergies.
- Having a history of traumatic injury.
- Living with a dog or being exposed to dogs. (At one time, canine distemper was suggested as a possible cause.)
Multiple Sclerosis: An Update

Multiple Sclerosis Types

MS takes several clinical forms and sometimes converts from one form to another. Typically, the disease begins with an acute episode but then exhibits varying degrees of remission or progression.1

Relapsing-Remitting

The most common form of the disease, occurring in about 85% of MS patients, is relapsing-remitting MS.4 Patients with relapsing-remitting MS experience flare-ups of symptoms, also known as relapses, that develop over days or weeks and then improve spontaneously. Relapses are followed by a period of remission that can last for months or years and can be either full or partial (ie, symptoms disappear completely or improve to varying degrees).3,6,22 However, the disease still is active even during periods when the patient is in remission.13

Primary Progressive

Primary progressive MS affects about 10% to 15% of MS patients and is characterized by gradual worsening of symptoms without periods of remission.5 This disease course occurs more often in people who are older than 40 years at the onset of disease.4 There is no effective treatment for primary progressive MS22,23; thus, management focuses on controlling symptoms.23

Multiple Sclerosis Types

MS takes several clinical forms and sometimes converts from one form to another. Typically, the disease begins with an acute episode but then exhibits varying degrees of remission or progression.1

Relapsing-Remitting

The most common form of the disease, occurring in about 85% of MS patients, is relapsing-remitting MS.4 Patients with relapsing-remitting MS experience flare-ups of symptoms, also known as relapses, that develop over days or weeks and then improve spontaneously. Relapses are followed by a period of remission that can last for months or years and can be either full or partial (ie, symptoms disappear completely or improve to varying degrees).3,6,22 However, the disease still is active even during periods when the patient is in remission.13

Primary Progressive

Primary progressive MS affects about 10% to 15% of MS patients and is characterized by gradual worsening of symptoms without periods of remission.5 This disease course occurs more often in people who are older than 40 years at the onset of disease.4 There is no effective treatment for primary progressive MS22,23; thus, management focuses on controlling symptoms.23

Secondary Progressive

Secondary progressive MS occurs when relapsing-remitting MS converts to a course of gradually progressive disease. Most people with relapsing-remitting MS eventually develop secondary progressive disease: about 50% within 10 years, 80% within 20 years, and 90% after 25 years.3,14

- Erectile dysfunction.
- Visual abnormalities including double vision, blurred vision, or unilateral vision loss.
- Pain on eye movement.
- Slurred speech.
- Cognitive deficits such as memory problems, reduced attention span, or difficulty with problem solving.
- Depression or mood swings.

Box 2

Differential Diagnoses for Multiple Sclerosis8,18-20

Numerous diseases and disorders mimic MS, and the diagnostic criteria for MS require that there be no better explanation for a patient’s signs and symptoms. Depending on a patient’s risk factors, personal and family history, and examination results, clinicians might consider and test for the following differential diagnoses:

Infectious Diseases
- HIV infection
- Lyme disease
- Meningitis
- Progressive multifocal leukoencephalopathy
- Rubella encephalitis
- Syphilis
- Whipple disease

Other Inflammatory and Immune-mediated Conditions
- Behcet disease
- Sarcoidosis
- Sjögren syndrome
- Sneddon syndrome
- Susac syndrome
- Systemic lupus erythematosus
- Vasculitis

Genetic Disorders
- Hereditary spastic paraparesis
- Leukodystrophies
- Mitochondrial disorders

Spinal Cord Conditions
- Cavernous malformation
- Intramedullary cord tumor
- Spondylotic myelopathy
- Syringomelia

Ischemic Disorders
- Amyloid angiopathy
- Antiphospholipid antibody disease
- Cardioembolic stroke
- Veno-occlusive disease

Cancer
- Metastatic disease affecting the central nervous system (CNS), particularly metastasis of primary cancers of the lung, breast, and kidney, as well as melanoma
- Lymphoma (CNS and intravascular)

Abnormalities and Injuries of the CNS
- Chiari malformation
- Herniated discs
- Spondylosis

Other Demyelinating Disorders
- Acute disseminated encephalomyelitis
- Neuromyelitis optica

Dietary Deficiencies
- Copper deficiency
- Vitamin B12 deficiency

Erectile dysfunction.
- Visual abnormalities including double vision, blurred vision, or unilateral vision loss.
- Pain on eye movement.
- Slurred speech.
- Cognitive deficits such as memory problems, reduced attention span, or difficulty with problem solving.
- Depression or mood swings.

Multiple Sclerosis Types

MS takes several clinical forms and sometimes converts from one form to another. Typically, the disease begins with an acute episode but then exhibits varying degrees of remission or progression.1

Relapsing-Remitting

The most common form of the disease, occurring in about 85% of MS patients, is relapsing-remitting MS.4 Patients with relapsing-remitting MS experience flare-ups of symptoms, also known as relapses, that develop over days or weeks and then improve spontaneously. Relapses are followed by a period of remission that can last for months or years and can be either full or partial (ie, symptoms disappear completely or improve to varying degrees).3,6,22 However, the disease still is active even during periods when the patient is in remission.13

Primary Progressive

Primary progressive MS affects about 10% to 15% of MS patients and is characterized by gradual worsening of symptoms without periods of remission.5 This disease course occurs more often in people who are older than 40 years at the onset of disease.4 There is no effective treatment for primary progressive MS22,23; thus, management focuses on controlling symptoms.23

Secondary Progressive

Secondary progressive MS occurs when relapsing-remitting MS converts to a course of gradually progressive disease. Most people with relapsing-remitting MS eventually develop secondary progressive disease: about 50% within 10 years, 80% within 20 years, and 90% after 25 years.3,14

- Erectile dysfunction.
- Visual abnormalities including double vision, blurred vision, or unilateral vision loss.
- Pain on eye movement.
- Slurred speech.
- Cognitive deficits such as memory problems, reduced attention span, or difficulty with problem solving.
- Depression or mood swings.
**Progressive-Relapsing**

In progressive-relapsing MS, the disease symptoms worsen progressively from onset, but the patient also experiences distinct attacks or relapses. This type is relatively rare, affecting approximately 5% of patients. As with primary progressive disease, there is no effective treatment for progressive-relapsing MS, only relief for symptoms.

**Clinically Isolated Syndrome**

Patients with clinically isolated syndrome have a single symptomatic episode lasting at least 24 hours, which can be a precursor to developing relapsing-remitting MS or another type of the disease. The syndrome also is sometimes described as a first clinical demyelinating event. Approximately 88% of patients with clinically isolated syndrome and CNS lesions apparent on magnetic resonance (MR) imaging develop MS within 14 years. However, many patients do not redevelop symptoms or show imaging evidence of the disease for several years after an initial symptomatic episode.

**Benign**

Benign MS is characterized by near-total remission between symptomatic episodes and little or no accumulation of disability. The definition of benign MS is debated, but it is generally considered to be relapsing-remitting MS with a disability score of less than 3 on the Expanded Disability Status Scale for a period of at least 10 years. On this scale, clinicians assign a score of 3 to patients who are fully ambulatory but have moderate disability in one functional system or minimal disability in 3 or 4 functional systems. The function of the following 7 systems is assessed:

- Pyramidal – weakness and paralysis.
- Cerebellar – control of body movement.
- Brainstem – nystagmus, ability to speak and swallow.
- Sensory – sense of touch, pain, and proprioception.
- Bladder and bowel.
- Visual.
- Mental.

