Multiple Sclerosis

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Faculty

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, primary care providers, and nurses who may intervene to improve the lives of patients with multiple sclerosis.

Accreditations & Approvals

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The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective

This course provides physicians, nurses, and other healthcare providers with a review of the pathogenesis, clinical expression, diagnosis, and management of multiple sclerosis. Clinical care topics include treatment of acute exacerbations, therapeutic options for disease modification, and management of common symptoms and complications. The purpose of this course is to address knowledge gaps, enhance clinical skills, and improve quality of care and treatment outcomes for patients with multiple sclerosis.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the risk factors for multiple sclerosis (MS).
2. Define the etiology and pathophysiology of MS.
3. Identify common signs and symptoms of MS.
4. Distinguish between the various MS disease courses, including relapsing-remitting, primary progressive, and secondary progressive subtypes.
5. Compare and contrast early-onset and late-onset MS.
6. Apply diagnostic criteria and select appropriate tests used to confirm the diagnosis of MS.
7. Assess the conditions that should be considered in the differential diagnosis of MS.
8. Select an appropriate treatment regimen for acute exacerbations of MS.
9. Discuss the role of disease-modifying therapy in the management of MS, including the expected benefit, mode of action, and selection of options available.
10. Anticipate and manage the various symptoms common to patients with active MS.
11. Devise a management plan for the patient with MS who is, or wishes to become, pregnant.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Multiple sclerosis (MS) is an acquired, life-long disease of the central nervous system (CNS) that usually begins in early adulthood. In most cases, the early phase of disease is marked by clinical exacerbations and remissions, followed eventually by the gradual onset of fixed neurologic deficits. The cause of MS is unknown. The pathogenesis appears to involve the interplay of genetic predisposition, environmental exposures, and immune-mediated inflammatory demyelination within focal areas of the brain and spinal cord. With chronicity, the disease results in fixed damage to myelin, axons, and oligodendrocytes, leading to cumulative disability and impaired quality of life. The propensity for repeated episodic flares (clinical exacerbations) and multiple foci of tissue injury within the CNS, followed by healing with scar tissue (sclerosis), is what gives the disease its name. There is great variability in the clinical expression, neuroradiographic features, pathologic findings, and response to therapy.

At onset of illness, the clinical presentation reflects the focal nature of the neuroinflammatory process. Common presentations include acute unilateral vision loss (optic neuritis), diplopia (brain stem involvement), ataxia and nystagmus (cerebellum), and asymmetric limb weakness or sensory symptoms (partial myelopathy) [1; 2]. In the early stage of disease, the dominant pathologic finding is a well-demarked, focal lymphocytic inflammatory process within white matter (the plaque) causing demyelination and axonal injury [1; 3]. Initially, the inflammatory reaction subsides, healing and remyelination take place to some degree, and clinical symptoms and signs remit. Over time, new lesions usually develop and clinical exacerbations of disease recur. In later stages, usually after 10 to 20 years, there is evidence of neuronal injury and multiple areas of degenerative change with some degree of brain atrophy. Treatment is based on the emerging body of evidence that MS is an autoimmune disorder characterized by activated T-cell, cytokine-mediated inflammation directed against components of axonal myelin. ß-interferon, monoclonal antibody, and other agents that modify certain sequences of the immune reaction have been utilized in the effort to modify the natural history of the disease and limit neurologic deficits. The response to these targeted therapies is variable; while they do reduce the frequency and expression of new episodes, the impact on disease progression and long-term neurologic disability is unclear.

Although some patients with MS experience a relatively benign course, most will eventually show signs of progressive neurologic deterioration, such as difficulty with ambulation and impaired cognition, that ultimately impact quality of life and impose a significant financial burden. In general, MS has minimal impact on life expectancy.

EPIDEMIOLOGY

MS is the most common immune-mediated (inflammatory) demyelinating disorder of the CNS. Most cases are diagnosed in persons between 15 and 50 years of age, and MS is a common cause of permanent disability in this segment of the population. MS in childhood and adolescence is being diagnosed more frequently, due in part to increased awareness and improved diagnostic imaging. Estimates are that 7,000 to 10,000 children and teenagers in the United States have MS [4; 5].

The lifetime incidence of MS in the general population is estimated to be 0.1%. The cumulative prevalence of MS in the United States is typically considered to be about 400,000, or 135 cases per 100,000 [1; 4; 6]. A 2019 study, using a method that employs a validated algorithm and healthcare datasets totaling 125 million adults, estimates the current prevalence of MS in the United States at close to 1 million individuals [4; 7]. Globally, approximately 2.5 million persons suffer from this disease. In general, MS is more prevalent in industrialized nations and in countries north of the equator.

The risk of developing MS is higher among women than men, with more than three times more women than men having the disease [4]. This is a trend that appears to have increased steadily in recent decades. A systematic review of incidence studies published between 1966 and 2007 found an incidence rate of 3.6 cases per 100,000 person-years in women, compared to 2.0 in men. The female-to-male ratio in MS incidence increased over time, from 1.4:1 in 1955, to 2.3:1 in 2000 [8]. Because MS follows a chronic course, this differential incidence leads to an even greater gender gap in prevalence of the disease.

The reason for female preponderance in MS is unknown and is the subject of intense scientific interest. The explanation may reside in the complex interplay of environmental, behavioral, and biologic factors, such as increasing exposure to environmental triggers associated with urbanization; decreasing number of pregnancies (a protective factor against relapses in MS); declining levels of vitamin D related to reduced sunlight exposure (affecting vitamin D-linked modulation of immune-mediated inflammation); and biologic differences in certain aspects of the immune system that are under the influence of sex hormones [9].

PREDISPOSING FACTORS

GENETICS

Genetic studies have demonstrated an inherited predisposition to acquiring MS, and epidemiologic investigations have identified several environmental factors that appear to increase the risk of developing MS [10; 11; 12]. Among first-degree relatives of an index case, the lifetime risk is 3% to 5%; for a monozygotic twin, the risk is 31% [4]. The identification of specific risk alleles, and the expression of their related gene products, is the subject of much interest and ongoing investigation [10; 11; 13; 14]. The largest and first identified genetic risk factor is an allele known as HLA-DRB1*15:01, which increases the risk of MS about threefold [15]. More than 200 genetic risk variants have now been described. Although single genetic effects are small in MS, they point to processes and cell subsets necessary for MS pathogenesis [15].

ENVIRONMENTAL FACTORS

Environmental factors are thought to play a significant role in the development of MS. Studies have shown an association between geographic latitude and risk, with the risk increasing from south to north [16; 17]. The lowest risk in found among persons living near the equator. As such, the prevalence of MS is higher in geographic locales having less sunlight exposure (and hence diminished production of vitamin D), suggesting that low levels of vitamin D may be a risk factor [17; 18; 19; 20]. In addition, persons who smoke have an increased relative risk compared to those who do not [17; 19; 21].

Certain infections acquired at a young age, and characterized by chronic latency and CNS trophism, have been implicated as risk factors [22]. These include mumps, rubella, Epstein-Barr virus, human herpesvirus 6, and *Chlamydia pneumoniae* [17; 23; 24; 25]. Patients with MS are more likely to have detectable levels of *C. pneumoniae* DNA in the cerebrospinal fluid (CSF) than patients with other neurologic diseases [17; 23]. The possibility that infection with one or more of these agents may be the principle cause, or trigger, for MS has also been investigated [17]. Genetic material and proteins specific to microbial agents have been identified in MS brain lesions, and specific T-cell or antibody responses in blood and CSF have been found in some patients with MS. However, the significance of these findings is uncertain.

There is considerable evidence that Epstein-Barr virus (EBV) infection acquired after childhood is a strong risk factor for MS [19]. EBV is a herpes-type virus most often acquired early in life; the prevalence of EBV seropositivity increases from about 50% in early childhood to greater than 90% by 30 years of age. Among young adults who are EBV seronegative, the risk of developing MS is 10 times lower than that of persons of the same age who are

EBV-positive. Further, if primary EBV infection results in clinical infectious mononucleosis, the risk of MS increases two- to three-fold greater than the risk observed among EBV-seropositive persons without a history of infectious mononucleosis [19]. The temporal association between EBV infection and onset of MS was examined in a military study of EBV-seronegative service personnel, among whom the rate of EBV seroconversion (denoting primary infection) occurred at the rate of 11% per year [26]. Ten cases of MS were documented during the study period, and in all cases, the first symptoms of MS developed in the early years following EBV seroconversion (average interval: 3.8 to 5.6 years).

The role of viral infection and autoimmunity in the pathogenesis of MS has intrigued investigators and is the subject of a 2013 review [27]. One proposed mechanism is that direct infection of the brain causes inflammation and injury to myelin-producing cells, following which T-cells within the inflammatory milieu become sensitized to exposed epitopes on myelin fragments. These autoreactive T-cells then induce a series of cytokine-mediated inflammatory events that lead to further myelin destruction. Another possible mechanism is that simple persistence of a viral infection within the CNS leads to chronic inflammation and demyelination as the host immune response attempts to eliminate the infectious agent from the brain. An alternate mechanism, for which there is growing experimental evidence, involves the complex interplay of multiple viral infections and the host immune response, whereby systemic infection (outside the CNS) leads to activation of peripheral T-cells that are able to recognize "self" (myelin) as well as the inciting virus. Thus, the immune response to the virus acquires the capacity to cross-react with self (CNS myelin). In the setting of acute infection, these activated T-cells traverse the blood brain barrier and incite focal, immune-mediated inflammatory demyelination and MS [27].

It may be postulated that susceptibility to MS is conditioned by genetic predisposition combined with one or more acquired risk factors that impact immune surveillance and integrity of the blood-brain barrier. As stated, environmental risk factors include geographic latitude (e.g., sun exposure, vitamin D deficiency) and infection (e.g., latent CNS sequelae of childhood infection, EBV infection in young adulthood). Behavioral risk factors (e.g., cigarette smoking, obesity) have also been associated with increased risk of MS [19]. A population-based, case-control study in Sweden found that adolescent obesity conferred a 90% increased risk of developing MS in subsequent years [28]

PATHOGENESIS

Conceptually, MS is now considered to be an autoimmune inflammatory disorder with complex and variable pathologic features [1; 29]. Susceptible individuals are those of genetic predisposition in combination with environmental factors and possibly latent infection. The etiology is unclear, but initiation of disease appears to involve the activation of peripheral T-lymphocytes, programmed to recognize components of the CNS axonal myelin sheath. The disease is triggered by events that permit these autoactivated T-cells to breach the blood-brain barrier and cross-react with myelin components within the white matter of the brain and spinal cord [30]. This precipitates a cascade of immune-mediated inflammatory tissue injury. As seen on radiographic imaging and pathologic examination, the hallmark of the disease is this well-defined, focal zone of injury ("plaque") containing elements of inflammation, demyelination, and axon degeneration [1; 6]. Such lesions may be single or multiple, and over time, they may be partially reparative, relapsing, or recurrent in new locations. The location of lesions is variable; early in the disease they appear in white matter, often clustering near the ventricles and sparing peripheral nerves [14].

The autoimmune hypothesis of pathogenesis is supported in part by the following observations [29; 31]:

- Myelin antigen-specific, autoreactive T-cells have been isolated from peripheral blood lymphocytes.
- Immunologic studies in patients with MS have shown that relapses are preceded by expansion and activation of CD4+ T-cells in the peripheral immune compartment having myelin basic protein specificity.
- The histopathology of the MS plaque often shows a T-cell mediated (Th1-type) pattern of inflammation with interleukin-2 (IL-2) and chemokine expression.
- There is a linkage between these immunologic abnormalities and the activity of disease, as measured by clinical and magnetic resonance imaging (MRI) features.
- Experimental autoimmune encephalomyelitis, with histopathologic features of inflammation and demyelination similar to that seen in MS, can be induced in an animal model by immunization with myelin autoantigen.

The pathologic examination of active lesions reveals considerable heterogeneity with respect to structural change and immunologic features, indicating that multiple pathogenetic mechanisms may be involved in the disease process. In one carefully conducted study, the pattern of demyelination was analyzed in a series of active lesions from patients with MS [32]. The lesions could be grouped into four distinct patterns: two showed similarities to T-cell mediated or T-cell plus antibody-mediated autoimmune encephalomyelitis, and two showed a pattern reflective of primary oligodendrocytic dystrophy, similar to that seen with virus- or toxin-induced demyelination. The pattern of demyelination was heterogeneous among different patients, but homogeneous with respect to multiple lesions within the same patient.

The mechanism by which autoreactive T-lymphocytes traverse the blood-brain barrier to initiate inflammation is poorly understood. There is some evidence that early in the disease process there is an increase in adhesion molecules, particularly intercellular adhesion molecule-1 (ICAM-1), on the vascular endothelium of brain and spinal cord. These molecules increase the permeability of the blood-brain barrier and could permit the entry of lymphocytes. Upon entry into the CNS compartment, previously activated T-lymphocytes proliferate and engage myelin-based antigens, triggering the autoimmune inflammatory cascade that leads to demyelination. The release of cytokines activates microglial cells (CNS macrophages), which, in turn, promotes the expression of class II major histocompatibility complex (MHC) molecules and the accumulation of additional cytokines and other inflammatory mediators, such as nitric oxide, free radicals, and superoxide. The net result is a sustained proinflammatory state that destroys myelin, disrupts oligodendrocyte integrity and function, and damages axons. ***Table 1*** provides an outline of the various components of the innate immune system, with a brief commentary on the role each cell type plays in the pathogenesis of MS [33].

Demyelination impairs nerve impulse transmission and leads to abnormal patterns of nerve conduction, which accounts in large part for the various clinical symptoms and signs of MS. Oligodendrocytes are cells that elaborate the myelin sheath that envelops the axon. During the early, remittent stage of the disease, as inflammation subsides, the number and function of these cells are sufficient to renew the myelin sheath (remyelination) and restore neurologic function. Over time, the repeated inflammatory insults associated with relapsing MS lead to a gradual depletion of functioning oligodendrocytes, and to degenerative changes marked by central scarring within the lesion and focal areas of cerebral atrophy. The clinical correlate is the gradual accumulation of fixed neurologic deficits as the patient with MS transitions to the chronic progressive stage of the disease.

ROLE OF INNATE IMMUNITY IN MS	
Innate Immune System Component	**Impact on Pathogenesis of MS**
Monocyte/macrophages	Hematopoietic monocytes and macrophages are the most abundant phagocytic cells of the innate immune system that infiltrate the MS lesion. Their morphology is very heterogeneous depending on which area of the MS lesion they have infiltrated. Monocytes/macrophages can contribute to neuroinflammation as well as promote neuroprotection in MS.
Microglial cells	Microglia provides the first-line of defense within the CNS. Microglial cells are phagocytic and clear debris resulting from inflammation. Upon activation, they can produce several proinflammatory cytokines (such as TNF) and reactive oxygen species that are toxic to infectious agents. They may also serve as antigen-presenting cells that directly activate T-cells.
Dendritic cells	Dendritic cells are potent antigen presenting cells and are considered to be the critical link that bridges the innate and adaptive immune responses. Because the CNS lacks conventional lymphatic circuitry, it is thought that dendritic cells perform their antigen presenting function to directly activate T-cells within the perivascular spaces of the CNS. Therefore, dendritic cells in the periphery and within the CNS may contribute to the initiation and perpetuation of immune mechanisms germane to the disease process in MS.
Mast cells	Mast cells release granules that are rich in histamine and other inflammatory mediators. Both mast cells and their mediators have been identified in MS lesions. Tryptase, an enzyme uniquely produced by mast cells, is increased in the CSF of MS patients.
Natural killer (NK) cells	Natural killer (NK) cells recognize and kill virally infected cells and tumor cells, and secrete cytokines including IFN-γ, IL-10, IL-5, and IL-13. NK cell numbers are decreased in the CSF and in lesions of MS patients, and cytolytic activity is diminished in comparison to healthy controls. In fact, studies suggest that increases in NK cells in pregnant MS patients may contribute to the decreased disease activity observed during pregnancy and indicate an immunoregulatory role for NK cells in MS.
NK-T cells	NK-T cells are T-cells that express an invariant TCR and some features of NK cells. NK-T cells have been identified in MS lesions and are thought to play a regulatory role in MS, but the conclusions of studies investigating NK-T cell numbers and function in MS patients are conflicting.
γδ T cells	γδ T cells are T lymphocytes that express the invariant γδ T cells receptor and are typically present in high numbers in the epithelium of the gut and are less frequent in the blood. γδ T cells have been identified in MS lesions but their contribution to the pathogenesis of MS has not yet been elucidated.
Non-cellular components	Nitric oxide synthase (NOS) is an inducible enzyme produced by myeloid cells, such as monocytes/macrophages, granulocytes, and dendritic cells, that is used to generate nitric oxide. Nitric oxide is one of several reactive oxygen and nitrogen intermediates that function as potent antimicrobials. NOS is associated with MS lesions, but the role of NOS in MS remains undefined.
CSF = cerebral spinal fluid, IFN = interferon, IL = interleukin, TCR = T-cell receptor, TNF = tumor necrosis factor.	
Source: Reprinted with permission from Frohman TC, O'Donoghue DL, Northrop D (eds). Multiple Sclerosis for the Physician Assistant: A Practical Primer. New York, NY: National Multiple Sclerosis Society; 2011. *Table 1*	

The B-lymphocyte arm of the immune system also contributes to the pathogenesis of MS, especially during the late stages of disease when inflammatory changes are more marked in the gray matter of the brain. In contrast to T-cell mediated inflammation of white matter, myelin-reactive B-lymphocytes and the secretion of myelin-specific antibodies appear to play a significant role in the pathogenesis of gray matter inflammatory injury. The potential mechanisms by which B cells influence pathogenesis include antigen presentation to T cells, autoantibody production, and release of pro-inflammatory cytokines. During periods of active MS inflammation, B-lymphocyte-rich immune cells collect within certain compartments of the CNS, including the meninges; such cell collections, in association with meningeal inflammation, may cause the adjacent subpial cortical demyelination and neurodegenerative features seen in chronic forms of MS [34].