**Asymptomatic**

Also known as preclinical, subclinical, or radiologically isolated MS, asymptomatic MS involves lesions that are detected incidentally on an MR examination or during an autopsy, but with no clinical indications of the disease. The rate of conversion from asymptomatic MS to clinical MS is approximately one-third at 5 years after initial detection of lesions. However, there is no consensus regarding follow-up assessment for individuals who have asymptomatic MS or what treatment, if any, they should receive. No risk factors have been identified to help predict which individuals are likely to convert from asymptomatic to symptomatic disease.

**Fulminant**

Fulminant MS is a rare, rapidly progressing disease that can lead to severe disability or death within weeks or months of onset. It also is termed malignant MS or the Marburg variant of MS, after physician Otto Marburg who described this course of the disease in the early 20th century. Whereas other forms of MS affect only the CNS, fulminant MS attacks the peripheral nervous system as well. Death often is due to involvement of the brainstem including herniation and mass effect from MS pathology, which is damage to the brainstem area similar to that caused by a tumor.

**Diagnosis**

MS is primarily a clinical diagnosis based on signs, symptoms, and patient history—particularly a history of relapses and progressive disability. Imaging examinations and paraclinical tests aid in diagnosis. These tests and examinations include MR imaging of the CNS, analysis of the cerebrospinal fluid, and visual evoked potentials testing to measure electrical activity in the brain. Previously, diagnosis of MS depended on multiple symptomatic attacks, and clinicians often took a “wait-and-see” approach to diagnosis. That approach has changed, however: Clinicians now know that early diagnosis is important because early treatment can reduce the likelihood of disability and additional relapses. Thus, the emphasis is on detecting MS in its initial stages and beginning treatment promptly.

**History of Diagnostic Criteria**

In 1965 Schumacher and colleagues proposed a means of standardizing MS diagnosis. They introduced the concepts of “dissemination in time” and
“dissemination in space,” which are still critical to diagnosing MS today. Dissemination in time refers to the requirement that MS flares or relapses be separated by at least 30 days. Dissemination in space requires evidence of MS activity in 2 or more separate areas of the CNS. The Schumacher criteria also specified that “The signs and symptoms cannot be explained better by another disease process,” which continues to be a requirement of MS diagnosis more than 50 years later.7 In 1983, the Posner criteria added spinal fluid evaluation and evoked potential testing to the criteria for MS diagnosis. These additional tests can document asymptomatic changes in the CNS and aid in establishing dissemination in space and dissemination in time.7

In 2000, an international panel of experts was convened to reassess the Posner criteria and recommend changes in light of new developments in MR imaging. W Ian McDonald served as the panel’s chairman, and the criteria have since been known as the McDonald criteria.7 Under the McDonald criteria, clinicians can use MR imaging of the CNS to establish both dissemination in space and dissemination in time. For example, a repeat scan performed 3 months or more after a baseline scan can demonstrate changes that confirm dissemination in time, and lesions that appear in different parts of the brain and spinal cord on MR images confirm dissemination in space.

The McDonald criteria were revised and updated in 2005 and 2010. The updates were intended to speed diagnosis without diminishing specificity and sensitivity.7 Nevertheless, the 2010 criteria have been criticized for their complexity and relatively low sensitivity of approximately 60%.8 A key goal of all versions of the McDonald criteria has been maximizing specificity (ie, reducing the number of incorrect MS diagnoses) rather than achieving the highest possible sensitivity (ie, identifying as many people as possible who have MS).8 Another criticism of the McDonald criteria is that they are based on data gathered from a population of European patients and therefore might not apply as effectively to people of non-European ancestry.4 Specifically, more study is warranted before the criteria are applied to African American and Latino patients with suspected MS.29

Other criteria for diagnosing MS have been developed, such as the Swanton criteria, which are reported to have comparable specificity, along with better sensitivity than the McDonald criteria. However, no other diagnostic criteria have been widely adopted by clinicians.14

Applying the 2010 McDonald Criteria
The 2010 McDonald criteria rely on current and previous symptomatic attacks and evidence of lesions seen on brain and spinal cord MR imaging to determine diagnosis. Under the 2010 criteria, dissemination in space can be demonstrated by clinical or imaging evidence of lesions in 2 or more of 4 key areas of the CNS: the periventricular, juxtacortical, and infratentorial areas, as well as the spinal cord.8 Dissemination in time can be demonstrated using clinical history, sequential MR images, or a single MR scan that shows both enhancing and nonenhancing lesions, which are indicative of at least 2 separate demyelinating events.7 The 2010 diagnostic criteria are summarized in Table 1.

Thus, it is possible to diagnose MS after a single symptomatic attack if MR imaging shows enhancing and nonenhancing lesions in 2 of the 4 designated areas.8 Previously, a second MR examination of the brain was required at least 30 days after an initial or baseline scan to confirm the diagnosis. As a result of the 2010 criteria, earlier diagnosis and treatment are possible, and more patients have been shifted from a diagnosis of possible MS to definite MS. However, experts caution that the patient’s clinical presentation should drive diagnostic classifications and treatment decisions8 and diagnosis should not be made solely on the basis of MR evidence, without consideration of the clinical picture. A survey of neurologists who treat patients with MS suggested that misdiagnosis of the disease might be common (see Box 3).

MR Imaging’s Role
MR imaging is the preferred method for confirming an MS diagnosis and monitoring disease progression.28 MR can be used to estimate the lesion load and level of disease activity and to provide prognostic information.7 Patients with more lesions apparent on MR images at diagnosis are known to experience greater disability later in the disease course than patients with fewer lesions at diagnosis.23

In addition to lesions, an MR finding commonly associated with MS is atrophy of the brain and spinal cord.33 The rate of atrophy ranges from 0.6% to 1.35%
Patients with the relapsing-remitting form have the highest rate of brain atrophy, and atrophy is significantly correlated with disability and cognitive impairment in patients with MS. Brain abnormalities are apparent on MR scans in 90% to 95% of patients with MS. Also, as many as per year, which is approximately 4 times greater than the normal consequence of aging. The atrophy primarily affects the brain’s gray matter. At one time, brain atrophy was considered characteristic of late-stage disease. However, researchers now know that CNS atrophy occurs during all stages, even in early MS cases. Patients with the relapsing-remitting form have the highest rate of brain atrophy, and atrophy is significantly correlated with disability and cognitive impairment in patients with MS. Brain abnormalities are apparent on MR scans in 90% to 95% of patients with MS. Also, as many as

### Table 1

**The 2010 McDonald Criteria for Diagnosis of Multiple Sclerosis**

<table>
<thead>
<tr>
<th>No. of Attacks</th>
<th>Evidence of Lesions</th>
<th>Additional Data Needed for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>Objective clinical evidence of ≥ 2 lesions or of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Dissemination in space, demonstrated by:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 lesion visible on T2-weighted MR images in at least 2 of 4 multiple sclerosis (MS)-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delay diagnosis until a further clinical attack* implicating a different CNS site occurs</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>Objective clinical evidence of 1 lesion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥ 2 lesions</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>1 year of disease progression (retrospectively or prospectively determined) and 2 of 3 of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>Evidence of DIS in the brain based on ≥ 1 T2 lesion(s) in the MS-characteristic regions (periventricular, juxtacortical, infratentorial)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; IgG, immunoglobulin G; MR, magnetic resonance.

*An attack is a neurological disturbance typical of MS, lasting at least 24 hours without fever or infection. Attacks must be separated by at least 30 days from the onset of one attack to the onset of the second and can be either reported or observed.*

---

**Table 1**

**The 2010 McDonald Criteria for Diagnosis of Multiple Sclerosis**

<table>
<thead>
<tr>
<th>No. of Attacks</th>
<th>Evidence of Lesions</th>
<th>Additional Data Needed for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>Objective clinical evidence of ≥ 2 lesions or of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Dissemination in space, demonstrated by:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 lesion visible on T2-weighted MR images in at least 2 of 4 multiple sclerosis (MS)-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delay diagnosis until a further clinical attack* implicating a different CNS site occurs</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>Objective clinical evidence of 1 lesion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥ 2 lesions</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>None</td>
<td>1 year of disease progression (retrospectively or prospectively determined) and 2 of 3 of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>Evidence of DIS in the brain based on ≥ 1 T2 lesion(s) in the MS-characteristic regions (periventricular, juxtacortical, infratentorial)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; IgG, immunoglobulin G; MR, magnetic resonance.

*An attack is a neurological disturbance typical of MS, lasting at least 24 hours without fever or infection. Attacks must be separated by at least 30 days from the onset of one attack to the onset of the second and can be either reported or observed.*
75% of patients’ MR images demonstrate spinal cord plaques. However, approximately 5% of patients with clinically apparent MS do not show signs of the disease on MR images at the time of diagnosis. Furthermore, in people older than 50 years, normal, age-related changes in the brain can appear similar to changes caused by MS.

Abnormalities seen on MR images do not always correlate well with clinical signs and reported symptoms. For example, a few patients have little impairment from MS, but show significant MS-related lesions on MR scans. This phenomenon is known as the clinical-radiologic paradox. Possible reasons for this lack of correlation have been suggested such as the brain’s ability to compensate for damage by adapting and reorganizing.

The Consortium of Multiple Sclerosis Centers updated its recommended MR protocols in 2015. The new guidelines recommend 3-D MR imaging over 2-D imaging whenever possible. The consortium supports use of a standardized brain MR imaging protocol with gadolinium contrast for initial diagnosis and follow-up (see Table 2). In addition, the spinal cord should be scanned with MR if initial brain imaging is nondiagnostic or if the patient presents with signs or symptoms suggesting spinal cord involvement (see Table 3).

T2-weighted imaging plus T1-weighted imaging with gadolinium contrast is the standard method for confirming an MS diagnosis (see Figure 2). T2-weighted or fluid-attenuated inversion recovery (FLAIR) images show the total number of MS lesions and the overall disease burden. T1-weighted images with gadolinium contrast can display new lesions that occur from breach of the blood-brain barrier and resulting inflammation. T1-weighted images obtained before or after contrast administration can show so-called black holes, which are older, inactive lesions.

One way to improve the overall sensitivity of MR imaging for detecting MS-related lesions is to use higher-field equipment (ie, 3 T vs 1.5 T). This can increase the detection rate by 20% to 50% and enable earlier treatment for more patients. However, higher-field imaging might not be useful for patients with an established MS diagnosis because increased sensitivity has not been shown to affect treatment decisions for this group.

Several advanced MR imaging techniques help assess MS patient outcomes as part of clinical trials. These techniques, which include diffusion tensor imaging and magnetization transfer imaging, are more specific than conventional MR sequences for

---

**Box 3**

**Second Opinion: Not Multiple Sclerosis After All**

To explore the occurrence, causes, and effects of incorrectly diagnosed MS, Solomon et al surveyed neurologists in the United States and Canada who specialized in caring for patients with MS. They invited 242 neurologists to participate via an email message with a link to the unvalidated survey instrument. Slightly more than 50% of those invited to participate completed and returned the survey form.

When presented with the question, “Have you ever evaluated a patient who carried an MS diagnosis (given by another provider) for longer than a year who, after your neurologic examination and review of lab data, you strongly felt did NOT in fact have MS?” almost all of the respondents (95.1%) indicated yes. In fact, during the preceding year, 40% of responding neurologists indicated that they had cared for between 3 and 5 patients who they believed to have been incorrectly diagnosed with MS. Furthermore, more than one-third of the respondents reported caring for 6 or more such patients in the past year. When asked for the most likely alternative diagnoses for these patients, respondents chose nonspecific white-matter abnormalities, small vessel ischemic disease, migraines, psychiatric illnesses, fibromyalgia, neuromyelitis optica, and a variety of other disorders.

Solomon and colleagues pointed to incorrect interpretation of MR imaging examinations as a likely cause of the misdiagnoses, along with the conviction that MS should be diagnosed promptly and therapy initiated as soon as possible. Among probable harms of misdiagnosing MS, the researchers mentioned the cost of disease-modifying therapy and the possible adverse effects associated with MS treatment.

Another troubling survey finding was that some neurologists (about 13% of the respondents) indicated that they had sometimes not informed a patient when they believed a misdiagnosis had occurred. The most commonly cited reason for not informing these patients was that the patient was not currently taking a disease-modifying therapy. Risk of psychological harm to the patient was the second most commonly mentioned reason for nondisclosure of suspected misdiagnosis.
Gadolinium enhancement also is useful for imaging optic neuritis (inflammation of the optic nerve) and lesions in the spinal cord. Numerous contrast media containing gadolinium are available; most are formulated at a concentration of 0.5 mol/L. Standard dosing for gadolinium-enhanced MR imaging of the CNS is 0.1 mmol/kg of body weight. Studies have indicated that detection of MS lesions and certain other pathologies, such as brain tumors, might be enhanced at concentrations of 0.2 mmol/kg to 0.3 mmol/kg. The higher dose can be administered for follow-up imaging in cases where the diagnosis is doubtful. Alternatively, a dose of 0.2 mmol/kg has been recommended for initial assessment. This might represent the most effective distinguishing demyelination and axon loss. However, these techniques are not yet part of routine MS diagnosis and follow-up.

**T1-Weighted Imaging**

T1-weighted images with gadolinium contrast provide information about recent disease activity by showing areas of active inflammation. Gadolinium enhancement occurs when there has been a breakdown of the blood-brain barrier. New MS lesions go through a period lasting from 2 to 6 weeks during which they enhance with gadolinium contrast. This is the inflammatory phase of lesion development.

MS lesions show 2 patterns of enhancement on T1 imaging. They can appear as nodules or rings. The ring pattern is characteristic of older lesions that have been reactivated, whereas gadolinium-enhancing nodules are new lesions. Gadolinium enhancement also is useful for imaging optic neuritis (inflammation of the optic nerve) and lesions in the spinal cord.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field strength</td>
<td>Good quality scans with adequate signal-to-noise ratio and resolution (in-section pixel resolution of $\leq 1$ mm $\times 1$ mm)</td>
</tr>
<tr>
<td>Scan prescription</td>
<td>Use of subcallosal plane to prescribe or reformat axial oblique sections</td>
</tr>
<tr>
<td>Coverage</td>
<td>Whole-brain coverage</td>
</tr>
<tr>
<td>Section thickness and gap</td>
<td>$\leq 3$ mm, no gap for 2-D acquisition or 3-D reconstruction</td>
</tr>
</tbody>
</table>
| Core sequences | Anatomic 3-D inversion recovery-prepared T1 gradient echo (eg, 1-mm to 1.5-mm thickness) Gadolinium single dose, 0.1 mmol/kg given for 30 seconds
3-D sagittal T2WI FLAIR$^b$ (eg, 1-mm to 1.5-mm thickness) 3-D T2WI$^b$ (eg, 1-mm to 1.5-mm thickness) 2-D axial DWI ($\leq 5$-mm sections, no gap) 3-D FLASH (non-IR prep) postgadolinium$^b$ (eg, 1-mm to 1.5-mm thickness) 3-D series would be typically reconstructed to 3-mm thickness for display and subsequent comparison for lesion counts |
| Optional sequences | Axial proton attenuation Pregadolinium or postgadolinium axial T1 spin-echo (for chronic black holes) SWI for identification of central vein within T2 lesions |

**Abbreviations:** DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; FLASH, fast low angle shot; IR, inversion recovery; SWI, susceptibility weighted imaging; T2WI, T2-weighted imaging.