The natural history of the plaque lesion in MS also includes late-developing degenerative features that are irreversible, such as gliosis (scarring), functional abnormalities of damaged axons, neuronal degeneration, and cerebral atrophy.

SIGNS AND SYMPTOMS

The early signs and symptoms of MS are typically mild and difficult to detect. They differ in duration and severity from one individual to another and at different times in the same individual. However, at first clinical presentation, most patients report multiple symptoms. Patients generally experience either acute attacks of neurologic compromise or are afflicted by a steadily progressive deterioration in functional capabilities, as will be discussed in detail later in this course [33].

MS symptoms can be organized into three categories: primary, secondary, and tertiary.

PRIMARY SYMPTOMS

Primary symptoms of MS are caused by the inflammation and demyelination that arises within focal areas of the CNS. The clinical presentation is varied but, in general, consists of some disturbance in vision, sensation, and/or motor function. The most common primary symptoms in patients with MS are:

- Fatigue
- Heat sensitivity
- Muscle spasms
- Dizziness
- Pain
- Paresthesias
- Ataxia
- Cognitive changes
- Visual complaints
- Bowel or bladder dysfunction
- Sexual dysfunction
- Gait problems
- Nausea/vomiting
- Speech problems
- Tremor
- Weakness

Fatigue

Fatigue is the most frequent and characteristic symptom of MS. It typically occurs in the mid-afternoon and may be associated with depression, increased muscle weakness, and drowsiness [35]. Fatigue is disabling in MS, resulting in a patient's inability to participate in daily activities and affecting quality of life and mental health [35].

Heat Sensitivity

Heat sensitivity (also known as Uhthoff phenomenon) is common in most individuals with MS. This occurs when the body becomes overheated due to fever, physical exercise, or exposure to a hot environment, such as hot weather, saunas, and hot baths. It is suspected that the increase in body temperature results in nerve conduction block in central pathways [36; 37]. Patients with MS reach this stage earlier and at comparatively lower temperatures than healthy individuals because nerves are demyelinated. The greater the degree of demyelination, the smaller the necessary increases in temperature to induce symptoms. In individuals with MS, a small increase in body temperature can temporarily result in worsening of neurologic signs and symptoms, including fatigue, cognitive impairment, ataxia, weakness, and urinary incontinence [38].

Spasticity

The majority of patients with MS report some level of spasticity. Painful muscle spasm is experienced by approximately 15% and is often a source of debilitation [39]. Spasticity usually affects the muscles of the extremities (more prominent in the lower extremities than the upper extremities) and can impair an individual's ability to freely move his or her muscles.

Demyelinated nerves are primarily responsible for the spasticity seen in MS, as slowed or interrupted nerve conduction affects the motor function of the muscles. Muscle relaxation is slow and sluggish, and there is involuntary muscle tightening or contraction for long periods or constantly. Amyotrophy of the disuse type can be seen in some patients with MS, usually in the small muscles of the hand.

Dizziness and Vertigo

Approximately 49% to 59% of patients with MS suffer from dizziness or vertigo, and this condition is usually associated with impairment of cranial nerves [40]. In one study, the effects of dizziness were reported to be moderate in 30.9% of patients and severe in nearly 8% [40]. It can substantially impact patients' quality of life, particularly if paired with other symptoms that affect mobility.

Pain

Up to 80% of patients with MS experience varying degrees of pain, and an estimated 50% experience chronic pain [41]. One study found that 63% of patients with MS reported one or more painful symptoms [39]:

- Headache (43%)
- Neuropathic extremity pain (26%)
- Back pain (20%)
- Painful spasms (15%)
- Lhermitte sign (16%)
- Trigeminal neuralgia (3.8%)

MS pain is mainly neuropathic—the result of nerve damage and faulty conduction—and can include stabbing, burning, and shock-like sensations (e.g., allodynia, dysesthesias, paresthesia). Lhermitte sign is often considered a classic sign of MS and consists of a brief, electric shock-like sensation that runs down the spine and is triggered by bending the neck forward or backward.

Some patients will experience musculoskeletal pain, likely the result of immobility and gait problems. Patients with spasticity are at greater risk for this type of pain.

Impaired Cognition

Approximately 40% to 70% of patients with MS experience varying degrees of cognitive impairment [42]. This may manifest as decreased capacity for concentration or memory and slowed thinking. Severe cognitive impairment can significantly impact patients' ability to carry out activities of daily living.

Vision Problems

Impaired vision is frequently present in patients with MS, most commonly unilateral optic neuritis, which is present in approximately in 66% of cases [43]. Optic neuritis usually manifests as acute or subacute unilateral eye pain that increases with eye movements [44]. It can also lead to blurring or graying of vision or blindness in one eye. However, while unilateral optic neuritis is common in MS, simultaneous bilateral optic neuritis (resulting in total blindness) is rare [43]. Approximately 90% of patients with MS regain normal vision over a period of two to six months after an acute episode of optic neuritis [43].

Patients may also present with intranuclear ophthalmoplegia (INO), a condition characterized by impaired nystagmus and defective horizontal ocular movements of the abducting eye. This type of visual impairment is caused by a lesion of the medial longitudinal fasciculus on the side of diminished adduction. When present in young patients, bilateral internuclear ophthalmoplegia is suggestive of MS [43].

Sensory Symptoms

Patients with MS often experience various sensory symptoms through the course of the disease. This includes impairment of vibration and joint position sense, decreased pain and light touch perception, "pins-and-needles" sensation, tightness, and coldness of the extremities. A dysesthetic itching specifically present around the cervical dermatomes is indicative of MS.

Bowel, Bladder, and Sexual Dysfunction

The severity of bowel sphincter impairment and sexual dysfunction is directly proportional to the extent of motor impairment in the lower extremities. Urgency is the most frequent urinary complaint in patients with MS, with frequent urinary incontinence common as the disease progresses. MS can also lead to atonic dilated bladder. Upper and lower motor neuron impairment can result in constipation. Erectile dysfunction is common in men suffering from MS. As many as 91% of men and 72% of women with MS report some form of sexual dysfunction [45].

Gait Imbalance

Gait disturbances and imbalance are characteristic symptoms of MS. Patients will experience varying degrees of difficulty executing coordinated actions because of damaged cerebellar pathways. Dysmetria and hypotonia are frequently seen in the upper extremities. Some patients exhibit intention (cerebellar) tremor, particularly in the head and limbs. These tremors can be incapacitating and refractory to treatment. Walking is also affected due to truncal ataxia. In severe cases, patients lose the ability to stand (astasia).

Paroxysmal Symptoms

Patients with MS frequently exhibit paroxysmal attacks of motor or sensory symptoms causing facial paresthesia, trigeminal neuralgia, ataxia, and diplopia. Dystonia (painful tonic contractions of muscles) is seen when the motor system is involved.

SECONDARY SYMPTOMS

Secondary symptoms arise as a result of the presence of certain primary symptoms. For example, pressure ulcers may form as a complication of paralysis, a primary symptom. Bladder problems or urinary incontinence can cause frequent, recurring urinary tract infections. These symptoms are treatable, but ideally, they should be avoided by treating the primary symptoms. The most common secondary symptoms present in patients with MS are [46]:

- Urinary tract infections
- Kidney or bladder stones
- Pressure ulcers
- Muscle contractures
- Respiratory infections

- Poor nutrition
- Difficulty breathing (severe)
- Disuse weakness
- Poor postural alignment and trunk control
- Decreased bone density
- Back pain

TERTIARY SYMPTOMS

Tertiary symptoms may be described as the "trickle down" effects of MS and include the social, psychological, and vocational complications associated with the primary and secondary symptoms [46]. Depression is a frequent tertiary symptom present among people with MS. Social isolation, job loss, marital or interpersonal conflict, and anxiety may all develop as a result of various primary and secondary symptoms of MS.

DISEASE ONSET AND CLINICAL SUBTYPES

In a given case, the onset and subsequent course of MS tends to follow one of four commonly observed clinical patterns (subtypes or phenotypes). Because accurate definitions and clinical course descriptions are important for purposes of communication, clinical trial design, and prognostication, an international panel of MS experts provided the first standardized descriptions of MS subtypes in 1996 [47]. In 2013, the International Committee on Clinical Trials of MS revised the definitions and clinical descriptors to more accurately reflect recently identified clinical aspects and imaging findings of the disease [48]. The 2013 revision classifies the four basic MS disease phenotypes as: clinically isolated syndrome, relapsing remitting, secondary progressive, and primary progressive [49].

CLINICALLY ISOLATED SYNDROME

Clinically isolated syndrome is a first episode of neurologic symptoms suggestive of MS but lacking clear confirmation of the diagnosis. The episode must last more than 24 hours. Symptoms may be unifocal or multifocal, and MRI may show subtle structural changes in the brain or spinal cord indicative of inflammatory demyelination [49]. This constellation of findings constitutes evidence for, but not confirmation of, the diagnosis of MS, as persons who present with a clinically isolated syndrome may or may not go on to develop MS [49]. In such cases, the patient is identified as someone possibly at risk of developing MS in the future. A cerebrospinal fluid analysis combined with MRI may be helpful in predicting likelihood of conversion to MS [49]. Some studies have shown that starting a disease-modifying treatment at this stage may delay both conversion to MS and onset of the progressive phase [50].

RELAPSING-REMITTING

Relapsing-remitting multiple sclerosis (RRMS) is characterized by alternating series of clearly defined clinical relapses (or exacerbations) followed by periods of partial or complete recovery (remissions). RRMS affects young adults, is three times more common in women than men, and accounts for about 85% of all cases of MS [51]. Functional and structural impairments suffered during relapses may either resolve or leave sequelae.

The majority of patients with RRMS subsequently enter a secondary progressive disease course. Studies have demonstrated that the time from RRMS onset to secondary progression is approximately 20 years [51]. A minority of patients with RRMS will have a relatively benign course.

The most frequent symptoms of RRMS include [51]:

- Episodes of visual loss or double vision
- Tingling or numbness
- Fatigue
- Urinary urgency
- Balance problems
- Weakness

SECONDARY PROGRESSIVE

Following an initial relapsing-remitting course, most patients with RRMS eventually transition to a secondary progressive pattern of MS (SPMS), characterized by fewer clinical relapses and a slowly progressive course of neurologic impairment without any well-defined periods of remission [47]. Of patients diagnosed with RRMS who do not receive treatment, 50% will develop SPMS within 10 years and 90% will progress to SPMS within 25 years [52]. Conversion of RRMS to SPMS is determined solely on clinical findings; biochemical markers or specific tests are not useful.

Persons with SPMS usually experience cognitive impairment, pain, and numbness. One of the characteristic features of SPMS is disabling tremor that can last for an extended period of time. This disease is characterized by a progressive deterioration of ability, and people with SPMS usually do not recover completely from a relapse.

PRIMARY PROGRESSIVE

Primary progressive MS (PPMS) is characterized by steady disease progression from the onset of symptoms, perhaps with occasional remissions and temporary minor improvements [47]. Approximately 10% to 15% of patients with MS carry the diagnosis of PPMS [49]. Patients diagnosed with PPMS tend to be older (mean age: 40 years) than those with RRMS, and there is no gender difference in incidence [49].

In PPMS, there is a progressive decline in function with an absence of acute inflammatory attacks. Patients exhibit steadily worsening motor dysfunction and increased disability. There is no established disease-modifying therapy for PPMS, which carries a worse prognosis for disability than does RRMS [53]. Disease-modifying therapies work primarily by reducing inflammation in the CNS. They do not work as well in a disease course that is characterized by nerve degeneration rather than inflammation. For this reason, they have not been shown to be effective in progressive forms of MS unless the patient relapses or has demonstrated MRI activity caused by inflammation [53]. Patients with PPMS may experience symptoms similar to those seen with RRMS. However, PPMS usually involves the spinal cord, and signs and symptoms are often related to spinal involvement. Approximately 80% of patients with PPMS have progressive weakness of the lower limbs with spasticity, known as spastic paraparesis [54]. Approximately 15% of patients with PPMS experience ataxia as a result of progressive cerebellar involvement. Other symptoms include altered sensation, muscle spasms and weakness, mobility problems, difficulty in speech or swallowing, visual impairments, fatigue, pain, and bladder and/or bowel difficulties. An estimated 6% of patients with PPMS suffer from hemiparesis [54].

The lesions associated with PPMS show a reduction in the number of oligodendrocytes and myelin repair when compared to other types of MS. Widespread inflammation with diffuse axonal damage in white brain matter is often present. This leads to cortical tissue and axonal damage, with associated irreversible and progressive disability. There is increased intrathecal production of IgG antibodies, and oligoclonal bands are found in the CSF of approximately 90% of cases [54].

UNCOMMON SUBTYPES

Progressive Relapsing

In a small subset of patients (less than 5%), the disease course is reflective of a mixed pattern, defined in the past as progressive-relapsing MS (PRMS), and characterized by a steady progression of clinical neurologic damage with clear acute exacerbations (with or without full recovery) and no total remissions [47]. Disease progression continues between relapses, leading to the permanent loss of neurologic function and cumulative disability. PRMS is associated with a severe disease course and a relatively high mortality rate.

Benign MS

Benign MS is a retrospective diagnosis characterized by long-term absence of symptoms with no functional impairments of neurologic systems 15 years after the disease onset. Approximately 15% of patients with an acute MS attack do not experience another relapse [55]. However, a relapse may occur after many years of inactivity, and it important not to assume that mild MS is truly benign.

Malignant MS

Malignant MS (also known as Marburg variant) is characterized by a rapidly progressive course resulting in major disability and usually death within one year of the onset. This disease course is most common in children, although older adults may be affected as well.

Malignant MS is associated with larger lesions, more often involving the brainstem. It shows poor response to treatment, but there may be some improvements with plasmapheresis or experimental therapies (e.g., stem cell transplantation).

Late-Onset MS

On occasion, a patient presents with new-onset MS at an unexpectedly late or early stage in life. Such cases are categorized as either late- or early-onset disease. These types of MS tend to have an atypical presentation and to follow a less predictable clinical course.

Late-onset MS is diagnosed in patients older than 50 years of age. Because many of the signs of late-onset MS are similar to other medical conditions associated with aging, misdiagnosis or delayed diagnosis is common. Late-onset MS is characterized by a progressive course, predominant motor symptoms, difficulties with treatment, and poor prognosis.

Some of the most frequent motor symptoms present in late-onset MS include:

- Gait disturbances
- Trouble moving arms and/or legs
- Muscle spasms
- Tremor
- Clumsiness
- Weakness

Most patients with late-onset disease experience only one symptom in the beginning and steadily accumulate more symptoms. The disease typically follows a primary-progressive course and is associated with poorer response to treatment than the relapse-remitting types seen more often in early-onset. Patients with late-onset MS frequently have memory and learning disabilities, difficulty with selective attention, and short-term memory deficits. Depression is also common. Disability progression appears to be faster and more severe in late-onset MS.

Early-Onset MS

Early-onset MS is usually diagnosed in patients younger than 20 years of age. It accounts for approximately 0.4% to 10.5% of all MS cases [56]. Usually, the disease is characterized by a relapsing-remitting course, a high recovery rate from initial attack, and a long remission and slow progression rate. Sensory symptoms are more common than motor symptoms in these patients, and vision loss (optic neuritis) is a common initial presentation. Other functional systems are involved with a variable frequency. Seizures, malaise, irritability, and low-grade fever may also be present.

DIAGNOSIS

Diagnosis of MS can be difficult, as initial signs and symptoms may be nonspecific or mimic other neurologic disorders. Careful and repeated neurologic examination and selected diagnostic testing over time may be required to confirm the diagnosis. During the course of evaluation, it is important to assess for clinical subtype, form a judgment as to certainty of the diagnosis, and define the extent of disability. The basic requirements for the diagnosis of MS include neurologic symptoms and signs compatible with the diagnosis; evidence of "dissemination in time" (sequential or relapsing symptoms) and "dissemination in space" (two or more lesions on MRI at different sites in the CNS); and no alternative explanation/diagnosis for the clinical and imaging findings [57].

There is no single test or gold standard for the diagnosis of MS. The process of reaching a diagnosis typically involves [57]:

- Evidence from the patient history
- Clinical examination
- One or more laboratory tests and neuroimaging studies

All three of these approaches are generally necessary in order to accurately diagnose MS and complete the differential diagnosis.

The diagnosis of MS often requires assessment at multiple phases of the clinical course [57]. Patients often experience varying degrees of neurologic dysfunctions at different stages, resulting from disease flares within varying regions of the brain or spinal cord. The diagnosis of MS must be concluded by careful assessment of all the evidence both for and against the disease. Final diagnosis will depend upon the extent to which the patient's overall picture has the expected findings typical of MS.

NEUROLOGIC EXAM

A thorough and accurate neurologic examination should be conducted to assess:

- Cranial nerve function
- Coordination
- Strength
- Reflexes
- Sensation

A variety of neurologic exam techniques are useful to evaluate the many areas in which dysfunction may be present (***Table 2***). Because no particular neurologic symptoms or findings are pathognomonic for MS, this process can be lengthy. Certain important clues from the history and/or physical exam often lead to the correct diagnosis. It is important to take into account, and prepare for, any cultural or language barrier to effective communication with the patient. When there is an obvious disconnect in the communication process between the practitioner and patient, an interpreter is required.

INO, especially a bilateral INO in young patients, is suggestive of MS, as it is rare in other conditions. Altered color vision, unilateral optic pallor, and/or Marcus-Gunn pupil may be indicative of optic neuritis. Patients with MS may also exhibit nystagmus.

A mild intention tremor can be an early sign of MS. Patients with early MS may also exhibit a positive Romberg sign, or decreased vibratory and proprioceptive sense in lower extremities. A positive Lhermitte sign in an adult younger than 60 years of age may indicate MS [58].

For some patients, clinical symptomatology and neurologic exam findings are inconclusive, especially in individuals who have experienced separate episodes of neurologic symptoms [58]. As such, additional diagnostic tests may be necessary to fully evaluate the patient and determine the diagnosis. This can include imaging, laboratory tests, and nerve stimulation.

NEUROLOGIC SIGNS AND TESTS		
Test	**Description**	**Notes**
Romberg test	Patient stands erect with feet together and eyes closed. Swaying or falling is considered positive.	Used for patients with ataxia. Indicates loss of proprioception.
Lhermitte sign	Patient bends the head forward or clinician puts pressure on the posterior cervical spine. An electrical shock sensation is considered positive.	Used to determine the presence of lesions on the cervical spine. Often considered a classic finding in MS but can be caused by a number of conditions.
Gait tests	Observe patient walking normally, walking heel-to-toe, and walking on only toes/heels. Any abnormalities should be noted.	This test evaluates ataxia in various parts of the body.
Point-to-point movement evaluation	Patients alternate touching their extended index finger to their nose and the examiner's outstretched finger.	These are tests to evaluate ataxia, dysmetria, and cerebellar dysfunction. Positive findings are indicative of loss of motor strength, loss of proprioception, or a cerebellar lesion.
	Supine patient places right heel on left shin just below the knee and slides it down to the top of the foot as quickly as possible without making mistakes. Repeat on opposite side. Inability to complete quickly is considered positive.	
Visual acuity and color tests	Patient reads letters from a board to assess visual acuity and from the Ishihara Color Vision Test to assess color vision. Inability to distinguish figures is considered positive.	These tests evaluate for the presence of optic neuritis, perhaps the most frequent symptom in MS.
Babinski sign	The lateral side of the sole of the foot is lightly stimulated from the heel along a curve to the toes. If the hallux dorsiflexes and the other toes fan out, this is considered a positive Babinski sign.	These tests evaluate for signs of disease process in the motor neurons of the pyramidal tract. They are positive in individuals with neurologic problems of the corticospinal tract, including those with MS.
Chaddock sign	Similar to Babinski's sign, this test involves stimulation over the lateral malleolus rather than the bottom of the foot. A positive response elicits an extensor response similar to Babinski sign.	
Hoffman reflex	Clinician taps the nail or flicks the terminal phalanx of the middle or ring finger. A positive response is seen with flexion of the terminal phalanx of the thumb.	This test evaluates problems in the corticospinal tract. However, it is also positive in hyper-reflexive patients. Findings that are acute or asymmetrical are more indicative of disease.
Halmagyi-Curthoys head impulse test	Clinician randomly moves the patient's head side to side. If the eyes remain stationary while the head is moved, this is considered positive.	Test reveals dissociation between movement of the eyes and of the head. Indicative of peripheral vestibular disease.
Perception tests	A monofilament, tuning fork, or pin is applied to patient's body. Ability to perceive the touch or vibration is considered positive.	Evaluates the level of sensory perception in certain parts of the body.
Muscle strength tests	Patient attempts to resist pressure applied by the clinician to various muscle groups. Level of resistance can be rated on a scale from none to normal strength.	Patterns of weakness can help localize a lesion to a particular cortical or white matter region, spinal cord level, nerve root, peripheral nerve, or muscle. Differences in strength between left and right sides are easier to evaluate than symmetrical loss unless the weakness is severe.
Reflexes	This is done with both ends of the hammer. The reflexes can be normal, brisk (i.e., too easily evoked), or non-existent.	—

Source: Compiled by Author *Table 2*

MAGNETIC RESONANCE IMAGING

Plaque lesions (foci of inflammation and demyelination) of MS are best detected using MRI of the brain or spinal cord. MRI will demonstrate the presence, location, number, and size of MS lesions. MRI is also important in excluding other pathologic diagnoses. It is used for diagnostic purposes and to monitor the course of disease and response to therapy. Most patients with symptomatic MS have demonstrable lesions, and MRI often reveals multiple lesions, even in patients with the clinically isolated syndrome [33; 57]. MRI with contrast enhancement (i.e., IV gadolinium) provides a better assessment of active inflammation within plaques and, by elimination, can reveal the presence of older lesions not associated with current symptoms [58; 59]. If present, these older lesions provide some evidence of a period of occult disease prior to the onset of symptoms. As MRI techniques become more sophisticated and pathologically specific, there is an increased likelihood of exploring the pathologic classification of MS.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the International Panel on Diagnosis of Multiple Sclerosis, brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of multiple sclerosis and can substitute for clinical findings in the determination of dissemination in space and/or time in patients with a typical clinically isolated syndrome.

(https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/fulltext. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In 2018, the Consortium of MS Centers (CMSC) published revised MRI protocol and clinical guidelines for the diagnosis and follow-up of MS [60]. A 2021 revision of previous guidelines on MRI use for patients with MS merged recommendations from the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) study group, CMSC, and the North American Imaging in Multiple Sclerosis Cooperative (NAIMS) [61]. In addition to emphasizing the value of three-dimensional (3D) acquisition techniques, the MAGNIMS-CMSC-NAIMS consensus group extends recommendations for the use of MRI in patients with MS to MS in childhood, during pregnancy, and in the postpartum period [61].

A brain MRI with gadolinium is recommended for the diagnosis of MS. If the brain MRI is non-diagnostic, or if presenting symptoms are referable to the spinal cord, then a spinal cord MRI is recommended [60; 61]. Follow-up brain MRI is recommended for the following clinical purposes [60]:

- To demonstrate "dissemination in time" for confirmation of diagnosis
- To detect clinically silent disease activity while on treatment
- To evaluate unexpected clinical worsening
- To reassess the original diagnosis or as a new baseline MRI before modifying therapy
- Every six months to two years for patients with relapsing MS

Small amounts of gadolinium-based contrast agents do accumulate in the brain of some persons who have received multiple doses. Although there is no current evidence that these deposits are harmful, the Consortium protocol and the MAGNIMS-CMSC-NAIMS consensus recommendations emphasize that gadolinium should be used judiciously [60; 61]. Gadolinium-based contrast is helpful but not essential for detecting subclinical disease activity. In addition to evaluating the patient with clinically isolated syndrome, the use of a gadolinium-based contrast agent is recommended in patients with highly active disease and when there is rapid onset of unexplained and unexpected clinical worsening [60; 61].

On occasion, MRI performed on a patient without overt or significant symptoms will demonstrate abnormalities suspicious for MS, based on location and morphology within the CNS [58]. These cases are classified as the "radiologically isolated syndrome," and follow-up studies have shown that the majority of such patients eventually develop more lesions and progress to a true clinical MS

ELOQUENT MS SYNDROMES		
Eloquent Syndrome	**Localization**	**Clinical Manifestations**
Optic neuritis	Optic nerve	Visual acuity loss Visual field suppression Color desaturation Pain Relative afferent pupillary defect
Internuclear ophthalmoparesis (INO)	Medial longitudinal fasciculus (MLF)	Slowing of adducting eye movements Diplopia Oscillopsia
Skew deviation	Otolith pathways	Vertical or oblique diplopia Subjective deviation of visual vertical
Cranial nerve palsies	Brainstem	Facial weakness Facial numbness (cranial nerve V) or pain Diplopia (cranial nerves III, IV, VI) Vestibulopathy (cranial nerve VIII or nucleus)
Rubral tremor	Superior cerebellar peduncle	Tremor
Ataxia	Cerebellum	Instability and reduced postural control
Trigeminal neuralgia	Trigeminal system	Paroxysmal facial pain
Myelitis	Spinal cord	Sensory disturbances Spasticity Bowel/bladder/sexual dysfunction Weakness

Source: Reprinted with permission from Frohman TC, O'Donoghue DL, Northrop D (eds). Multiple Sclerosis for the Physician Assistant: A Practical Primer. New York, NY: National Multiple Sclerosis Society; 2011. *Table 3*

exacerbation. These patients likely represent an early, preclinical stage of MS, identified by MRI in the course of evaluation for other reasons [33].

When there is a weak association between common neuroradiologic markers of MS and clinical disability, this is referred to as a clinicoradiologic paradox. This partly relates to the principle of eloquence and non-eloquence. Non-eloquent lesions are lesions that tend to develop in particular anatomic locations and are not always associated with clinically consistent symptoms; they are also referred to as silent or subclinical. Eloquent lesions usually develop in particular anatomic locations or pathways and almost always result in the manifestation of a characteristic inflammatory demyelinating syndrome [33]. These lesions are associated with expected clinical neurologic manifestations (***Table 3***).

A number of MRI sequences are done to reveal different histopathologic features of the MS plaque. These MRI sequences are "weighted" to demonstrate water or fat. T1-weighted, T2-weighted, and proton-density scans are used in the diagnosis of MS, and all are sensitive to the higher-than-normal water content found in MS lesions. These images are partially confounded by the intense signal of the water content of the CSF. 3D fluid-attenuated inversion recovery imaging is an imaging technique that nulls fluids and is used to suppress CSF effects and enhance the periventricular hyperintense lesions present in MS [62]. The use of 3D acquisition techniques is preferred to two-dimensional acquisitions, as 3D techniques have become more routinely available on clinical scanners. They also improve lesion detection and the realignment of anatomic orientation that is necessary to detect new lesions when comparing serial MRI scans [61]. 3D techniques also are more sensitive in depicting lesions in cortical and infratentorial locations than dual-echo sequences [63].

MRI of the brain in a patient with MS typically shows multifocal T2-hyperintense white matter lesions in characteristic locations. Spinal cord lesions, most commonly in the cervical region, are seen in about half of patients at first presentation and in 80% to 90% of patients with established MS [2]. The scan is considered strongly predictive of MS if it shows at least four lesions in the brain or three lesions with at least one present in the periventricular region. However, while these criteria are considered sensitive, they are not very specific. More accurate criteria require at least three lesions be present, fulfilling at least two of the following criteria:

- Periventricular lesion
- Lesion at least 6 mm in diameter
- Infratentorial lesion

T1-weighted, T2-weighted, and proton-density scans also reveal complementary information about the nature of MS. T1-weighted scans provide a better anatomical picture of the brain and are useful for detecting older lesions and abnormal areas. These scans are often used with contrast to illuminate areas of recent inflammation that may be associated with active MS. T2-weighted scans do not show the best anatomical picture of brain compared to T1-weighted scans, but they can detect both new and old lesions. These scans are repeated over a period of time to track the development of MS. Proton-density scans also detect both old and new lesions and are particularly useful in detecting periventricular plaques.

High-field and ultra-high-field MRI can detect a greater number and volume of T2-hyperintense and gadolinium-enhancing brain lesions than those operating at lower fields [64; 65]. These high-power MRIs can detect MS at a very early stage and are more sensitive to cortical lesions [66].

The diverse disease processes associated with the subtypes of MS can be detected by MRI as well. In PPMS, MRI will show small lesions that do not enhance with a contrast agent, indicating little or minimal inflammation. This particular characteristic is a clear differentiation from relapsing-remitting disease. The severity and extent of the physical symptoms of MS can be confirmed by visualization of the anatomic location of lesions within the CNS. For example, a lesion present in the spinal cord may result in numbness in the limbs and bladder disturbance. Lesions in the optic nerve are usually responsible for optic neuritis, leading to blurred vision and a loss of color perception.

There is a correlation between the "lesion load" (i.e., total volume of CNS tissue affected by the MS disease process) and the probability that a key part of the brain or spinal cord will be affected, resulting in clinical symptoms. However, studies have demonstrated only weak correlation between MRI lesion load and age at disease onset, disease duration, and progression [67]. MRI lesion burden is not considered a good indicator of disease progression, especially in cases of advanced MS.

MS lesions found in the spinal cord usually give rise to identifiable symptoms and are highly eloquent of the disease process; new spinal MS lesions are strongly correlated to new clinical manifestations. Approximately 75% of patients with MS have lesions within the spinal cord, principally the cervical cord, and most spinal cord lesions are located in the dorsal columns [68]. These lesions are usually oval or cigar-shaped and can span one or two vertebral segments (referred to as skip lesions).

Advances in MRI Imaging

Despite its many advantages, the principal handicap of MRI is its low sensitivity in detecting grey-matter involvement and diffuse damage in white matter. Advances made in conventional and non-conventional MRI methods are enabling better assessment of CNS tissue damage in patients with MS. New techniques that can provide more insight into MS include:

- Proton magnetic resonance spectroscopy (1H-MRS)
- Magnetization transfer imaging
- Diffusion imaging

- Functional MRI
- Optic-nerve imaging
- Spinal-cord imaging
- Myelin water fraction (MWF) imaging
- Perfusion MRI
- Ultra-high-field MRI

MRI assessment of lesions on noncontrast T1- and T2-weighted images and on gadolinium-enhanced T1-weighted images provides an important imaging tool for close monitoring of the disease course [69]. However, conventional MRI is weakly correlated with clinical status of MS and has low sensitivity [70; 71]. New approaches in the field of data management and post-processing have the potential to change the way MS is diagnosed currently. With the help of serial analysis of images, it is now possible to detect a shift in the patient's disease from more inflammatory to more degenerative pathologic processes. This shift may be indicative of possible atrophy and clinical disability [72]. Another method called subtraction imaging displays changes over time between two scans in a single map [73]. This method is more sensitive to lesion evolution compared to conventional techniques.

Voxel-based morphometry is a novel method that explores the association between regional patterns of atrophy and particular functional impairment [74; 75]. Researchers are searching for a method that delineates the relationship between regional atrophy and white matter tract damage and the resulting clinical implications. Diffusion tensor MRI technique has the potential to map the white-matter architecture in details. This novel technique can then be used to correlate quantitative measures of CNS tissue damage and its functional significance, leading to more clinically relevant assessment of the burden of disease.

Grey matter damage in MS occurs largely independent of white matter lesions and shows stronger correlation with clinical parameters than white matter damage. One meta-analysis used differential mapping to assess global and regional grey matter volume differences in MS [76]. Potential effects of disease duration and degree of functional disability also were analyzed. A highly localized pattern of regional grey matter volume loss was observed in RRMS, and grey matter volume loss in left pre- and postcentral regions correlated with increased functional disability [76].