$^a$Minimum 5-minute delay before obtaining postgadolinium T1. The 3-D sagittal FLAIR may be acquired immediately after contrast injection before the 3-D FLASH series.

$^b$If unable to perform a 3-D acquisition, then perform 2-D axial and sagittal FLAIR, axial fast spin-echo proton attenuation/T2, and axial postgadolinium T1WI spin-echo at $\leq 3$-mm section thickness.

Gadolinium contrast is contraindicated or should be used cautiously in patients who have acute renal failure or severe renal insufficiency. This is because of the risk of nephrogenic systemic fibrosis, a rare but disabling approach in terms of balancing time, cost, and sensitivity. Guidelines recommend a minimum 5-minute delay between contrast injection and imaging to optimally enhance MS lesions.

 guided reading

Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field strength</td>
<td>Scans should be of good quality, with adequate signal-to-noise ratio and resolution (in-section pixel resolution of ≤ 1 mm × 1 mm)</td>
</tr>
<tr>
<td></td>
<td>Closed magnets (large bore for patients with claustrophobia) preferred</td>
</tr>
<tr>
<td>Coverage</td>
<td>Cervical cord coverage*</td>
</tr>
<tr>
<td>Section thickness and gap</td>
<td>Sagittal: ≤ 3 mm, no gap; axial: 5 mm, no gap</td>
</tr>
<tr>
<td>Core sequences</td>
<td>Sagittal T2</td>
</tr>
<tr>
<td></td>
<td>Sagittal proton attenuation, STIR, or PSTI-IR</td>
</tr>
<tr>
<td></td>
<td>Axial T2 through lesions</td>
</tr>
<tr>
<td>Optional sequences</td>
<td>Axial T2 through complete cervical cord</td>
</tr>
<tr>
<td></td>
<td>Gadolinium* and postgadolinium sagittal T1</td>
</tr>
<tr>
<td></td>
<td>Sagittal T1</td>
</tr>
</tbody>
</table>

Abbreviations: PSTI-IR, phase-sensitive T1 inversion recovery; STIR, short tau inversion recovery.

*Thoracic and conus coverage recommended if symptoms localize to this region to rule out an alternate diagnosis.

Minimum 5-minute delay before obtaining postgadolinium T1. Additional gadolinium does not need to be administered for spinal cord imaging if it follows a contrast brain MR imaging study.


Figure 2. Axial magnetic resonance (MR) images of the brain of a 30-year-old woman with relapsing-remitting multiple sclerosis (MS). A. T2-weighted MR image. B. FLAIR (fluid-attenuated inversion recovery) image. C. Contrast-enhanced T1-weighted image. The lesions on FLAIR usually are prominent and several small lesions are depicted only on FLAIR (arrows). Reprinted with permission from Ge Y. Multiple sclerosis: the role of MR imaging. AJNR Am J Neuroradiol. 2006;27(6):1165-1176.

Gadolinium contrast is contraindicated or should be used cautiously in patients who have acute renal failure or severe renal insufficiency. This is because of the risk of nephrogenic systemic fibrosis, a rare but disabling
in gray matter, especially the cerebral cortex and basal ganglia. Gray matter lesions tend to be less inflamed than white matter lesions and might therefore be less visible on MR imaging. Although most MS lesions are small, some are as large as several centimeters and thus can mimic tumors and other abnormalities. Spinal cord lesions associated with MS appear more frequently in the cervical spinal cord than in the thoracic spinal cord (see Figure 4). Spinal cord lesions usually are less than 2 vertebral bodies long and commonly appear on the dorsolateral aspect of the spinal cord. In addition, these lesions tend to be asymmetric and multifocal.

One limitation of T2-weighted imaging in MS diagnosis is its lack of specificity. In addition to demonstrating demyelination and loss of axons, T2-weighted images reflect inflammation and edema. This lack of specificity might be part of the explanation for the clinicoradiologic paradox.

Follow-up Imaging
Guidelines recommend follow-up brain imaging with gadolinium contrast for patients with MS or suspected MS to:
- Demonstrate changes over time as part of the diagnostic process, if necessary.
- Assess unexpected worsening of MS symptoms.
- Reassess the original diagnosis, if in doubt.
- Establish a baseline before treatment begins or when planning changes in treatment.

In addition, patients who have relapsing-remitting MS and are taking a disease-modifying drug should have a follow-up scan 6 to 12 months after starting treatment. Follow-up scanning might be indicated sooner if concerns about disease progression arise.

Paraclinical Tests for MS Diagnosis
Physicians previously relied on paraclinical tests to help diagnose MS including analysis of the cerebrospinal fluid and evoked potential tests. These tests were dropped from the 2010 McDonald criteria. However, a group of Canadian MS experts states that paraclinical tests still should be part of the diagnostic workup for certain patient populations and situations. These groups include:
- Patients older than 50 years and younger patients with vascular risk factors, both of whom can have...
Patients with vague, nonspecific symptoms, in which case clinicians should use all available diagnostic tools.

- Patients for whom MR imaging is contraindicated.

One of the paraclinical tools used in the diagnosis of MS is evoked potentials. These are measurements of the CNS response to different types of stimuli including visual, somatosensory, and brainstem stimuli. In the visual evoked potential test, the most widely used in MS diagnosis, patients watch an alternating checkerboard pattern on a screen. Electrodes attached to the patient’s head record electrical responses to the stimulus. A delayed latency indicates demyelination of the anterior visual pathway.

Evoked potential tests are not specific or sensitive for MS, however.

In fact, visual evoked potential test results are abnormal in fewer than one-third of patients with clinically isolated syndrome and in about half of MS patients who do not have a history or indication of optic nerve damage. In addition, visual evoked potential tests are not necessary if the clinician finds evidence of optic nerve damage.

Another test that can support an MS diagnosis is analysis of cerebrospinal fluid. In 90% of patients with MS, cerebrospinal fluid analysis shows an increase in immunoglobulin concentration and 2 or more oligoclonal bands. However, detection of oligoclonal bands in the cerebrospinal fluid is associated with a number of other diagnoses, in addition to MS.

Prognosis

The prognosis for people who have MS varies considerably among individuals and for different forms of the disease. Between 10% and 20% of patients have an indolent course of disease with minimal disability over a period of 20 years, and approximately 5% of patients have fulminant disease in which disability progresses quickly. MS presentations in other patients fall between these 2 extremes. Box 4 lists some factors associated with a poorer prognosis in patients with MS.

Before the development of disease-modifying therapies, the average time from diagnosis until a patient required a cane was about 15 years, and about 26 years between diagnosis and becoming bedbound. The degree to which disease-modifying drugs slow the brain lesions on MR imaging due to aging or ischemia rather than MS.

- Patients who have migraines, as migraines also can cause white-matter lesions that are visible on MR scans.
contraindicated or ineffective for a particular patient, plas-
mapheresis could be an effective second-line treatment.44
A plasmapheresis procedure involves removing plasma
from the patient’s whole blood and replacing it with donor
plasma or a plasma substitute, thus removing antibodies
attacking the immune system.44

Symptoms
Many MS symptoms can be treated with medication
including1,41:
- Fatigue – amantadine or modafinil.
- Difficulty walking – dalfampridine.
- Neurogenic bladder – oxybutynin.
- Neuropathic pain – pregabalin or duloxetine.
- Spasticity – baclofen, gabapentin, tizanidine.
- Erectile dysfunction – sildenafil.
- Tremor – clonazepam, propranolol.