Newer MRI contrast agents composed of iron particles (i.e., nano-size particles of iron oxide or superparamagnetic iron oxide particles) are being used in patients with MS to track macrophages [77; 78]. Studies using these agents have confirmed a mismatch of MRI enhancement, signifying heterogeneity of the underlying MS pathology [77; 78]. Tracking macrophages with these tiny iron particles can help monitor the efficacy of drugs in MS treatment. Gadofluorine M, a gadolinium-based MRI contrast agent, is very sensitive in the detection of inflammatory CNS lesions, as it selectively accumulates in nerve fibers undergoing Wallerian degeneration [79].

1H-MRS

1H-MRS can be used to measure N-acetylaspartate levels to monitor CNS damage. Levels of choline-containing compounds usually increase during myelin breakdown, remyelination, and inflammation. 1H-MRS is helpful in detecting levels of glutamate, glutamine, and gamma-aminobutyric acid (GABA), and advances in 1H-MRS techniques could revolutionize the diagnosis of MS.

Magnetization Transfer MRI

Another nonconventional technique, magnetization transfer MRI, can detect the magnetization transfer ratio (MTR), which helps in monitoring disease progression in patients with MS. A low MTR indicates damage to neurons, particularly myelin and axonal membranes. Decreased MTR is particularly pronounced in patients with the progressive forms of MS and has a tendency to deteriorate over time [80]. Studies have demonstrated that this technique has prognostic value for subsequent disease evolution [80].

Diffusion MRI

Diffusion MRI is helpful in noninvasively mapping the diffusion process of molecules in biologic tissues and can detect focal MS lesions. Research is focusing on the role of direct MRI detection of neuronal activation, either by diffusion-weighted imaging or by the effect that neuronal currents have on a local, externally applied magnetic field [81; 82]. In the future, this technique could provide vital information about the disease processes of MS and the effects of these processes on motor and cognitive function. Diffusion tensor imaging (DTI) is useful in evaluating normal-appearing white matter and other lesions in MS that are difficult to evaluate with routine MRI. Advanced diffusion MRI is capable of capturing in vivo microstructural changes in the brain and spinal cord in both normal and pathological states in greater detail than DTI [83]. Another advanced MRI technique, diffusion basis spectrum imaging, shows differences between MS subtypes related to the severity and composition of underlying tissue damage [84].

Functional MRI

Functional MRI, or fMRI, measures brain activity by detecting the changes in blood oxygenation and flow that occur in response to neural activity. fMRI uses the blood-oxygen-level-dependent contrast mechanism and may be useful in detecting alterations in visual, cognitive, and motor networks in patients with MS.

Myelin Imaging

Research on MS has emphasized the need to develop MRI techniques that can measure the invisible burden of disease in the CNS and establish highly sensitive and specific markers of disease progression. Myelin-selective MRI is a promising technique that allows accurate mapping of MWF, a parameter that is linked to brain white matter myelination [85]. Studies suggest that a 30% to 50% decrease in MWF occurs in MS lesions and a 7% to 15% decrease is seen in normal-appearing white matter in patients with MS [86; 87].

OPTIC-NERVE IMAGING

Imaging of the optic nerves is difficult because of the limited resolution of MRI and patient motion artefacts. However, optic neuritis can be an excellent model to understand the pathophysiology of MS. A link has been observed between acute inflammation and conduction block in optic neuritis [88]. Dynamic MTR changes indicate myelin damage and repair due to axonal degeneration and demyelination [89].

Optical coherence tomography shows promise as a potential marker of axonal loss in assessing neurodegeneration in MS [90; 91]. This technique can detect thinning of the retinal nerve fiber layer.

CEREBROSPINAL FLUID ANALYSIS

Performing lumbar puncture for CSF analysis is not essential for confirming diagnosis of MS; however, it can be helpful in the differential diagnosis. CSF analysis can detect intrathecal synthesis of antibodies, which is evident by the presence of oligoclonal bands, IgG index elevation, and an increased IgG synthesis rate. It is important to note that the presence of oligoclonal bands in CSF is suggestive of MS, but its presence in serum is not. CSF analysis should always be interpreted with regard to the clinical situation.

Oligoclonal bands are found in the CSF of approximately 75% to 85% of patients with MS [58; 92]. However, a similar pattern of antibody synthesis is present in various types of infectious, inflammatory, vascular, neoplastic, and paraneoplastic conditions as well. Conditions other than MS are considered when CSF analysis reveals pleocytosis (>50 white blood cells/mm^3) or a CSF protein concentration greater than 100 mg/dL [93].

Detection of oligoclonal bands in CSF by isoelectric focusing is the most sensitive laboratory test for MS and the most sensitive predictor of conversion from clinically isolated syndrome to MS. It is also the best test to show local intrathecal IgG synthesis. Patients with suspected MS who lack oligoclonal IgG bands

in CSF should be investigated for other diagnoses, although it is important to remember that not all patients with MS display oligoclonal bands. Studies have demonstrated that the frequency of oligoclonal bands in the CSF of patients with MS varies in different regions of the world, with higher rates in Northern Europe and North America and lower rates in Asia [93].

The association between the presence of oligoclonal bands in CSF and progression of disability in MS is not yet clear. However, one literature review found that the presence of both IgG and IgM bands are associated with a worse MS prognosis [94]. The oligoclonal band pattern in CSF does not change during the course of the disease, but banding patterns do vary among patients.

EVOKED POTENTIAL TESTING

Evoked potential testing consists of electrical tests of the nerve pathways, which are less responsive to stimulation in individuals with MS. This noninvasive and sensitive test checks brain responses by visual- and sensory-evoked potentials, identifying CNS lesions or damaged areas.

There are three main types of evoked potential tests used in the diagnosis of MS:

- Brainstem auditory evoked potentials: A series of clicks played in each ear via headphones
- Visual evoked potentials: A series of alternating checkerboard patterns shown on a screen
- Somatosensory evoked potentials: Short, mild electrical shocks administered to a patient's arm or leg

The patient's responses are analyzed carefully for response size and the speed in which the brain receives the signal. Demyelination can be indicated by weak or slow brain response to the test, suggesting possible MS.

Only results of visual evoked potentials are considered part of the diagnostic criteria for MS. Visual evoked potentials can detect sluggish neurotransmission along the optic nerve pathways, a finding common in individuals with asymptomatic MS. However, a positive finding on evoked potential testing is not specific to MS, and the abnormalities detected may also be present in other conditions.

DIAGNOSTIC CRITERIA

The McDonald criteria established by the International Panel on the Diagnosis of MS are used to determine both diagnosis and subtype of MS based on brain imaging, extent of symptoms, and duration of symptoms (***Table 4***) [58]. These criteria were first introduced in 2001 and were most recently revised in 2017 [95].

The 2010 revision of the McDonald criteria improved the sensitivity from 46% to 74%, with a slight tradeoff in specificity (decreased from 94% to 92%) [58]. Major changes in the 2010 revision included simplification of the demonstration of CNS lesions in space and time through MRI imaging and consideration of application to non-Western White populations [58].

The 2017 modification of the McDonald criteria focused on differentiating those patients with clinically isolated syndrome who have a high probability of incipient MS and therefore would benefit from early introduction of disease-modifying therapy. The 2017 revision eliminates the requirement for dissemination in time to diagnose MS in patients with a typical clinically isolated syndrome and fulfillment of clinical or MRI criteria for dissemination in space with demonstration of CSF-specific oligoclonal bands in the absence of other CSF findings. In addition, symptomatic and asymptomatic MRI lesions can be considered in the determination of dissemination in space or dissemination in time. Previously, only asymptomatic MRI lesions could fulfill these criteria. Finally, cortical lesions (in addition to juxtacortical lesions) can be used in fulfilling MRI criteria for dissemination in space [95].

2017 MCDONALD CRITERIA FOR THE DIAGNOSIS OF MS	
Clinical Presentation	**Additional Data Needed for MS Diagnosis**
In a patient with a typical attack/CIS at onset	
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 symptomatic or asymptomatic T2 lesion in at least 2 MS-typical regions of the CNS (periventricular, juxtacortical/cortical, infratentorial, or spinal cord)[d]; or await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	CSF-specific (i.e., not in serum) oligoclonal bands Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic or symptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space: ≥1 symptomatic or asymptomatic T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical/cortical, infratentorial, or spinal cord)[d]; or await a second clinical attack[a] implicating a different CNS site For dissemination in time: Simultaneous presence of symptomatic or asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
In a patient with progression of disability from onset	
Insidious neurologic progression suggestive of MS (primary progressive)	1 year of disease progression (retrospectively or prospectively determined) plus two of the following three criteria[d]: • Evidence for dissemination in space in the brain based on ≥1 symptomatic or asymptomatic T2 lesions in the MS-characteristic (periventricular, juxtacortical/cortical, or infratentorial) regions • Evidence for dissemination in space in the spinal cord based on ≥2 T2 lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the criteria 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 clinical presentation, then the diagnosis is not MS.

[a]An attack (relapse, exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurologic examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurologic findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurologic examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurologic symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurologic findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

Source: [95] *Table 4*

CONDITIONS THAT MAY MIMIC MS		
Disease	**Symptoms Similar to MS**	**Differentiating Symptoms**
Systemic lupus erythematous	Common in young women and may affect the nervous system, especially the optic nerve and spinal cord. MRI white-matter changes are common, and up to 60% have oligoclonal bands and IgG abnormalities in CSF.	Positive serology with ANA and double-stranded DNA autoantibodies. Systemic involvement, especially including the kidneys and skin, and hematologic changes.
Sjögren syndrome	Occasional reports of neurologic symptoms, especially progressive myelopathy. MRI may show white-matter lesions and CSF may show oligoclonal bands with increased IgG.	Positive serology for SS-A (Ro) and SS-B (La) autoantibodies. Prominent dry eyes and mouth. Salivary gland biopsy can be definitive.
Lyme disease	Can cause persistent focal neurologic findings and signal abnormalities on MRI scan of the brain.	History of erythema migrans rash. Western blot is the most definitive serology, and CSF will show positive PCR.
Syphilis	Can cause optic neuritis, myelopathy, and other focal neurologic findings.	MRI is usually normal. Negative serology rules out syphilis. Advanced infection now rare except in HIV-positive or immunocompromised patients.
HIV/AIDS	May cause optic neuritis, myelopathy, mental status changes, and focal deficits with white-matter changes on MRI scan and abnormal CSF.	Occurs in high-risk populations who may have diminished CD4 cell counts and positive HIV serology.
Vitamin B12 deficiency	May cause CNS deficits, especially a progressive myelopathy, rarely with MRI signal abnormalities.	Complete blood count is often abnormal and serum B12 levels are low. Methylmalonic acid and homocysteine are often abnormal.
CNS lymphoma	Focal neurologic deficits with multifocal enhancing MRI lesions.	CSF does not have IgG abnormalities but will often show positive cytology. Lesions are highly steroid responsive. Brain biopsy may be necessary.
Chiari malformation	May cause cranial neuropathies, including ophthalmoplegia, nystagmus, and ataxia.	MRI scanning, especially on sagittal images, will detect the malformation. MRI of the brain is otherwise normal, as is CSF.
Chronic fatigue syndrome and fibromyalgia	May report neurologic symptoms that mimic MS in a similar population (young women).	Neurologic examination is objectively normal. Difficulties arise when the MRI shows "nonspecific" abnormalities, but MRI, CSF, and VERs should be normal.
ANA = antinuclear antibody, CSF = cerebral spinal fluid, HIV/AIDS = human immunodeficiency virus/ acquired immunodeficiency syndrome, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, VER = visual evoked response.		
Source: [96]		*Table 5*

DIFFERENTIAL DIAGNOSIS

Because there are a variety of conditions that may mimic MS, differential diagnosis can be complicated (***Table 5***) [96]. A diagnosis of MS should be questioned if clinical or laboratory findings are unexpected or atypical. These unusual features, or "red flags," should raise suspicion that another condition is the underlying cause of symptoms.

Atypical clinical features that suggest an alternate diagnosis include [96]:

- Normal neurologic examination
- Abnormality in a single location (i.e., no dissemination in space)
- Progressive from onset (i.e., no dissemination in time)

- Onset in childhood or at an age older than 50 years
- Psychiatric disease present
- Systemic disease present
- Prominent family history (may suggest genetic disease)
- Gray matter symptoms (e.g., dementia, seizures, aphasia)
- Peripheral symptoms (e.g., peripheral neuropathy, fasciculations)
- Acute hemiparesis
- Lack of typical symptoms (e.g., no optic neuritis, bladder problems, Lhermitte sign)
- Prolonged benign course (i.e., diagnosis made several years ago with few current findings)

Atypical laboratory findings that point to a diagnosis other than MS as the cause of symptoms include [96]:

- Normal or atypical MRI
- Normal CSF
- Abnormal blood tests (though false positives are possible)

Most patients with other diseases will be identified by the presence of one or more of these atypical features. A number of studies have demonstrated that patients who do not have MS have two things in common: absence of typical MS symptoms such as optic neuritis, Lhermitte sign, sensory dysfunction, neurogenic bladder, or other common deficits; and absence of typical findings on MRI and CSF examination [96]. Very few patients with MS have a normal brain MRI and/or normal CSF.

In the absence of a clear-cut typical clinically isolated syndrome, the International Panel on Diagnosis of Multiple Sclerosis asserts that caution should be exercised in making the diagnosis of multiple sclerosis, and the diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.

(https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/fulltext. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Misdiagnosis of MS

Although uncommon, a misdiagnosis of MS can result in unnecessary and prolonged therapies that impose potentially harmful risks to patients. In a multi-center study of 110 misdiagnosed patients, alternate diagnoses included migraine (22%), fibromyalgia (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI (12%), conversion or psychogenic disorders (11%), and neuromyelitis optica spectrum disorder (6%) [97]. The duration of misdiagnosis was 10 years or longer in one-third of patients. Seventy-seven patients (70%) had received disease-modifying therapy and 34 (31%) experienced unnecessary morbidity because of the misdiagnosis. The most common errors in diagnosis pertained to misinterpretation of MRI findings or misapplication of clinical and radiographic criteria for the diagnosis of MS.

TREATMENT

There is no cure for MS. However, effective treatment strategies are available to modify the disease course, treat or reduce exacerbations, prevent relapses, manage signs and symptoms, improve overall function and safety, and provide psychological support. The treatment strategy depends on the patient's clinical condition and disease course. In cases of mild MS without relapses, usually no treatment is necessary. If a patient experiences relapses or if symptoms become more severe, treatment should be initiated as soon as possible.

TREATMENT OF ACUTE EXACERBATIONS

Treatment of the acute exacerbations seen with relapsing types of MS relies primarily on corticosteroids and adrenocorticotropic hormone (ACTH). These agents have been found to promote speedier resolution of the neurologic deficits, lessen the severity of an attack, and effectively reduce the risk of permanent residual deficits. Both corticosteroids and ACTH are capable of restoring the breakdown of the blood-brain barrier, reducing inflammation, and immunomodulating mononuclear trafficking mechanisms. Corticosteroids also promote quick recovery from disability [98; 99].

Corticosteroid therapy is indicated for patients with MS who present with an acute exacerbation (relapse) accompanied by objective evidence of functional neurologic impairment, such as impairment of vision, signs of optic neuritis, motor deficits or cerebellar symptoms and signs, or sensory deficits that impose undue discomfort (e.g. paresthesias).

The first-line treatment of MS-related exacerbations involves administration of high doses of IV corticosteroids, usually methylprednisolone (1 g daily), for five to seven days [100; 101]. Alternative approaches for patients who do not tolerate large intravenous dosage or have poor venous access include:

- Repository ACTH (corticotropin injection gel): 80–120 units daily for one to three weeks
- Oral prednisone: 500–1,250 mg daily divided for three to seven days
- "Smoothie Medrol:" 1 g methylprednisolone mixed in smoothie or juice taken orally with breakfast for three to seven days
- Dexamethasone: 160–200 mg orally/IV daily divided for three to seven days

Although frequently used, the evidence to support low-dose oral prednisone in the treatment of acute relapses is poor and is therefore not recommended [102].

An evidence-based assessment of the use of ACTH and corticosteroids in the treatment of MS was undertaken by the Therapeutics and Technology Assessment Committee of the American Academy of Neurology. The Committee concluded that [99]:

- Treatment with corticosteroids promotes quicker recovery from acute attacks of MS.
- Long-term benefits of corticosteroids and ACTH on the course of MS are yet to be seen.
- Although high-dose corticosteroids are used to treat acute exacerbations, there is no compelling evidence that using one specific type of agent, route of administration, or dose is more beneficial than another.

Potential side effects of corticosteroids include osteoporosis, changes in mood, and memory defects [103; 104]. Patients treated with oral corticosteroids also may experience alterations in blood glucose, glaucoma, gastrointestinal symptoms, and psychiatric disorders [105].

Patients on interferons or glatiramer acetate can receive the initial pulse of corticosteroids or ACTH with or without subsequent tapering of the corticosteroid dose. Patients taking natalizumab should limit corticosteroids to a shorter duration (i.e., two to three days) without a taper to avoid the risk of developing an opportunistic infection, such as progressive multifocal leukoencephalopathy [99]. An oral steroid taper is not generally recommended. However, if there has been a dramatic response to IV corticosteroids (the so-called "Lazarus" effect), then a short taper may prevent rebound edema and a consequent deterioration [102].

IV immunoglobulins (0.4 g/kg/day for five days) are also used in some cases to treat MS relapse in patients who are intolerant or refractory to steroid treatment (second- or third-line) [106]. However, clinical studies have not resulted in conclusive supporting evidence for its efficacy.

Several other drugs that suppress the immune system (e.g., cyclophosphamide, methotrexate, azathioprine, cladribine, cyclosporine) can also reduce the symptoms of MS. These agents suppress the number of circulating immune cells, which in turn slows the autoimmune process and prevents neural damage. However, use of immunosuppressive agents results in increased susceptibility to various types of infection, and the long-term use of these medications may result in additional side effects.

PLASMAPHERESIS

It is now known that B-cell immunity also plays a key role in the pathogenesis of MS. Plasma exchange may be beneficial for relapsing forms of MS in which severe neurologic exacerbations prove refractory to parenteral corticosteroid therapy. It may also be beneficial for some patients with severe, rapidly progressive MS and similar disorders; however, it does not show any efficacy for SPMS or PPMS.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Neurology, plasmapheresis as adjunctive therapy is probably effective for the management of exacerbations in relapsing forms of MS, based on a single class I study.

(https://www.aan.com/PressRoom/Home/GetDigitalAsset/8468. Last accessed December 12, 2022.)

Level of Evidence: Class I (Randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population)

A randomized, sham-controlled study of plasma exchange was conducted in 28 patients with recently acquired severe neurologic deficits resulting from acute inflammatory demyelinating diseases (43% with MS) [107]. Treatment consisted of plasma exchange every 2 days for 14 days. Moderate or greater improvement in neurologic disability was observed during 8 of 19 (42%) courses of active plasma exchange treatment compared with 1 of 17 (6%) courses of sham treatment. Improvement occurred early in treatment and, with the exception of four patients, was sustained over six months follow-up [107].

Plasmapheresis is indicated for patients with severe relapses who have failed to respond to IV corticosteroids. Treatment effects can be dramatic. Research has linked treatment response to type II pathology (i.e., IgG deposition and complement activation) [102].

DISEASE-MODIFYING THERAPY

The use of disease-modifying drugs has been shown to reduce the number of clinical and subclinical attacks and delay the progression of disease in patients with RRMS (***Table 6***) [108; 109; 110]. Early successful control of disease activity is important in preventing the accumulation of disability and protecting quality of life. At present, there are more than one dozen therapeutic agents approved by

APPROVED LONG-TERM TREATMENTS FOR MS				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Self-injected medications				
ß-interferon 1a[a] (Avonex)	Immunomodulator with antiviral properties	Flu-like symptoms, headache	30 mcg IM injection weekly	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
ß-interferon 1b[a] (Betaseron, Extavia)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	250 mcg SC injection every other day	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Glatiramer acetate (Copaxone, Glatopa, generic)	Immunomodulator that inhibits attacks on myelin	Injection-site skin reaction as well as an occasional systemic reaction—occurring at least once in approximately 10% of those tested	20 mg SC injection daily or 40 mg SC injection three times per week	Systemic reactions such as flushing, dizziness, anxiety, and chest tightness arise 5 to 15 minutes following injection. The symptoms persist for a few minutes and lack long-term adverse effects; specific treatment is unnecessary.
ß-interferon 1a[a] (Plegridy)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site reaction, blood count and liver test abnormalities	125 mcg SC injection once every two weeks	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
ß-interferon 1a[a] (Rebif)	Immunomodulator with antiviral properties	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	44 mcg SC injection three times per week	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Ofatumumab (Kesimpta)	Monoclonal antibody that binds to and depletes B cells associated with MS disease activity	Upper respiratory tract infection, headache	20-mg dose monthly self-administered SC	Serious side effects include infections, HBV reactivation, PML, weakened immune system, injection-related reactions.
Infused medications				
Alemtuzumab (Lemtrada)	Humanized monoclonal antibody that rapidly depletes or suppresses immune system cells (T and B cells), which can damage the myelin and nerves of the CNS	Rash, itching, headache, pyrexia, nasopharyngitis, nausea, diarrhea and vomiting, insomnia, numbness/tingling, dizziness, pain, flushing, infection	Five-day course of IV infusion followed one year later by a second three-day course	Adverse events can include infusion reactions, an increased risk of infection, emergent autoimmune diseases, immune thrombocytopenic purpura (ITP), and an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders. For early detection and management of these risks, the drug is only available through a restricted distribution program.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Infused medications (Continued)				
Mitoxantrone (Novantrone)	Antineoplastic immunomodulator/ immunosuppressor	Usually well tolerated; side effects include nausea, thinning hair, amenorrhea, bladder infection, and mouth sores. Additionally, urine and whites of the eyes may turn a bluish color temporarily.	IV infusion once every three months (for two to three years maximum)	Carries the risk of cardiotoxicity and leukemia; it may not be given beyond two or three years. People undergoing treatment must have regular testing for cardiotoxicity, white blood cell counts, and liver function. Because of the potential risks, it is seldom prescribed for MS. Anyone who is taking or has taken mitoxantrone should have annual evaluations of his or her heart function, even if no longer receiving this medication.
Ocrelizumab (Ocrevus)	Humanized monoclonal antibody designed to selectively target CD20-positive B cells	Infusion reactions, increase in infections, most commonly upper respiratory tract in patients with RMS and PPMS or skin and lower respiratory tract infection in patients with PPMS	600 mg IV every six months. For the initial dose, two 300-mg doses are given, separated by two weeks.	Should not be used in patients with hepatitis B infection or a history of life-threatening infusion-related reactions to the drug. Other rare adverse events, including cancer and progressive multifocal leukoencephalopathy (PML), could potentially occur, but these risks are still being studied.
Natalizumab (Tysabri)	Humanized monoclonal antibody	Headache, fatigue, depression, joint pain, abdominal discomfort, infection	IV infusion every four weeks	Risk of infection (including pneumonia) was the most common serious adverse event (occurring in a small percentage of patients). The TOUCH Prescribing Program monitors patients for signs of PML, an often-fatal viral infection of the brain. Risk factors for PML include the presence of JC virus antibodies, previous treatment with immunosuppressive drugs, and taking natalizumab for more than two years.
Oral medications				
Teriflunomide (Aubagio)	Immunomodulator affecting the production of T and B cells	Headache, elevations in liver enzymes, hair thinning, diarrhea, nausea, neutropenia, paresthesia	7 mg or 14 mg tablet once daily	More severe adverse events include the risk of severe liver injury and the risk of birth defects if used during pregnancy. A TB test and blood tests for liver function must be performed within six months prior to initiation of therapy, and liver function must be checked regularly. If liver damage is detected, or if a patient becomes pregnant while taking this drug, accelerated elimination is prescribed.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Drug	**Type**	**Side Effects**	**Administration**	**Notes**
Oral medications (Continued)				
Fingolimod (Gilenya)	S1P-receptor modulator	Headache, flu, diarrhea, back pain, abnormal liver tests, cough	0.5 mg capsule once daily	Other adverse events include a reduction in heart rate (dose-related and transient); infrequent transient AV conduction block of the heart; a mild increase in blood pressure; macular edema; reversible elevation of liver enzymes; and a slight increase in lung infections (primarily bronchitis). Infections, including herpes infection, are also of concern. A six-hour observation period is required immediately after the first dose to monitor for cardiovascular changes.
Cladribine (Mavenclad)	Selectively targets and depletes the immune system's B cells and T cells, followed by a "reconstitution," as new B cells and T cells are produced	Upper respiratory tract infections, headache, and decreased lymphocyte counts	Two annual courses of up to 20 days over two years. No treatment is needed for years 3 and 4.	Potential adverse events include lymphopenia and herpes zoster infection. Increased risk of malignancy and fetal harm. Should not be used in patients with an increased risk of cancer or who are pregnant; men and women of reproductive potential must use effective contraception.
Siponimod (Mayzent)	Primary actions at the S1P1 and S1P5 receptors, blocking movement of lymph cells from lymph nodes	Headache, hypertension, changes in liver function tests	After starting at a low dose, the recommended maintenance dosage is 2 mg taken orally once daily starting on day 6	Serious adverse events include a decrease in white blood cells, heart rate, and rhythm abnormalities, as well as hypertension, swelling of the macula of the eye, varicella zoster reactivation, and convulsions. Patients should be monitored for changes in vision caused by macular edema, transient decreases in heart rate, decline in lung function, and changes in liver enzymes. Women who could become pregnant should use contraception to avoid potential risk of fetal harm.
Dimethyl fumarate (Tecfidera)	Immunomodulator with anti-inflammatory properties	Flushing and gastrointestinal events, reduced lymphocyte counts, elevated liver enzymes (rare)	240 mg tablet twice daily	Other possible adverse events include mild or moderate upper respiratory infection, pruritus, and erythema. In studies, the only serious adverse events to occur in two or more patients were gastroenteritis and gastritis. Reduced lymphocyte counts were seen during the first year of treatment. Liver enzymes were elevated in 6%, compared to 3% on placebo.
Monomethyl fumarate (Bafiertam)	Immunomodulator with anti-inflammatory properties	Flushing, gastrointestinal events, redness, itching, rash, diarrhea	Starting dose one 95-mg tablet twice daily for 7 days. Maintenance two 95-mg tablets (total 190 mg) twice daily.	Side effects similar to those listed for dimethyl fumarate, including allergic reactions, PML, serious infections, and liver injury.

Table 6 continues on next page.

APPROVED LONG-TERM TREATMENTS FOR MS *(Continued)*				
Ponesimod (Ponvory)	S1P-receptor modulator	Upper respiratory tract infections, elevated liver enzymes, hypertension	Using a 14-day starter pack, the dose starts low and gradually increases to 20 mg taken orally, once per day.	Adverse effects can include more serious infections and a slowed heartrate (bradycardia or bradyarrhythmia). Contraindicated in those with certain heart conditions, or women who are planning to be or are currently pregnant.
Diroximel fumarate (Vumerity)	Immunomodulator with anti-inflammatory properties	Flushing, stomach problems	231 mg twice daily	The exact mechanism of action by which this medication exerts therapeutic effect in MS is not completely understood. However, upon entering the body, the medication is rapidly converted into the molecule monomethyl fumarate, which is the same active component found in dimethyl fumarate.
Ozanimod (Zeposia)	S1P-receptor modulator	Upper respiratory infection, elevated liver enzymes, orthostatic hypotension	0.92 mg once daily	This medication is started at a lower dose and gradually increased until the full dose is reached, reducing the risk of a transient decrease in heartrate and atrioventricular conduction delays, which may occur if introduced too quickly. Warnings include an increased risk of infections, heart rhythm issues, liver injury, fetal risk, a decline in pulmonary (respiratory) function, and macular edema (swelling behind the eye).

[a]Additional information about interferons: Some individuals develop neutralizing antibodies to the interferons, but their impact on the effectiveness of these medications has not been established. Many continue to do well on these drugs despite the presence of neutralizing antibodies. Others may have sub-optimal results even without neutralizing antibodies present. The MS Council and the American Academy of Neurology have concluded that the higher-dosed interferons are likely to be more effective than lower-dosed interferons. Several factors, however, must be considered when selecting one of these drugs, and this decision must be made on an individual basis.

AV = atrioventricular, IM = intramuscular, IV = intravenous, JC = John Cunningham virus, PML = progressive multifocal leukoencephalopathy, SC = subcutaneous, TB = tuberculosis.

Source: Reprinted with permission from Multiple Sclerosis Association of America. Long-Term Treatments for Multiple Sclerosis. Available at https://mymsaa.org/ms-information/treatments/long-term. *Table 6*

the U.S. Food and Drug Administration (FDA) for treatment of relapsing forms of MS. This includes five preparations of interferon beta and a growing number of monoclonal antibodies. The exact mechanism of action of these drugs is still not clear, but it is believed to be the result of immunomodulation regulating the activation of impaired immune cells. Additionally, the blood-brain barrier becomes less permeable with immunomodulation, allowing fewer immune cells to enter the brain and reducing the autoimmune reaction between the immune cells and neuronal tissue. All medications differ in their efficacy, and additional data related to their long-term effects are necessary [111; 112; 113; 114; 115].

In 2018, the American Academy of Neurology published its practice guideline *Disease-Modifying Therapies for Adults with Multiple Sclerosis*, providing evidence-based recommendations for initiating treatment, switching therapies, and discontinuing disease-modifying agents. The full guideline is available at https://www.aan.com/Guidelines/home/GuidelineDetail/898.

Initiation of treatment with an FDA-approved disease-modifying agent is indicated upon diagnosis of relapsing MS, regardless of the patient's age. For the patient with a first clinical event (clinically isolated syndrome) who meets the revised McDonald diagnostic criteria for MS, disease-modifying therapy should be offered and the option of initiating treatment versus expectant management (awaiting a second clinical event) should be thoroughly discussed. Once initiated, disease-modifying treatment is continued indefinitely unless there is a suboptimal therapeutic response, intolerable side effects, or unsatisfactory adherence to the regimen.

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Neurology, clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, varicella zoster) according to prescribing information before initiating the specific immunosuppressive or immunomodulating medication planned for use and should treat patients testing positive for latent infections before MS treatment according to individual prescribing information.

(https://n.neurology.org/content/93/13/584. Last accessed December 12, 2022.)

Strength of Recommendation: A (Must be offered) and B (Should be offered)

ß-Interferons

The main disease-modifying drugs used in the treatment of MS are ß-interferons. These are naturally occurring immunomodulating agents that inhibit inflammatory reactions and limit cytokine secretion and lymphocyte migration. Two types of ß-interferon are available: ß-interferon 1a and ß-interferon 1b. ß-interferon 1a is produced by mammalian cells, while ß-interferon 1b is produced in modified Escherichia coli. The mechanisms of these two types are similar, but the dosage and method/frequency of administration may vary.

The use of ß-interferon reduces the risk and severity of clinical exacerbations of MS by about 30%, reduces the risk of developing new MRI lesions by 70% to 90%, and improves the integrity of the blood-brain barrier [99]. As such, it has been shown to slow disease progression and positively impact physical, emotional, and intellectual capacities.

The potential side effects of the interferons include flu-like symptoms and headache. Arthralgias may occur but can be reduced significantly by starting nonsteroidal anti-inflammatory drugs (NSAIDs) before the treatment. Patients treated with interferon should be monitored with periodic laboratory tests to check for liver dysfunction, anemia, leukopenia, and thyroid dysfunction. These studies should be performed at baseline, at three months after initiating the interferon therapy, and every six months thereafter [99]. Skin breakdown at the injection site is also possible.

Approximately 30% of patients with MS do not respond to treatment with a ß-interferon [116; 117]. For these individuals, other pharmacotherapies are available.

Glatiramer Acetate

Another disease-modifying drug approved for the treatment of RRMS is glatiramer acetate (also known as copolymer-1). Glatiramer is believed to block myelin-damaging T-cells, although its exact mechanism of action is not clearly understood. It is a potent immunomodulator that increases the number of immune regulatory cells. These cells reduce inflammation by suppressing the immune response.

Glatiramer acetate reduces the risk and severity of MS attacks and reduces MRI lesions over time. Studies comparing treatment with ß-interferon 1b or glatiramer have demonstrated similar efficacy. Glatiramer acetate has fewer adverse effects compared to the ß-interferons. Good injection technique and site rotation can help to reduce post-injection site reactions, but in some cases, repetitive injection of glatiramer acetate can cause lipoatrophy [118].

Mitoxantrone

Mitoxantrone, a cytostatic drug and a powerful anti-inflammatory, is used in the treatment of both RRMS and progressive forms of MS [119; 120]. It is considered one of the most effective drugs in resolving relapses; however, due to the risks for leukemia and cardiotoxicity, it should only be prescribed to patients with rapidly advancing disease who are refractory to other therapies [121]. Some patients, especially with a subtype of RRMS called rapidly worsening MS, do not respond to immunomodulators and are managed with immunosuppressants, particularly mitoxantrone [122; 123].

Mitoxantrone promotes quick resolution of relapses due to larger lesions in the brain and spinal cord. Various studies have demonstrated a positive effect in people with relapsing-remitting, secondary progressive, and progressive-relapsing subtypes of MS, but it is most beneficial in secondary progressive subtype [124]. Mitoxantrone is discontinued as soon as remission is achieved and replaced with another disease-modifying agent with a better safety profile.