Lifestyle modifications might reduce MS symptoms
and improve quality of life. Many of the tips suggested
for people with MS are the same as for good health in
general: getting enough sleep; eating a healthy, well-
balanced diet; exercising regularly; and finding ways
to reduce stress.6

In one study of people with MS, clini-
cally significant fatigue was found to be associated
with a poor diet and obesity, whereas a reduced likelihood
of fatigue was associated with exercise.45

Overheating
can aggravate MS symptoms, so patients might prefer
exercise that allows them to avoid getting too warm.
Swimming and water aerobics can be good choices.
Other exercise options recommended for people with
MS include stationary bicycling, walking, and low-
impact aerobics. Relaxation techniques that can help
reduce stress include yoga, meditation, tai chi, and mas-
sage. Joining an MS support group or talking with a
counselor also can be beneficial.6

Primary Progressive Disease
No drugs are approved for modifying the course of
primary progressive MS.2 However, some patients with
primary progressive disease have been treated with immu-
nosuppressant drugs used off label, and randomized trials
have indicated that immunosuppressants might help slow
the course of primary progressive MS.7 For now, however,
treatment for this form of the disease focuses primarily on
managing symptoms and disabilities.2

---

Box 4

Unfavorable Prognostic Indicators for People
With Multiple Sclerosis7
- Aged 40 years or older at onset of disease.
- Asian or African ancestry.
- Frequent attacks at onset of disease.
- Lesions enhance with gadolinium on initial MR examination.
- Male.
- MS-associated cognitive impairment at diagnosis.
- Oligoclonal immunoglobulins in the cerebrospinal fluid.
- Polyregional symptoms at diagnosis.
- Rapidly progressing disability.
- Short intervals between initial attacks.

progression of disability is not yet known.7 However,
most patients with MS eventually require some type
of mobility assistance such as a cane, walker, or wheel-
chair.7 The most disabling effects of MS continue to be
fatigue, cognitive impairment, and difficulty walking.6

The life expectancy for people with MS is reduced by 7
to 10 years on average.7 Approximately half of people with
MS die of MS-related complications; for the other half,
reported causes of death generally are similar to those
for people who do not have MS such as heart disease and
cancer.7 However, suicide is significantly more common
among MS patients than in the general population.4

Treatment
The 2 primary goals of MS treatment are to slow
progression of the disease and improve quality of life by
relieving the patient’s symptoms.42 MS treatment has
distinct components: treatment for acute relapses, man-
agement of chronic symptoms, and treatment to modify
the long-term course of the disease. Many patients also
incorporate lifestyle modifications and complementary
or alternative medicine into their treatment plans.

Acute Relapses
Treatment of acute relapses is necessary if the relapse
affects the patient’s quality of life.1 Clinicians treat acute
relapses of MS with corticosteroids such as prednisone,
an oral medication, or methylprednisolone, which is
administered intravenously.1,6,43 These drugs reduce the
length of the relapse but have not been shown to affect
the long-term course of the disease.1 If steroid treatment is
Disease-modifying Treatment for Relapsing-Remitting MS

As of January 2016, 12 drugs are approved by the U.S. Food and Drug Administration as “disease-modifying treatments” for the relapsing-remitting form of MS (see Table 4). These drugs suppress or modulate the immune system in various ways. They can slow the progression of MS and retard the development of plaques in the brain and spinal cord but also are associated with adverse effects that range from mildly bothersome to life threatening. Some of the drugs are injected subcutaneously or intramuscularly; others are taken orally or administered via IV infusion. Disease-modifying MS drugs do not cure the disease or repair existing damage to the CNS. However, these drugs can help control the disease, probably by reducing inflammation. In some cases, the exact mechanism of action of the drugs is unknown or not fully understood.

Reducing the rate of MS relapses is important because doing so improves patients’ comfort and quality of life and reduces the number of days patients must miss work and other activities. Furthermore, fewer relapses lower the risk of residual neurological deficits in patients with MS. Initiating disease-modifying treatment early in the disease process, such as after an initial attack or clinically isolated syndrome, appears to delay development of a second attack and slow the long-term progression of the disease.

Disease-modifying therapies are not helpful for patients with progressive MS and have shown limited usefulness in slowing the transition from relapsing-remitting disease to secondary progressive MS. Another limitation of disease-modifying drugs is that their effectiveness varies among patients and over time for each patient. Some disease-modifying treatments should be used with caution in patients who have certain comorbid conditions. For example, injection of interferon beta-1a (Avonex and Rebif) can worsen seizure disorders and some psychiatric illnesses; interferon beta-1b (Betaseron) should be used cautiously in patients with asthma or a history of anaphylactic reactions.

Typically, the decision regarding which disease-modifying drug to choose is based on a discussion between the patient and the treating physician. The choice might depend on patient preferences, possible adverse effects, and the clinician’s experience with the drugs. In some cases, insurance coverage also might be a consideration. Because patients vary in their susceptibility to and tolerance for adverse effects, as well as their willingness and ability to follow dosing regimens or take drugs with different routes of administration, physicians should consider all options to find the best treatment for each patient.

Some patients with MS should not be started on a disease-modifying therapy including women planning a pregnancy, people who are unlikely to follow the treatment regimen correctly, and people who might have benign MS (ie, no relapses in the previous 2 years and no MS-associated disability or disease activity evident on MR scans).

The first disease-modifying drugs were approved for use in the 1990s. These included the interferon beta drugs (Betaseron, Rebif, and Avonex) and glatiramer acetate (Copaxone). In clinical trials, these medications proved to reduce the rate of MS relapses by approximately 30% and to be within acceptable safety limits. However, the interferons are associated with adverse effects including injection site reactions, flu-like symptoms, elevated liver enzymes, thyroid dysfunction, anemia, and depression. Also, because these drugs require injection, patient compliance sometimes is problematic. The first-line injectable drugs vary somewhat in terms of their effectiveness and patient tolerability; however, data directly comparing these drugs are limited.

Oral disease-modifying drugs for MS include fingolimod (Gilenya), dimethyl fumarate (Tecfidera), and teriflunomide (Aubagio). The oral medications are considered second-line treatments because of their association with more serious adverse effects. For example, fingolimod causes lymphopenia and occasionally has been associated with opportunistic infections such as herpes simplex encephalitis. Also, because of a case of cardiac-related death in a patient with MS less than 24 hours after beginning treatment with fingolimod, the drug is contraindicated for patients with a history of heart disease or stroke and those taking antiarrhythmia medications. Dimethyl fumarate also causes lymphopenia; however, studies have not shown
which increases risk of developmental malformations in an embryo or fetus.\textsuperscript{13} Because of the risks to a developing fetus, patients are advised to avoid pregnancy while taking teriflunomide. If a patient becomes pregnant, she