Mitoxantrone causes reduced contraction of cardiac muscles, which can be confirmed by a reduction in ejection fraction measured through multiple gated acquisition scan. Studies have shown that patients receiving doses greater than 140 mg/m^2 have an increased risk of vacuolar cardiomyopathy. As such, it is contraindicated in patients with an estimated ejection fraction less than 50% or a 10% to 15% interval reduction of the ejection fraction [118].

Natalizumab

Natalizumab, a monoclonal antibody, may be used in the treatment of RRMS, and it is considered one of the most effective drugs in reducing the relapse rate (although long-term studies are lacking) [125; 126; 127]. Natalizumab prevents migration of autoreactive lymphocytes into the brain, which results in a profound decrease in CNS mononuclear cell trafficking that reduces MS exacerbations by 70% and disease progression by about 50% [128]. It also accelerates repair of myelin sheath lesions. Some studies have demonstrated that natalizumab can reduce new gadolinium-enhancing lesions by more than 90% [128; 129].

Natalizumab should be prescribed to patients with active RRMS that is refractory or resistant to ß-interferons and glatiramer or patients who cannot tolerate these medications [130]. Natalizumab may be indicated as a first-line treatment in patients with very active disease or in individuals with poor prognosis (e.g., MS targeting the brainstem, cerebellum, and/or spinal cord motor tracks). Studies have demonstrated that a combination of natalizumab with ß-interferon 1a reduces relapses and disability progression more than ß-interferon 1a alone [131]. A biosimilar to natalizumab (natalizumab-sztn) was approved in 2023 and may be considered for any patients with relapsing forms of MS [275].

Several potential side effects are associated with natalizumab. Approximately 1% of patients treated with natalizumab suffer from infusion-related hypersensitivity. This reaction usually occurs at the time of the second dose in natalizumab-naïve patients and can result in the development of a natalizumab-neutralizing antibody that can reduce the bioavailability of the agent and even render the drug useless. Natalizumab is also associated with an increased risk of developing progressive multifocal leukoencephalopathy. This disorder is caused by the John Cunningham virus, a type of human polyomavirus that infects oligodendrocytes and causes rapid and potentially life-threatening demyelination.

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody that binds to CD20, a cell surface antigen found on mature B-lymphocytes but not on precursors or plasma cells. Ocrelizumab selectively depletes CD20-expressing B cells. For treatment of MS, the dose is 600 mg by IV infusion every six months. Side effects include infusion reactions, opportunistic infection, and possibly an increased risk of malignancy. In a comparison study against placebo and interferon beta, ocrelizumab achieved a 46% relative reduction in the annualized relapse rate and a 95% reduction in the number of T1 lesions per MRI scan [132].

Ocrelizumab is the only FDA-approved disease-modifying therapy for patients with the PPMS subtype, based on a randomized, placebo-controlled clinical trial that showed lower rates of clinical and MRI disease progression in the treatment arm [133].

Ofatumumab (Kesimpta) received FDA approval in 2020 for adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive disease [115; 118]. Ofatumumab is the first self-administered B-cell therapy for MS. It is dosed at 20 mg once weekly for three doses (weeks 0, 1, and 2), with a maintenance dose of 20 mg per month beginning at week 4 [118]. Results of the ASCLEPIOS I and II studies found that ofatumumab demonstrated significant reduction in annualized relapse rate compared with oral teriflunomide. Ofatumumab additionally significantly reduced the mean number of T1 lesions and new or enlarging T2 lesions. A separate post hoc analysis demonstrated that ofatumumab also reduced new disease activity in patients with relapsing forms of MS [134].

Fingolimod

Treatment with fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, results in reduction of the relapse rate in patients with RRMS; however, it is associated with an increased risk of opportunistic infections, which can be fatal [135; 136; 137; 138]. Fingolimod was the first oral agent with a labeled indication for relapsing forms of MS [136]. It promotes the redistribution of lymphocytes from the circulation to the lymphoid organs and prevents the entry of lymphocytes back into circulation. Several studies have demonstrated that it significantly reduces both clinical and radiographic MS disease activity. Its side effects include first-dose bradycardia, arrhythmia, reactive airway events, macular edema, skin cancers, and increased susceptibility to infections [118]. Fingolimod is the only drug approved for the treatment of highly active (or rapidly worsening) RRMS.

The American Academy of Neurology recommends that clinicians prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS.

(https://n.neurology.org/content/90/17/777. Last accessed December 12, 2022.)

Strength of Recommendation: B (Should be offered)

Ozanimod

Ozanimod (Zeposia), another S1P receptor modulator, received FDA approval in 2020 for the treatment of relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive disease [139]. Ozanimod blocks the lymphocytes' ability to emerge from lymph nodes, thereby decreasing the amount of lymphocytes available to the CNS and intestine [118]. Unlike earlier drugs of its class, ozanimod is the only FDA approved S1P receptor modulator that does not require genetic testing or first-dose observation [140].

Ponesimod

Ponesimod (Ponvory) received FDA approval in 2021 for treatment of relapsing forms of MS [115]. This S1P receptor modulator is administered orally once per day, beginning at 2 mg and gradually increasing to 20 mg daily [118].

Dimethyl Fumarate

In 2013, dimethyl fumarate (BG-12, Tecfidera) was approved for the initial treatment of relapsing forms of MS [141]. It has not been evaluated in either SPMS or PPMS, so it is generally not recommended in patients without evidence of active inflammation. This agent acts through modulation of oxidative pathways to decrease autoimmunity. Clinical trials indicated a 69% reduction in contrast-enhancing lesions (phase II trial), a 53% reduction in annualized relapse rate, a 38% reduction in disability progression, and a 49% reduction in disability progression after two years [141]. Dimethyl fumarate is taken orally at a dose of 120–240 mg twice daily [141]. Possible side effects include elevated liver enzymes, nausea, diarrhea, flushing, and cramps.

Teriflunomide

Teriflunomide, an active metabolite of the antirheumatic drug leflunomide, is approved for the treatment of RRMS [142]. It has been shown to inhibit cell division in certain immune cells. Results from a phase III trial showed a significantly reduced annualized relapse rate compared to placebo. The risk of disability progression was reduced by 30% for the 14-mg dose and by 24% for the 7-mg dose. Common side effects include headache, nausea, diarrhea, and hair thinning. Use has been associated with rare reports of hepatotoxicity, hepatic failure, and death [118]. Treatment with teriflunomide should not be initiated in patients with pre-existing acute or chronic liver disease, and use is contraindicated in patients with severe hepatic impairment.

Cladribine

Cladribine is a purine analog approved for the treatment of relapsing forms of MS [143]. In a clinical trial in 1,326 patients with relapsing forms of MS who had at least one relapse in the previous 12 months, cladribine significantly decreased the number of relapses and the progression of disability compared with placebo. The usual oral dose is 3.5 mg/kg over a two-year treatment course [143].

However, the drug includes boxed warnings for malignancy and fetal harm, and other possible adverse effects include hematologic toxicity, bone marrow suppression, and decreased lymphocyte counts. Because of its safety profile, the use of cladribine is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS [143].

Immunoablation and Stem-Cell Transplantation

Limited studies over the past decade have shown that immunoablation and autologous hematopoietic stem-cell transplantation (AHSCT) can be a highly effective and relatively safe form of therapy in select patients with severe MS. The efficacy of AHSCT relies on achieving profound suppression of inflammatory MS activity, followed by reconstitution of the immune system that confers long-lasting disease remission without need for additional disease-modifying agents. Candidates for this approach are young patients with aggressive inflammatory RRMS refractory to usual treatment. Complete suppression of MS disease activity for four to five years has been documented in 70% to 80% of patients who have undergone AHCST, with a disease-associated mortality of 0.3% [144].

AHSCT is occurring more frequently, with a better safety profile. One review assessed studies from January 2016 to November 2020 that included 20 or more patients [145]. The authors assessed benefits of AHSCT, including no evidence of disease activity, functional and patient-reported outcomes, novel biomarkers (e.g., brain atrophy), and cost-effectiveness of the treatment. The overall efficacy of AHSCT was found to be better than standard treatments. Younger patients with highly active disease had a greater chance for improvement. Patients with comorbidities and more failed treatments who are in a more progressive disease phase may not respond as well to AHSCT. Results from currently enrolling randomized controlled trials, as well as ongoing registries, will provide more evidence for the safe and appropriate use of AHSCT [145].

SYMPTOM MANAGEMENT

The primary goal of symptomatic MS therapy is to improve quality of life by eliminating or reducing symptoms affecting patients' functional abilities. The approaches to symptomatic treatment focus on controlling the symptom rather than the underlying disease process.

The interventions chosen will depend on the patient's symptoms, medical history, and overall health. A comprehensive approach that incorporates pharmacotherapy, physiotherapy, and psychotherapy is superior to medical management alone.

Fatigue

Approximately 80% of patients with MS experience significant fatigue at some stage of their disease, often to the point of affecting their ability to complete activities of daily living [146]. This fatigue differs from normal exhaustion or tiredness, which usually increases during the day; it may be present at any time, even upon waking, and can limit a patient's professional and social life. MS-associated fatigue is aggravated by increases in body temperature (referred to as Uhthoff phenomenon). Depression can often be masked by symptoms of fatigue, so this is an important differential diagnosis, particularly in early stages of MS.

The Modified Fatigue Impact Scale (MFIS) is commonly used in patients with MS to assess the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. The full-length MFIS consists of 21 items and takes 5 to 10 minutes to administer; the abbreviated version contains five items and can be administered in 2 to 3 minutes. The MFIS is a structured, self-report questionnaire [147]. The MFIS items are divided into three subscales (i.e., physical, cognitive, psychosocial) as well as a total score. All items are scaled so that higher scores indicate a greater impact of fatigue on the patient's activities [148].

There are no licensed therapies for MS-related fatigue, but both amantadine and modafinil are widely prescribed off-label [102]. These drugs and pemoline and L-carnitine have been shown to be effective in improving fatigue severity [149]. However, stimulants should be used with caution—there is little evidence to support their efficacy, and they commonly cause anxiety and insomnia [102]. Physiotherapy, occupational therapy, and lowering body temperature may also help reduce fatigue and improve quality of life. Aminopyridines are effective in the amelioration of Uhthoff phenomenon [38].

Spasticity

More than 80% of patients with MS experience some spasticity, with 30% having symptoms so significant that they modify or eliminate daily activities as a result. Patients should be screened for pain, infection, fever, and bowel distention, as these factors are associated with more severe spasticity.

Spasticity may be classified as:

- Tonic: Muscle tone is constantly elevated.
- Phasic: Muscle tone is intermittently elevated and is usually accompanied by pain.

Classification is usually done using the Modified Ashworth Scale, which measures resistance to passive stretch (***Table 7***) [150; 151]. A higher score is indicative of more severe spastic hypertonia. Clinical assessment of spasticity may also include muscle grading, deep tendon reflexes, and measurements of range of motion. The Modified Ashworth Scale is also useful for evaluating and determining the response to therapy over time.

Treatment of spasticity involves an optimum amalgamation of drug therapy, maintenance and restorative therapies, and assistive devices. In addition to reducing hypertonia, the multidisciplinary approach may include interventions to relieve pain, improve overall motor function, and prevent or treat complications such as pressure ulcers and contractures.

MODIFIED ASHWORTH SCALE FOR SPASTIC HYPERTONIA	
Score	**Description**
0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

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Tonic spasms usually manifest as part of an acute relapse and are self-limiting. They typically respond to low or moderate doses of sodium-channel blockers [102]. However, phasic spasms require more intensive treatments.

Baclofen and tizanidine are commonly used to treat and reduce spasticity, and the benzodiazepines (e.g., diazepam) also have a beneficial effect. Other possible agents include gabapentin and dantrolene [102]. In general, baclofen is considered the drug of choice for spasticity in patients with MS [152]. An intrathecal baclofen pump may be indicated for patients with unilateral or bilateral phasic lower limb spasticity. Dantrolene should be used with caution because of the potential for hepatotoxicity [102].

Injectable forms of botulinum toxin, phenol, or alcohol are especially beneficial in patients with focal spasticity or difficulty tolerating oral medications; however, there is limited evidence for the use of botulinum toxin for the treatment of MS spasticity [153]. Studies are ongoing to determine the safety, efficacy, and potential for such use of botulinum toxin [154; 155; 156]. Surgical intervention (tenotomy) is indicated in severe cases.

Patients should be advised to avoid or minimize exposure to triggers and maintain proper positioning, posture, and ergonomics as much as possible. Stretching exercises are recommended for patients with MS in order to maintain normal muscle tone, especially in the popliteus, gastrocnemius, and lumbricals. Patients with significant lower limb weakness often rely on spasticity to splint their legs for weight bearing and walking [102].

Bladder Dysfunction

Bladder dysfunction is seen in approximately 80% of patients with newly diagnosed MS and in 96% of patients after 10 years [33]. Bladder dysfunction can lead to urgency, detrusor hyperactivity with restricted storage capacity, incontinence, and frequent micturition. A careful history and physical examination should be conducted on these patients, usually involving urinalysis and uroflowmetry (ultrasound) with a postvoid residual. This is especially important because a patient's subjective assessment of his or her bladder function may not correlate with postvoid residual volumes. High postvoid residual volumes (>100 cc) are associated with an increased risk for recurrent infections, calculi, and hydronephrosis. In such cases, the patient should be referred to a neurourologist for further evaluation. A thorough pelvic floor examination is required.

Patients who experience failure-to-store syndrome (also referred to as a "spastic" or "small" bladder) will usually report urgency, frequency, and nocturia. They usually have small bladder volumes and demonstrate a spastic detrusor muscle pattern on urodynamic testing. Failure-to-store may be treated with an antimuscarinic, an anticholinergic, or a mixed agent like oxybutynin [102]. The tricyclic antidepressant imipramine may also be beneficial in such cases.

Patients with the primary problem of failure to empty usually have an outlet disorder, such as an overactive sphincter or a hyporeflexic or areflexic bladder. These patients often suffer from frequency, hesitation, slow stream/dribbling, and prolonged voiding time. Failure-to-empty conditions are generally treated with an alpha-antagonist, such as doxazosin, prazosin, terazosin, or tamsulosin. The highly selective agent silodosin may also produce good results, although its affinity for the prostate can cause erectile dysfunction. Prophylactic antibiotic treatment with nitrofurantoin or sulfamethoxazole/trimethoprim may be indicated in patients with recurrent urinary tract infections.

The National Institute for Health and Clinical Excellence recommends offering bladder wall injection with botulinum toxin type A to adults with MS and symptoms of an overactive bladder in whom antimuscarinic drugs have proved to be ineffective or poorly tolerated.

(https://www.nice.org.uk/guidance/cg148. Last accessed December 12, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Patients who experience nocturia or nocturnal enuresis should be advised to empty their bladder before going to bed and decrease or avoid fluid intake two to three hours prior bedtime. Caffeinated products, alcoholic beverages, and spicy and acidic foods can cause bladder irritation and urinary frequency and should be avoided. If these behavioral strategies are ineffective, treatment with oral desmopressin is indicated [157].

Sacral neuromodulation may be beneficial for patients with incontinence related to overactive bladder, particularly if it is refractory to other treatments. Patients can be instructed to practice the Valsalva or Credé maneuver to help with hesitancy (in conjunction with pharmacotherapy). Chemical denervation of the detrusor muscle using intravesical capsaicin or botulinum toxin injections may be helpful in some cases [102].

Clean, intermittent or permanent catheterization is used for patients who do not respond to other treatments. A suprapubic catheter is preferred over intraurethral (Foley) because of the lower risk of infection and urethral damage. Surgical options (e.g., augmentation cystoplasty, ileovesicostomy, ileal conduit urinary diversion) should be considered for patients with severely impaired emptying or patients with repeated MS exacerbations triggered by recurrent infections. Other nonpharmacologic options that may be incorporated into the treatment plan include:

- Pelvic floor muscle strength training
- Bladder retraining
- Biofeedback
- Pessaries

Bowel Dysfunction

Bowel dysfunction affects approximately 70% of patients with MS [157]. The majority of patients experience either constipation or fecal incontinence.

Constipation

Clinically, constipation is defined as infrequent bowel movements (fewer than three per week). The etiology of constipation in patients with MS is multifactorial, and a careful assessment of diet and fluid intake is essential. Reduced fluid intake due to bladder disturbances or dysphagia may be a contributing factor. Certain drugs used to treat other symptoms of MS, such as spasticity, pain, or bladder dysfunction, can also result in constipation. Decreased physical activity and mobility can, in turn, reduce the frequency of bowel movements. A screening of secondary medical causes should also be completed.