<table>
<thead>
<tr>
<th>Trade Name; Year Approved</th>
<th>Generic Name</th>
<th>Route; Frequency</th>
<th>Possible Adverse Effects</th>
<th>Pregnancy Category\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aubagio; 2012</td>
<td>Teriflunomide</td>
<td>Oral; daily</td>
<td>Hepatotoxicity, harm to developing fetus, potential increased risk of malignancy, nausea, diarrhea; carries a black box warning\textsuperscript{b}</td>
<td>X</td>
</tr>
<tr>
<td>Avonex; 1996</td>
<td>Interferon beta-1a</td>
<td>Intramuscular injection; weekly</td>
<td>Flu-like symptoms, reaction at injection site, elevated liver enzymes</td>
<td>C</td>
</tr>
<tr>
<td>Betaseron; 1993</td>
<td>Interferon beta-1b</td>
<td>Subcutaneous injection; every other day</td>
<td>Flu-like symptoms, reaction at injection site, elevated liver enzymes</td>
<td>C</td>
</tr>
<tr>
<td>Copaxone; 1996</td>
<td>Glatiramer acetate</td>
<td>Subcutaneous injection; daily or 3 times weekly</td>
<td>Reaction at injection site, flushing, palpitations, chest tightness, dyspnea</td>
<td>B</td>
</tr>
<tr>
<td>Extavia; 2009</td>
<td>Interferon beta-1b</td>
<td>Subcutaneous injection; every other day</td>
<td>Flu-like symptoms, reaction at injection site, elevated liver enzymes</td>
<td>C</td>
</tr>
<tr>
<td>Gilenya; 2010</td>
<td>Fingolimod</td>
<td>Oral; daily</td>
<td>Bradycardia, hypertension, macular edema</td>
<td>C</td>
</tr>
<tr>
<td>Lemtrada; 2014</td>
<td>Alemtuzumab</td>
<td>IV infusion; daily for 5 consecutive days in first year, then daily for 3 days in second year</td>
<td>Glomerulonephritis, autoimmune thyroiditis, thrombocytopenia, infections, myalgia, arthralgia; carries a black box warning\textsuperscript{b}</td>
<td>C</td>
</tr>
<tr>
<td>Novantrone; 2000</td>
<td>Mitoxantrone (available as a generic since 2006)</td>
<td>IV infusion; every 3 months</td>
<td>Cardiotoxicity, acute leukemia, nausea/vomiting, amenorrhea/infertility, alopecia; carries a black box warning\textsuperscript{b}</td>
<td>D</td>
</tr>
<tr>
<td>Plegridy; 2014</td>
<td>Pegylated interferon beta-1a</td>
<td>Subcutaneous injection; every 14 days</td>
<td>Flu-like symptoms, reaction at injection site, elevated liver enzymes</td>
<td>C</td>
</tr>
<tr>
<td>Rebif; 2002</td>
<td>Interferon beta-1a</td>
<td>Subcutaneous injection; 3 times weekly</td>
<td>Liver damage, white blood cell disorders, reaction at injection site</td>
<td>C</td>
</tr>
<tr>
<td>Tecfidera; 2013</td>
<td>Dimethyl fumarate</td>
<td>Oral; twice daily</td>
<td>Flushing, diarrhea, nausea, reduced white blood cell count</td>
<td>C</td>
</tr>
<tr>
<td>Tysabri; 2006</td>
<td>Natalizumab</td>
<td>IV infusion; every 28 days</td>
<td>Hepatotoxicity, progressive multifocal leukoencephalopathy (an opportunistic brain infection); carries a black box warning\textsuperscript{b}</td>
<td>C</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The U.S. Food and Drug Administration categories for risk to fetuses are as follows: A, controlled studies show no risk; B, no evidence of risk in humans, but remains a possibility; C, evidence suggests chance of fetal harm but benefits might outweigh risks; D, positive evidence of risk from studies or postmarketing data, but the benefits might outweigh the risks; X, positive evidence of animal or human fetal abnormalities from studies or postmarketing data with risks outweighing any possible benefit.

\textsuperscript{b}FDA warning designed to call attention to serious or life-threatening risks.

an increased risk of infection with this drug.\textsuperscript{26} Some of the potential adverse effects associated with teriflunomide include hepatotoxicity, risk of infection, possible increased risk of malignancy, and risk of teratogenicity,
should undergo rapid elimination of the drug from her plasma.\textsuperscript{20}

Other second-line disease-modifying drugs include natalizumab (Tysabri), a monoclonal antibody given by intravenous infusion. A serious concern with long-term use of natalizumab is the possibility of developing progressive multifocal leukoencephalopathy.\textsuperscript{48} This infection causes cognitive impairment through activation of the John Cunningham virus (JCV). Progressive multifocal leukoencephalopathy can be fatal or cause permanent disability. Therefore, an annual anti-JCV antibody titer is required for all patients taking natalizumab.\textsuperscript{41} Any patient who develops progressive multifocal leukoencephalopathy while taking natalizumab should stop using the drug immediately and have an MR examination of the brain and a lumbar puncture to check for the virus.\textsuperscript{41} In addition, the patient should undergo plasmapheresis to remove natalizumab from the blood.\textsuperscript{41} The overall risk of developing progressive multifocal leukoencephalopathy in patients using natalizumab is 3.78 per 1000; however, the risk jumps to 13 per 1000 in patients who have taken natalizumab for 2 years or longer.\textsuperscript{20}

Some clinicians opt to begin treatment for relapsing-remitting MS with one of the first-line disease-modifying drugs, which tend to be safe, moderately effective, and associated with relatively mild adverse effects. Physicians still prescribe these drugs for most patients with MS, despite the introduction of newer medications.\textsuperscript{50} However, if the response to a first-line treatment is not sufficient, the patient might be switched to a second-line drug which, although more effective, might carry greater risks.\textsuperscript{2} Initial treatment with a second-line disease-modifying drug might be indicated for patients with severe or frequent relapses.\textsuperscript{2}

For example, glatiramer acetate is associated with fewer adverse effects than are the interferons and has comparable effectiveness, so it is recommended as an initial, first-line treatment by some physicians. However, use of glatiramer acetate requires daily injections. Patients who prefer not to use an injected drug might receive prescriptions for fingolimod or dimethyl fumarate.\textsuperscript{41} Natalizumab might be reserved for patients with breakthrough disease or those who cannot tolerate the adverse effects of other therapies.\textsuperscript{20}

Various disease-modifying drugs have different mechanisms of action, so if a particular drug does not work well for one patient, another might work better.\textsuperscript{13} In general, it is appropriate to consider switching to a different disease-modifying therapy if the patient has not responded adequately to treatment after one year or experiences intolerable adverse effects.\textsuperscript{2} Patients should continue with their disease-modifying therapy indefinitely, unless\textsuperscript{13}:

- It is not controlling the disease sufficiently.
- The patient considers the adverse effects unacceptable.
- The patient cannot or will not comply with the treatment regimen.
- A better treatment for the patient becomes available.

Disease-modifying drugs should be stopped whenever the patient reports a serious adverse effect, becomes pregnant, or the disease becomes progressive.\textsuperscript{2}

Assessing the Effectiveness of Disease-modifying Treatments

To evaluate the effectiveness of disease-modifying therapies, Tramacere and colleagues performed a meta-analysis of randomized controlled trials of these drugs in adults with relapsing-remitting MS.\textsuperscript{51} Their analysis included interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, and immunoglobulins.\textsuperscript{51} Some of these drugs are under investigation for treating MS and are not approved by the U.S. Food and Drug Administration for that purpose.

The researchers’ objective was to rank the treatments according to their benefits and acceptability to patients. Thirty-nine trials were included in the meta-analysis, representing approximately 25,000 participants. The average length of the studies included in the analysis was 24 months. In most cases (60%), the treatment was compared with a placebo; 40% of the trials compared 2 different treatments.\textsuperscript{41} Most of the studies included in the analysis were sponsored by pharmaceutical manufacturers; thus, results might be affected by bias.\textsuperscript{41} Specifically, the investigators examined the drugs’ ability to prevent relapses and worsening of MS-related
disability. They concluded that alemtuzumab, natalizumab, and fingolimod were the best choices for preventing clinical relapses. However, this conclusion was based on data reflecting only the first 24 months of treatment; long-term results might differ. As far as preventing the worsening of disability in the short term, only natalizumab showed a beneficial effect based on moderate-quality evidence.51

Tramacere et al stressed that additional research on disease-modifying therapies is needed. In particular, more long-term studies are called for because MS affects many patients for decades. The authors noted that additional studies that directly compare treatments, as opposed to studies comparing a single drug with a placebo, would be helpful. Finally, more data are needed about the safety of these drugs, particularly their long-term safety.51

Adherence to Disease-modifying Treatment

Several studies have concluded that significant numbers of patients with relapsing-remitting MS either stop taking their disease-modifying drug or do not take the drug consistently. This is concerning because the effectiveness of disease-modifying MS drugs depends on long-term, consistent use.52,53

For example, a group of German researchers studied pharmacy data of patients who began treatment for MS with one of 4 commonly prescribed disease-modifying therapies: interferon beta-1a intramuscular (Avonex), interferon beta-1a subcutaneous (Rebif), interferon beta-1b subcutaneous (Betaseron), or glatiramer acetate (Copaxone).52 The researchers collected medication information for 50,057 patients, focusing on the first 2 years after treatment began.52 They concluded that between 30% and 40% of patients were consistently compliant with their prescribed drug regimen 2 years after beginning treatment.52

A study conducted in Alberta, Canada, examined patterns of adherence to disease-modifying treatment over a period of 18 years in a cohort of 1471 patients with MS.53 As with the German study, all of these patients were prescribed an injectable drug, either an interferon beta-1a or beta-1b or glatiramer acetate. The Canadian researchers found that the median time until patients stopped taking the first disease-modifying drug prescribed for them was 8.6 years. However, 54% of the patients who began treatment with an injectable drug and then stopped taking it either switched to an oral or other second-line drug or resumed their initial treatment within 90 days.53 Few patients went without treatment for extended periods of time.53

In this study, the most common reasons reported for stopping the initially prescribed disease-modifying drug were intolerance (48%) and inefficacy (34%).53 Younger patients (ie, those aged 30 years or younger at the time treatment began) and patients with a higher level of disability were more likely to stop taking their first-prescribed disease-modifying drug.53 Patients who began treatment with glatiramer acetate tended to continue taking the drug longer than did patients who were taking an interferon beta.53

The Health Outcomes and Lifestyle Interventions in a Sample of people with Multiple Sclerosis (HOLISM) study was an international survey of more than 2200 people with MS recruited via social media forums and MS society Web sites. The purpose of the HOLISM study was to examine health and lifestyle behaviors and their relationship to self-reported quality of life, disability, and disease activity among MS patients over 5 years.42 In this survey, 752 participants (33%) indicated they had never taken a disease-modifying drug; 384 (16.9%) said they had taken a disease-modifying drug previously but were not currently taking one; 421 people (18.5%) reported switching disease-modifying drugs; and 719 (31.6%) were taking a disease-modifying drug and had not switched.48 The study’s lead author suggested that the large numbers of survey respondents who stopped taking a disease-modifying drug or switched to a different drug were probably attributable to a drug’s adverse effects.48

Costs

Because MS typically strikes younger adults, it can cause significant disability over time, usually requires lifelong treatment, and is an expensive disease. By one estimate, average medical expenses and indirect costs, such as lost income, total $1.2 million over the course of one patient’s lifetime.46 A study of people filing for bankruptcy because of medical expenses suggested that MS is a greater financial burden on individuals and families than are a variety of other disabling conditions.
including stroke, heart disease, and mental illnesses (see Box 5).  

**Future Directions in Pharmacologic Treatment**

Researchers are looking for treatments that promote remyelination or neuronal repair of MS-related damage, as well as neuroprotective agents that prevent the lesions and atrophy associated with MS. For example, a sodium-channel blocker, lamotrigine, was investigated as a potential neuroprotective drug in a group of 120 patients with secondary progressive disease. However, study results were negative. After 2 years, patients on lamotrigine showed similar brain volume losses as did control patients taking a placebo.

**Alternative and Complementary Treatments**

Many patients with MS (more than 88%, according to a 2014 pilot study at the University of Delaware) take vitamin D supplements, often at the suggestion of their physician. If serum levels of vitamin D are low (< 75 nmol/L), patients often are advised to take 2000 to 4000 IU per day to raise the level to the recommended amount.

Surveys suggest that significant numbers of MS patients use other types of complementary and alternative treatments as well. In many cases, however, patients do not discuss these treatments with their health care providers. For example, results of the HOLISM survey indicated that many patients were taking combinations of over-the-counter, herbal, and prescription medications, as well as dietary supplements, to treat various MS symptoms. Some common examples include paracetamol (acetaminophen), St John’s wort, and magnesium. Specifically, more than one-third of respondents were taking at least 3 medications and 15% were taking 5 medications or more, in addition to a disease-modifying drug.

**Quality of Life**

MS significantly reduces the self-reported quality of life for many patients. One study indicated that the average quality of life for people with MS was one full standard deviation lower than for the general population. In particular, men, older patients, those who had long-standing MS, and people with progressive disease tended to report a lower quality of life. Pain or discomfort, depression, limited mobility, and difficulties with daily activities were commonly noted problems that affect quality of life. Up to half of all patients with MS have depression during their lifetime, a much higher rate than for the general population. In addition, the suicide rate for people with MS is 7.5 times higher than for the general population.

**Special Patient Populations**

**Pediatric Patients**

MS most often strikes young adults and is rare in children. Only about 3% to 5% of MS cases in the United States are pediatric onset. However, MS is known to be more aggressive in children and adolescents, making prompt diagnosis and treatment even more critical.
However, the likelihood of a relapse increases after delivery. About 30% of patients have a relapse during the first few months after giving birth. Decisions about when to stop and restart MS treatment in women who are pregnant, planning to become pregnant, or postpartum should be based on the individual patient’s condition and her level of disease activity before the pregnancy. In general, disease-modifying treatments are discontinued when a patient becomes pregnant, and teriflunomide definitely is contraindicated during pregnancy because of risks to the developing fetus.

Conclusion

MS is a challenging condition for patients affected by the disease and for the health professionals who care for them. Diagnosis can be challenging because many diseases mimic the signs and symptoms associated with MS. Another challenge is predicting whether, when, and how much MS-related disability eventually will occur. Identifying the best treatment for each individual is challenging because a therapy that works well for one patient might not be tolerable, effective, or appropriate for another patient. Finally, paying for MS treatment can be an enormous challenge for patients, families, insurers, and society. Nevertheless, the outlook for patients with MS has never been brighter, with refined criteria for diagnosing the disease earlier and several new drug treatments approved in recent years.

Kathryn Faguy, MA, ELS, is a freelance medical writer and editor and former publications manager at ASRT. Her Directed Reading article on obesity in children and adolescents and its implications for medical imaging appeared in the January/February 2016 issue of Radiologic Technology.

Reprint requests may be mailed to the American Society of Radiologic Technologists, Publications Department, at 15000 Central Ave SE, Albuquerque, NM 87123-3909, or emailed to publications@asrt.org.