The first step in addressing mild-to-moderate constipation is to start behavioral changes. This includes increasing physical activity, ensuring appropriate fluid intake (1.5–2 liters per day), and increasing dietary fiber (at least 25–35 g per day) [102]. Biofeedback therapy may also be effective in improving motility.

Osmotic agents, such as magnesium oxide and magnesium sulfate, are often used in the treatment of mild-to-moderate constipation. Compared to magnesium oxide, magnesium sulfate can lead to violent bowel movements with liquid-like consistency, and therefore, it should be avoided in the elderly and those with limited mobility [157]. Prokinetic agents such as lubiprostone increase intestinal fluid secretion and may be used in some cases. In MS, chronic constipation is often due to gastrointestinal hypomotility; therefore, bulk laxatives may exacerbate the problem [102]. A combination of prokinetic and bulk laxatives may be necessary. Lactulose, polyethylene glycol, and sorbitol are helpful for patients with more severe chronic constipation [157].

Enemas or suppository agents can work quickly and efficiently to soften and expel stool. Saline enemas are reported to be the safest approach [157]. Caregivers should be encouraged to monitor the type of enema being used and its frequency in order to prevent electrolyte imbalance. Various commercial enema products are available, and these may be used at home in cases of chronic constipation. Analgesic or antiemetic rectal suppositories help relieve rectal pain or nausea and vomiting in constipated patients with MS.

Stimulant agents such as senna, cascara, and castor oil increase intestinal motility and secretions and are effective in combating constipation. Senna is the preferred agent because of greater tolerability [157]. Docusate sodium, a stool softener, in combination with senna is effective in treating mild-to-moderate constipation in patients with MS. Surgery is indicated in rare cases of refractory constipation and fecal impaction [157].

Fecal Incontinence

Fecal incontinence is defined as the loss of regular control of the bowels, and in patients with MS, it is usually caused by reduced anal squeeze pressures, correlating with duration of disease and disability status. It is experienced by approximately 24% of mildly disabled patients and 66% of those with severe disease [157]. Evaluation of the patient's diet and fluid history is essential to determining possible triggers. The overall goal is to treat the underlying cause of fecal incontinence.

The opioid-receptor agonist loperamide can be prescribed to patients with chronic diarrhea with or without fecal incontinence, but it is not recommended in patients with symptoms of diarrhea and concomitant constipation [157]. Biofeedback training is helpful in strengthening pelvic floor muscles and improving anal squeeze pressures. Surgical repair (e.g., pelvic floor muscle repair, forming a new external anal sphincter, use of hydraulic rings) is indicated for medically refractory cases.

Cognitive Impairment

Approximately 40% to 70% of patients with MS experience intellectual impairments that progressively increase with disease duration and result in significant disability, decreased quality of life, and inability to maintain employment [157]. The most common cognitive deficits include poor attention and executive functioning, slowed information processing, and reduced memory retrieval. Patients with MS are capable of consolidating new memories; dementia is rare.

Baseline neuropsychological investigations should be performed at the time of an MS diagnosis so future monitoring of cognitive changes is accurate and can guide medical interventions. Cognitive-behavioral therapy, psychotherapy, and counseling are effective interventions; pharmacotherapy may also be indicated. Some studies have found amphetamines to be effective in improving cognitive performance; however, this may be due to reduction in fatigue

and mood changes rather than a beneficial effect on cognition [157]. There is emerging evidence that suggests the centrally acting acetylcholinesterases, such as donepezil, improve memory in subjects with memory impairment [102].

Depression

Due to the potentially overwhelming nature of the medical consequences of MS, psychiatric issues are often overlooked and undertreated. However, an estimated 50% of patients with MS have clinical depression, and the suicide rate is higher among persons with MS than the general population [157; 158]. Common signs and symptoms include insomnia, early morning awakening, loss of appetite, anhedonia, loss of concentration, fatigue, short-term memory deficits, and cognitive impairment.

The Beck Depression Inventory (BDI-II) is often used in the diagnosis and evaluation of depression in patients with MS [158]. The BDI-II is a questionnaire that consists of 21 multiple choice questions that allow self-reporting of a multitude of depressive symptoms. It also is used to measure the severity of depression; higher total scores indicate more severe depressive symptoms.

All patients should be reassured that depression is treatable. A sedating tricyclic antidepressant such as amitriptyline or one of the newer selective serotonin reuptake inhibitors (e.g., citalopram) may be effective in the treatment of depression in patients with emotional lability and/or depression [102]. Venlafaxine or bupropion may be prescribed for mood stabilization if lack of energy or loss of concentration is the main presenting symptom [158]. Patients with anxiety may be treated with an anxiolytic, such as lorazepam, alprazolam, or clonazepam [158]. Buspirone is also prescribed in patients with anxiety and is particularly effective for panic attacks. Hypomania and psychosis are rare manifestations of MS and should be managed according to standard psychiatric principles [102].

Cognitive-behavioral therapy is helpful in patients with MS to address depressive symptoms and maintain commitment to the established care plan. Patients who express suicidal ideation or planning should be referred to emergency psychiatric care immediately.

Uhthoff Phenomenon

Approximately 60% to 80% of patients with MS experience Uhthoff phenomenon, which is characterized by reversible and often stereotypic worsening of neurologic symptoms triggered by increased body temperature [38]. Exposure to high temperature, intense exercise, various infections, and stress can all increase core body temperature. Any factors that cause sweating can result in worsening of neurologic symptoms.

Eliminating undue heat exposure, limiting exercise, and avoiding psychosocial stressors while promoting subsequent cooling can reverse the neurologic deficits caused by Uhthoff phenomenon. Simple strategies to cool the body, such as cold showers, ice packs, and regional cooling devices, provide mild-to-moderate benefits [38]. Cooling suits may be helpful in patients with profound heat sensitivity [102]. Although efficacious, use of 4-aminopyridine, a centrally acting potassium-channel blocker, is limited by side effects [102].

Oculomotor Symptoms

Oculomotor symptoms are experienced by approximately 30% to 50% of all patients with MS [159]. Internuclear ophthalmoplegia and nystagmus are the most common oculomotor conditions, although other visual disturbances can develop.

Oculomotor symptoms that emerge in the relapse period should be treated with high-dose IV methylprednisolone [159]. An eye patch is beneficial during the acute phase to avoid diplopia. Patients with pendular nystagmus are usually treated with gabapentin or memantine; baclofen is the drug of choice for treatment of upbeat/downbeat nystagmus [159]. 3, 4-DAP 20 mg is also effective in treating downbeat nystagmus. In internuclear ophthalmoplegia, drug treatment is rarely needed.

Sexual Dysfunction

Sexual dysfunction is a frequent complication of MS, usually in combination with bladder dysfunction. It tends to develop later in the disease course and is more common in men (90%) than women (70%) [45]. Sexual health and activity should be a part of the regular assessment of patients with MS.

Sexual dysfunction can adversely affect patients' self-esteem, quality of life, and spousal relationships. It can be categorized as primary, secondary, or tertiary depending on cause, and each type requires a different therapeutic approach. Primary sexual dysfunction is the direct consequence of the demyelinating lesions formed in the CNS influencing sexual response and sexual feelings. Secondary sexual dysfunction occurs as a result of other MS symptoms (e.g., spasticity) and/or secondary to the side effects of medications used to treat MS. Tertiary sexual dysfunction is the result of psychological, emotional, and/or cultural influences that may adversely affect sexual response and activity.

Type of sexual dysfunction varies. Reduced libido is the most frequent manifestation of primary sexual dysfunction for women with MS. Among ambulatory men with MS, approximately 60% experience erectile dysfunction, 50% report orgasmic dysfunction, and 40% experience reduced libido [160].

Prostaglandin-5 inhibitors (e.g., sildenafil, vardenafil, tadalafil) are used in the treatment of primary sexual dysfunction in men. Penile prostheses, meatal urethral alprostadil suppository, testosterone supplements, vacuum erection devices, and intracavernosal injections of alprostadil may also be helpful [45; 157].

One single-center, open-label study was conducted from 2011 to 2012 for 24 weeks. The study included 45 patients 18 to 65 years of age with relapsing forms of MS who were natalizumab-naïve and who had a suboptimal response to or tolerability issues with other disease-modifying therapies [161]. Enrolled patients received natalizumab 300 mg IV every 28 days and completed the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19), a self-report tool designed to sel-assess how various MS symptoms have interfered with sexual activity or sexual satisfaction over the previous six months. Patients with known sexual dysfunction reported a decrease in these symptoms while on natalizumab therapy, as demonstrated by a reduction on the primary subscale of the MSISQ-19. However, the small sample size was a limiting factor in the interpretation of the results [161].The EROS Clitoral Therapy Device is the only FDA-approved therapy for women experiencing sexual dysfunction, and it is only indicated in cases of impaired sexual response [162]. This device stimulates clitoral engorgement, resulting in significantly improved vaginal/clitoral sensations, lubrication, ability to achieve orgasm, and overall sexual satisfaction [162]. Use of high-frequency wall-power vibrator devices may be recommended for women who have diminished arousal, sensation, and difficulty achieving orgasm. Over-the-counter water-soluble lubrication agents are helpful for women with vaginal dryness and related pain with intercourse.

Tertiary sexual dysfunction is managed with counseling or therapy, either as monotherapy or as adjunctive treatment in combination with pharmacotherapy or devices. The patient should be educated about sexual stimulation techniques and interpersonal communication. Body mapping, a self-exploration technique in which the patient gently touches all parts of the body to identify erogenous stimulation, may be incorporated into the treatment plan.

Dysphagia

Dysphagia for liquids and solids is a relatively common complication of MS. Studies indicate that it is more likely to occur in patients with severe brainstem impairment and more severe disease [163]. The potential risk of aspiration, pneumonia, and malnutrition and the high efficacy of swallowing rehabilitation suggest that patients with MS should have a careful evaluation of swallowing function, especially high-risk patients [163].

Screening for dysphagia, both solid and liquid, is required at each office visit. Individuals with liquid dysphagia usually complain of coughing or choking while eating, whereas those with solid food dysphagia have a sensation of food "sticking" in the throat or chest. Other clinical manifestations include dysphonia, coughing, and gastroesophageal reflux disease.

Patients with dysphagia should undergo a thorough assessment that includes a comprehensive history and examination related to particular symptoms of dysphagia, ear/nose/throat and neurologic examination, and a functional swallowing test. A videofluorographic swallowing study or transnasal fiberoptic endoscopic examination of swallowing is also helpful. A careful physical examination should include inspection and palpation of the neck and throat for structural abnormalities or masses. A videofluoroscopic swallowing study can be performed in the form of a modified barium swallow.

If present, treatment focuses on proper fluid and food intake, prevention of aspiration and secondary pneumonia, and improvements in quality of life using pharmacologic, rehabilitative, and/or surgical interventions. Anticholinergic drugs (e.g., scopolamine) may be prescribed if hypersalivation is an issue; transdermal patches are the preferred administration method. Injections of botulinum toxin can increase esophageal sphincter tone. Proton pump inhibitors are highly effective in controlling symptoms of gastroesophageal reflux.

However, the basis of dysphagia treatment in patients with MS is functional swallowing therapy. This involves restitution (restoration of impaired function using exercises), compensation (postural changes and dietary modifications), and adaptation (modification of the environment to improve nutrition). This therapy is conducted by a speech-language pathologist.

For patients with severe neurogenic dysphagia or hypersecretion, a nasogastric or percutaneous endoscopic gastrostomy tube may be temporarily or permanently required to maintain adequate nutritional and fluid intake. These tubes have been found to lower choking risk and improve quality of life and survival rate in certain patients. A nasogastric tube is indicated when enteral feeding is required for a short duration (i.e., less than 30 days). However, direct enteral access is preferred when enteral feeding is required for a longer period, as nasogastric tubes cause considerable discomfort and epistaxis.

Dysarthria

Dysarthria is a motor speech disorder caused by impairment of the nerves that control the muscles involved with speaking. Approximately 40% of patients with MS experience some level of dysarthria, which is usually heightened during times of stress or fatigue [164].

No drug treatment is effective for the treatment of dysarthria, but speech therapy can be very beneficial in improving voice volume and language. Speech-language pathologists can also recommend the use of voice amplifiers to aid communication.

Pain

Acute, intermittent bouts of pain may occur in association with optic neuritis, trigeminal neuralgia, dysesthesias, or Lhermitte sign, and treatment is dependent on the causative condition [165]. Corticosteroids are the drug of choice in the treatment of optic neuritis. Acute pain due to trigeminal neuralgia can be successfully managed with anticonvulsants such as carbamazepine or phenytoin [166; 167]. Carbamazepine, clonazepam, or amitriptyline is effective in reducing pain resulting from Lhermitte sign or dysesthesias [168; 169]. Both intermittent neuralgias and central pain respond to sodium-channel blockers. Pain associated with clonic muscle spasms may respond to antispasticity agents [102].

Subacute pain is often secondary to the disease; treatment will depend on the condition. Chronic pain is very common and is usually caused by dysesthesias. It is difficult to manage, but carbamazepine, phenytoin, gabapentin, lamotrigine, topiramate, and tricyclic antidepressants are options [102].

Tremor

Tremor is one of the most disabling and difficult to treat neurologic impairments in MS [102]. Available treatments, depending on severity of the tremor, include mechanical damping (e.g., diving weights), high doses of isoniazid (600–1,200 mg/day), clonazepam, beta blockers, or neurosurgery (thalamotomy or thalamic deep brain stimulation). It is important to monitor liver function tests when using high-dose isoniazid, which should be taken in combination with pyridoxine to prevent the development of peripheral neuropathy [102]. Clonazepam is only moderately effective and is limited by sedation. Thalamotomy and deep brain stimulation can provide dramatic short-term results, but often fail because of long-term disease progression.

REHABILITATION

Disease-modifying treatments slow the progression of MS but do not stop it; symptoms will continue to increase. As ultimate cure is as yet unattainable, management of these functional deficits is of utmost importance. Neurorehabilitation together with occupational therapy is the best approach.

Few studies have assessed the effectiveness of neurorehabilitation on outcomes and disease progression in patients with MS, partly because the highly variable and unpredictable nature of the disease course makes such research difficult [170; 171]. Its general effectiveness is well established in conditions such as stroke and head trauma, and it is believed to be of use in cases of MS [172]. Furthermore, even if rehabilitation has no direct influence on disease progression, it has been shown to improve ability to carry out activities of daily living, participation in social activities, and quality of life [173].

A multidisciplinary approach is best when establishing a rehabilitation program for patients with MS [174; 175]. This rehabilitation consists of physiotherapy, cognitive rehabilitation, speech and language therapy, and occupational therapy to control symptoms and disabilities [176; 177]. Cognitive rehabilitation is under the supervision of neuropsychologists, while psychologists and psychiatrists play a key role in the treatment of depression and emotional distress [178; 179]. Several studies have demonstrated that exercise, cognitive therapy and energy conservation instruction have a beneficial effect on self-reported quality of life [180; 181; 182]. Physical therapy, specifically gait training, can result in fatigue reduction [183]. Robotic-assisted, body-weight-supported treadmill training has demonstrated positive impact in rehabilitation of patients with severe walking disabilities, whereas over-ground gait training shows more beneficial effects in patients with less severe impairments [184].

Motor deficits are most often treated with physical and occupational therapy. However, in 2021, the FDA approved a neurostimulation device to address ataxia and other gait disturbances in patients with mild-to-moderate MS [185]. It is a portable, nonimplantable device that delivers mild neuromuscular electrical stimulation to the dorsal surface of the patient's tongue. The device is intended to be used by prescription only as an adjunct to a supervised therapeutic exercise program in patients 22 years of age and older [185].

INDIVIDUAL TREATMENT PLANS

Clinically Isolated Syndrome

As discussed, clinically isolated syndrome is considered one of the earliest clinical presentations of RRMS. Studies have demonstrated that treatment with an immunomodulatory drug (specifically interferon) early in this initial period can decrease the likelihood of developing into symptomatic MS [186; 187; 188]. It is believed that immediate treatment has modest efficacy compared to delayed initiation of treatment [186; 187; 188].

RRMS

Managing attacks or exacerbations is the cornerstone of the treatment of patients with RRMS. An attack of RRMS is defined as the onset of new or exacerbation of existing neurologic symptoms resulting in deterioration of the patient's condition by at least one step on a validated disability status scale that persists for a minimum period of 24 hours and is not related to infection [58]. It is important to remember that even with appropriate and adequate use of drugs, the majority of patients with RRMS will still experience some attacks and many will develop some degree of disability. The aim of treating an acute exacerbation is to reduce the duration and intensity of neurologic impairment. A complete recovery to the baseline level and prevention of long-term disability remains elusive.