© 2016 American Society of Radiologic Technologists

References


more important in this age group. Almost all children and adolescents with MS (97%) have the relapsing-remitting form of the disease; primary progressive MS is quite rare in this age group. 69

The sensitivity and specificity of the McDonald diagnostic criteria were assessed in a group of 212 pediatric patients with possible MS who were examined clinically and with MR imaging over a 2-year period. In this group of patients, the criteria demonstrated 100% sensitivity and 86% specificity. 49 In addition, the positive predictive value was 59% and the negative predictive value was 100%. 59

During the first 3 years following MS diagnosis, pediatric patients’ relapse rates are 2 to 3 times higher than relapse rates for adults. 59 Also, up to 40% of children with MS develop cognitive impairment in the first few years after diagnosis, which often affects academic performance. 13

First-line disease-modifying drugs have been shown to be safe and effective for use in pediatric patients. 59,60 A study of 300 pediatric patients with MS concluded that the safety profile for interferon beta-1a was similar for children, adolescents, and adults. This held true even among children younger than 12 years old. 59 Also, glatiramer acetate has not been associated with any major adverse events in pediatric patients, although one incident of hepatotoxicity associated with glatiramer acetate in a pediatric patient with MS was noted in the literature. 59 However, about 30% of children cannot tolerate first-line injectable disease-modifying drugs, and many pediatric patients prefer oral medications. 59

Newer disease-modifying drugs, including the oral and infusion drugs, have not been tested in pediatric patients as of this writing, but trials are planned. 59

Pregnant Women

In the past, women with MS sometimes were advised to avoid pregnancy because of perceived risks. However, most studies that examined the subject showed that these patients have similar pregnancy outcomes and rates of pregnancy complications as women who do not have MS. 61

MS disease activity decreases during pregnancy, especially during the third trimester, when it drops by about 70% compared with prepregnancy levels. 1

During the first 3 years following MS diagnosis, pediatric patients’ relapse rates are 2 to 3 times higher than relapse rates for adults. 59 Also, up to 40% of children with MS develop cognitive impairment in the first few years after diagnosis, which often affects academic performance. 13

First-line disease-modifying drugs have been shown to be safe and effective for use in pediatric patients. 59,60 A study of 300 pediatric patients with MS concluded that the safety profile for interferon beta-1a was similar for children, adolescents, and adults. This held true even among children younger than 12 years old. 59 Also, glatiramer acetate has not been associated with any major adverse events in pediatric patients, although one incident of hepatotoxicity associated with glatiramer acetate in a pediatric patient with MS was noted in the literature. 59 However, about 30% of children cannot tolerate first-line injectable disease-modifying drugs, and many pediatric patients prefer oral medications. 59

Newer disease-modifying drugs, including the oral and infusion drugs, have not been tested in pediatric patients as of this writing, but trials are planned. 59

Pregnant Women

In the past, women with MS sometimes were advised to avoid pregnancy because of perceived risks. However, most studies that examined the subject showed that these patients have similar pregnancy outcomes and rates of pregnancy complications as women who do not have MS. 61

MS disease activity decreases during pregnancy, especially during the third trimester, when it drops by about 70% compared with prepregnancy levels. 1

However, the likelihood of a relapse increases after delivery. About 30% of patients have a relapse during the first few months after giving birth. 1 Decisions about when to stop and restart MS treatment in women who are pregnant, planning to become pregnant, or postpartum should be based on the individual patient’s condition and her level of disease activity before the pregnancy. 1 In general, disease-modifying treatments are discontinued when a patient becomes pregnant, and teriflunomide definitely is contraindicated during pregnancy because of risks to the developing fetus. 1
Multiple Sclerosis: An Update


Multiple Sclerosis: An Update

To earn continuing education credit:
- Take this Directed Reading quiz online at asrt.org/drquiz.
- Or, transfer your responses to the answer sheet on Page 644 and mail to:
  Processing Center, 2908 Stewart Creek Blvd., Charlotte, NC 28216.

New and rejoining members are ineligible to take DRs from journal issues published prior to their most recent join date unless they have purchased access to the quiz from the ASRT. To purchase access to other quizzes, go to asrt.org/store.

* Your answer sheet for this Directed Reading must be received in the ASRT office on or before this date. Some quizzes are renewed and the expiration date extended. Check online at asrt.org/drquiz or call Member Services at 800-444-2778.

Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. Women are ______ likely than men to develop multiple sclerosis (MS) and tend to develop the disease at a(n) ______ age than men.
   a. more; older
   b. less; older
   c. more; younger
   d. less; younger

2. A leading hypothesis regarding the cause of MS is that it occurs as a result of a combination of:
   1. genetic susceptibility.
   2. exposure to a specific virus or toxin.
   3. a triggering event such as a traumatic injury.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

3. Which of the following are possible symptoms of MS?
   1. fatigue
   2. numbness or weakness
   3. visual disturbances such as double vision
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

4. Most patients with relapsing-remitting MS eventually develop ______ disease.
   a. fulminant
   b. benign
   c. radiologically isolated
   d. secondary progressive

continued on next page
5. Patients with clinically isolated syndrome have a single:
   a. brain or spinal cord lesion detectable on magnetic resonance (MR) imaging.
   b. symptomatic episode lasting 24 hours.
   c. area of damage in the central nervous system (CNS).
   d. relative with MS or no family members with the disease.

6. Which of the following criticisms have been made regarding the 2010 McDonald diagnostic criteria for MS?
   1. They are complex.
   2. They require analysis of cerebrospinal fluid and visual evoked potential testing, which are costly and can delay diagnosis.
   3. They are based on data from European patients and might not apply as effectively to other patient populations.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

7. Regarding MS diagnosis, experts caution that:
   a. it is only possible to diagnose MS after more than one symptomatic attack.
   b. the patient’s clinical presentation should drive diagnostic classifications and treatment decisions.
   c. only MR images can confirm a diagnosis.
   d. even with McDonald diagnostic criteria, early diagnosis and treatment are unattainable.

8. The spinal cord should be scanned with MR for patients with suspected MS:
   1. in cases of benign disease.
   2. when initial brain imaging is nondiagnostic.
   3. when the patient’s signs or symptoms suggest spinal cord involvement.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

9. When do MS lesions appear nodular on gadolinium-enhanced MR images?
   a. during all stages of the disease process
   b. when they are at least 2 years old, indicating areas of permanent axon loss
   c. only when they exceed 10 mm in diameter
   d. when they are new

10. MS lesions in the brain typically appear on T2-weighted, proton-density, and fluid-attenuated inversion recovery (FLAIR) MR images as:
    a. asymmetrical hypodensities.
    b. large, irregular isointense areas.
    c. small round or oval hyperintensities.
    d. “black holes.”

11. Paraclinical tests, such as cerebrospinal fluid analysis, might be helpful in MS diagnosis for patients:
    1. who have vague or nonspecific symptoms.
    2. for whom MR imaging is contraindicated.
    3. who have migraines.
    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

continued on next page
12. Disease-modifying drugs repair damage to the CNS caused by MS.
   a. true
   b. false

13. Which of the following is a serious possibility with long-term use of natalizumab?
   a. cardiomyopathy
   b. harm to a developing fetus
   c. increased risk of malignancy
   d. progressive multifocal leukoencephalopathy

14. A patient with MS should stop taking a disease-modifying drug when:
   1. he or she reports a serious adverse effect.
   2. she becomes pregnant.
   3. the disease becomes progressive.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

15. According to one study, on average, patients with MS have a reported quality of life one standard deviation lower than the general population. In particular, which of the following groups of MS patients tend to report reduced quality of life?
   a. younger patients
   b. patients who recently received a diagnosis
   c. men
   d. people of northern European ancestry

16. During pregnancy, MS disease activity _______, but likely will _______ after delivery.
   a. decreases; increase
   b. increases; decrease
   c. stops completely; resume gradually
   d. accelerates rapidly; slow significantly