It is essential to rule out infection before initiating therapy, as symptoms may be similar, and the most common treatment used for acute attacks (glucocorticoids) can be life-threatening in patients with preexisting infection [99]. Because most of the immune response in MS occurs early in the disease course, aggressive early treatment with disease-modifying drugs is essential [189]. The choice of agent is usually guided by available evidence, but patient response and tolerability are the most important factors.

The later stages of RRMS tend to be less inflammatory and more degenerative, and treatment during these stages focuses on symptom reduction and quality of life. Immunomodulation with disease-modifying drugs continues, although, as noted, the long-term efficacy is not well established.

Progressive Types

Both SPMS and PRMS are comparatively more difficult to treat than the relapsing forms of MS. Several types of immunosuppressive therapies have shown at least some beneficial effects in the treatment of progressive MS disease. However, these immunosuppressive therapies only briefly halt a rapidly progressive course and are dangerous if prescribed for longer periods [99]. The interventions that have shown some efficacy in progressive types of MS include cyclosporine, total lymphoid radiation, mitoxantrone, methotrexate, interferon, cyclophosphamide, azathioprine, corticosteroids, and IV immunoglobulins [190].

Mitoxantrone is beneficial in patients with SPMS and PRMS and effectively reduces the disease progression and frequency of relapses in patients in short-term follow-up [191]. However, long-term use of this medication causes cardiotoxicity. Rituximab, a monoclonal antibody, is frequently used off-label to treat MS. One study compared the effectiveness and safety of mitoxantrone and rituximab in patients with active relapsing MS [192]. A total of 292 patients were included in the study; 119 received rituximab and 173 received mitoxantrone. While there was no significant effect favoring treatment with either agent, regarding worsening disability or relapse occurrence, treatment with rituximab was associated with a significantly lower probability of severe adverse events [192].

Treatment with interferon leads to fewer relapses and less disease activity. Interferons show a great promise in treating SPMS, but more validation is required for their widespread use [193].

Intravenous cyclophosphamide and glucocorticoid monthly pulses may have a beneficial effect in younger patients with progressive MS. Methotrexate may alter the disease course in patients with SPMS and PPMS, but this is not proven [194].

Until recently, no therapy had been approved specifically for the treatment of PPMS, though several trials have been conducted to assess the potential efficacy of interferons and mitoxantrone, glatiramer acetate, methylprednisolone pulses, and an open-label study of riluzole [195; 196; 197]. As noted, ocrelizumab is now approved for patients with the PPMS subtype.

Benign MS

As discussed, benign MS is mild form of MS in which the patients do not develop any disability. Benign MS is typically treated with one of the disease-modifying drugs immediately after a confirmed MS or clinically isolated syndrome diagnosis [99; 198].

ALTERNATIVE TREATMENTS

Approximately 60% of patients with MS use complementary and alternative medicine. However, with the exception of vitamin D, there is little or no available evidence to support the use of these therapies to improve MS symptoms or disease course [199; 200].

Vitamin D's ability to modulate the immune system may prevent or slow the progression of MS [201]. Results of a study presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting indicated that every 50 nmol/L increase in average serum vitamin D levels translated into a 57% decrease in the rate of new active MS-defining lesions [202]. In fact, the presence of rare variants in CYP27B1, which encodes the enzyme that converts vitamin D to its active form, is strongly associated with MS risk; this supports a causal role of vitamin D deficiency in the development of MS [201]. However, one small study found that high-dose vitamin D supplementation did not result in improvements in symptoms compared to patients with adequate vitamin D [203]. Additionally, results of two clinical trials presented at the 2022 ECTRIMS conference suggest that high doses of vitamin D do not reduce MS disease activity [204; 205]. More research is necessary to determine the role of vitamin D supplementation (e.g., dose, optimum time to initiate therapy) in the treatment of MS.

Some ecologic studies have found a correlation between high intake of polyunsaturated fats and low MS prevalence, and some have suggested that increasing intake of omega fatty acids might improve MS symptoms [206]. However, no specific diet has been shown to have any effect on MS lesions or symptoms [207]. Furthermore, a 2012 trial found no beneficial effects on disease activity with omega-3 fatty acids when compared with placebo as monotherapy or in combination with interferon beta-1a [206].

The use of cannabis to alleviate symptoms of MS remains controversial. Some patients report that smoking cannabis reduces spasticity and other MS-related symptoms [208; 209]. The impairment of neurotransmission seen with MS can be controlled by endocannabinoid receptors and endogenous cannabinoid ligands, which can limit spasticity and may influence the processes that drive the accumulation of progressive disability [210]. However, the cognitive deficit experienced by smoking cannabis that is currently available (e.g., "street" cannabis) may outweigh the benefits [211]. Researchers continue to explore the role of cannabinoids in the treatment of MS symptoms, particularly muscle stiffness and spasms, neuropathic pain, and sleep and bladder disturbance [212].

Derivatives of the herb *Ruta graveolens*, also known as common rue, have been traditionally used to reduce MS symptoms [213]. However, strong evidence of efficacy is lacking.

Bee venom therapy is also believed to have beneficial effects because of its anti-inflammatory properties and possibly its ability to block IL-6 as a pro-inflammatory cytokine, but the research has shown only marginal evidence of benefit [214]. Bee venom therapy can also be potentially lethal because of high risk of anaphylactic shock [199].

Hyperbaric oxygen therapy has been used in patients with MS based on the theory that poor oxygenation of affected nerves may exacerbate symptoms. Studies have demonstrated that hyperbaric oxygenation has no proven benefits on patients with MS [215].

Antioxidants are believed to reduce blood-brain barrier permeability, and levels are reduced in patients with MS [216; 217]. It has been reported that raising uric acid levels protects the integrity of the blood-brain barrier by removing peroxynitrite, an oxidant that is linked to axonal degeneration. Further research is ongoing to explore the role of antioxidants in the treatment of MS [218; 219].

Studies have demonstrated that intestinal parasites such as hookworm may have a protective role against MS by inducing changes in immunoregulation [220]. One study found that the introduction of helminths reduced the number of lesions detected by MRI [221]. Preliminary trials indicate that helminthic therapy is safe, but serious adverse effects are possible.

Yoga and general exercise have been found to reduce fatigue and improve overall quality of life in patients with MS [222]. Small studies of acupuncture in patients with MS have found improvements in pain, muscle spasm, and quality of life [223]. Further clinical trials are necessary to establish efficacy.

ONGOING RESEARCH: POSSIBILITIES FOR FUTURE TREATMENT

Advances in MS treatment have progressed at a rapid pace since 2000. Ongoing research for new treatments is aimed at drugs that:

- Have improved efficacy and are well tolerated
- Target both inflammation and neurodegeneration
- Promote remyelination and repair
- Are conveniently administered, preferably orally
- Effectively treat PPMS
- Effectively treat the chronic symptoms of MS, particularly fatigue
- Improve patient adherence

Alemtuzumab

Alemtuzumab is used for the treatment of RRMS, and researchers continue to explore its efficacy. It is a humanized monoclonal antibody that depletes lymphocytes, causing long-term immunomodulation, and is approved for the treatment of chronic lymphocytic leukemia and T-cell lymphoma. In phase III studies, alemtuzumab showed greater reductions in MS relapse rate and disease activity compared to ß-interferon [224]. It has also shown a beneficial effect on disability progression. Significant side effects include idiopathic thrombocytopenic purpura and Graves' disease.

Daclizumab

Daclizumab is an anti-IL2 monoclonal antibody, originally approved for the prevention of rejection after organ transplantation. In 2016, daclizumab received FDA approval for the treatment of adults with relapsing forms of MS. In 2018, daclizumab was withdrawn from the market, following reports from Germany, the United States, and Spain about the development of inflammatory encephalitis and meningoencephalitis in patients receiving the agent [225; 226].

Tcelna

Tcelna is a therapeutic vaccine against autologous T-cells utilizing myelin-reactive lymphocytes from peripheral blood. A phase IIb trial of Tcelna demonstrated a 55% reduction in annualized relapse rate as compared to placebo [227]. Financial issues experienced by the manufacturer have made research progress slow [228].

The pathogenesis of progressive MS is a complex, multi-level process that causes therapeutic difficulties. Along with variables such as age and duration of the disease, pathogenetic mechanisms change from inflammatory to neurodegenerative processes. This, therefore, limits in time the efficacy of available approved anti-inflammatory drugs (e.g., ocrelizumab, siponimod). Innovative solutions continue to be sought and research studies have been conducted to evaluate the effectiveness of drugs with neuroprotective or remyelinating effects in progressive MS. Among these are biotin, ibudilast, simvastatin, alpha-lipoic acid, clemastine, amiloride, fluoxetine, riluzole, masitinib, opicinumab, and lamotrigine [229; 230; 231; 232].

PROGNOSIS

A number of factors have been identified as potential prognostic indicators in MS, capable of modifying the disease course or predicting exacerbations. These include demographics, type of MS, lesion load, and psychosocial stress.

DEMOGRAPHIC FACTORS

As discussed, White patients, especially of Northern European ancestry, are more susceptible to developing MS, while people living near the equator carry the lowest risk [6]. Although the prevalence of MS is higher among persons of European ancestry than those of African descent (2:1), patients in the latter population group are older at disease onset, more likely to have multiple lesions affecting vision and mobility at diagnosis, and tend to follow a more progressive course [4; 6]. Additionally, susceptibility rates vary among these groups, with recent findings suggesting that African American women have a higher than previously reported risk of developing MS [233].

Older studies suggest that women tend to have a more benign course then men [234]. However, studies have challenged this notion and have concluded that an individual's sex does not determine the disease prognosis independently [235]. A 2019 prevalence study found that MS is three times more common in women than in men, suggesting that hormones may play a significant role in determining susceptibility to MS [236]. Younger age at disease onset has a better prognosis compared with late onset [234]. One study observed that disability in MS is correlated more with the patient's age of onset than disease subtype (i.e., relapsing or progressive) [237; 238].

SUBTYPE OF MS

The relapsing form of MS has a much more favorable prognosis compared with progressive disease [234; 235]. One observational study showed that patients with a progressive form of MS acquired irreversible disability earlier compared to patients with relapsing-remitting onset [239]. After irreversible disability occurred, however, the time course of progressive disability was similar in the two groups. Data have suggested that the development of a progressive course in patients with MS may be the most important prognostic factor [240].

EARLY SYMPTOMS

In the past, the presence of specific MS symptoms at disease onset was thought to predict the disease course; for example, sensory symptoms and optic neuritis indicate a favorable prognosis, while pyramidal, brainstem, and cerebellar symptoms portend an unfavorable prognosis [234]. However, subsequent studies have observed that this theory is false and the onset symptoms are not independent prognostic factors [235; 241]. An observational study found that clinical variables assessed early in RRMS predicted time to irreversible disability (i.e., Expanded Disability Status Scale score of 4 or limited walking without

aid); however, this was not true for subsequent disability progression [242]. Data from a large clinical trial cohort showed that younger patients (38 years of age or younger) with high baseline relapses and MRI lesion burden have the highest risk of subsequent disease activity [243].

LESION LOAD

A serial MRI study observed a strong relationship between the development of lesions early in the disease course and long-term disability [244]. The correlation seems to plateau at higher levels of disability, indicating that MRI lesion burden is a poor determinant of disease progression in patients with advanced disease. A pooled data study showed that MRI lesion load is weakly correlated with age at disease onset, duration of the disease, and disease progression [245].

PSYCHOSOCIAL STRESS

Some studies have suggested that MS relapses may be more frequent after stressful life events, although others have found no relationship between MS exacerbations and life-event stress [246; 247]. It appears that the number, not the severity, of stressful life events is most important. The results of a 2022 study suggest that the coupling of blunted central stress processing and blunted immune system sensitivity to stress hormones are related to key severity measures of MS [248]. The exact mechanism of a relationship between stress and MS exacerbations is still unknown. Stress management therapy may have a beneficial effect in reducing the development of new MRI brain lesions while patients are in treatment [249].

PREGNANCY AND MS

MS is more prevalent in women of child-bearing age, and pregnancy can pose a challenge in the management of MS [250]. As stated, the incidence of MS has increased, with a corresponding higher female-to-male ratio [236; 251; 252]. These factors emphasize the need for more research in the subject of pregnancy in women with MS. Previously, women with MS were discouraged from having children, but this has not been supported by evidence. Today, pregnancy is believed to have no adverse effect on the course and prognosis of MS [253; 254].

The significant hormonal changes that occur during pregnancy result in a physiologic shift from T-helper 1 to T-helper 2 immune response, leading to an increase in anti-inflammatory cytokines [255]. This shift is partly responsible for the reduction in MS relapses in pregnant women [256]. The increase in estrogen levels during this period also suppresses T-cell proliferation and cytokine production [257; 258]. Alpha-fetoprotein, which is produced by the liver and yolk sac of a developing fetus, decreases neuroinflammation and disease severity [259]. Overall, pregnancy appears to have a beneficial effect on MS disease activity.

There is no evidence that MS affects fertility and conception [253; 254]. However, patients with MS have a high rate of sexual dysfunction that may be associated with a number of neurologic symptoms and disabilities [260]. These factors can adversely affect the overall quality of sexual life and impede conception [261].

In cases of very aggressive MS, there is a risk of inadequate maternal care. Therefore, adequate disease control should be achieved prior to pregnancy. Women with MS who are pregnant or considering pregnancy are often concerned about the genetic transmission of MS to their child. The absolute risk of disease transmission ranges from 2% to 4%, but there are no genetic or prenatal screening tests that can detect MS [262].

TREATMENT DURING PREGNANCY

If safe, women intending to conceive should stop their MS treatment for at least three months prior to conception. A study conducted in Sweden concluded that pregnancies that were not exposed to the ß-interferon in utero for at least a two-week period prior to conception resulted in healthier infants than pregnancies with such exposure [263]. A small Canadian study found that pregnancies exposed to ß-interferon resulted in a higher number of miscarriages, low birth weight, and prematurity [264]. However, a larger study did not find a significantly higher rate of complications in pregnancies accidentally exposed to immunomodulators [265]. In general, even the higher incidence of complications observed in some studies was only slightly greater than that of the general population. If continued treatment is necessary, modifications to the prescribed regimen (with preference for lower risk options) may be necessary. Many drugs used to treat MS and its related symptoms are contraindicated during pregnancy.

For disease modification, the safest options are glatiramer acetate and immunoglobulin, which appear to do no harm to the fetus and are pregnancy category B. ß-interferons, mitoxantrone, and corticosteroids are pregnancy category C, as animal studies have demonstrated adverse effects to the fetus. The risk-benefit ratio should be considered prior to using these medications in pregnant women. Category D drugs, which have evidence of fetal risk and should only be considered in life-threatening situations or when safer drugs are ineffective, include azathioprine, cyclophosphamide, and mitoxantrone. Category X drugs such as methotrexate pose an extremely high risk to the fetus and should not be used for women who are or may become pregnant.

Apart from immunomodulatory or immunosuppressive agents, the medications used to control the symptoms of MS should also be reconsidered. Oxybutynin and pemoline, prescribed for incontinence and fatigue respectively, are pregnancy category B, and their continued use should be safe. Many of the drugs used in the treatment of MS are category C, including:

- Gabapentin and carbamazepine for paroxysmal disorders
- Amantadine and potassium channel blockers for fatigue
- Selective serotonin reuptake inhibitors for depression
- Baclofen and dantrolene for spasticity

Benzodiazepines and phenytoin (used for pain and insomnia) are category D and should be avoided. Fingolimod or natalizumab may pose a risk of rebound disease activity after stopping the medication for pregnancy [266].

Unplanned pregnancy, without proper adjustment of treatment, carries a high inherent risk to the fetus. As such, women should be counseled to discuss childbearing plans with their physician prior to conception and to maintain adequate birth control if pregnancy is not desired.

MS AND DELIVERY

There is no evidence that MS leads to an increased number of spontaneous abortions (miscarriage), stillbirths, or congenital malformations. Several studies of large numbers of women have repeatedly demonstrated that pregnancy, labor, delivery, and the incidence of fetal complications are no different in women who have MS than in women who do not have MS [254].

The mode of delivery is guided by obstetric indications rather than the presence of MS. However, a study conducted in the United States found that the rate of non-vaginal delivery was higher among women with MS than the general population [267]. If cesarean delivery is necessary, proper attention should be provided during preoperative evaluation to reduce postoperative neurologic complications. During labor, epidural injection is considered to be a safer option than spinal block for anesthesia in patients with MS, as spinal block is suspected to be associated with neurotoxic effects [268; 269]. Autonomic dysreflexia, a very rare, potentially life-threatening condition related to spinal cord lesions, can arise in women with MS during delivery [270]. Patients should be duly informed about the type of anesthesia and its possible side effects and complications.

RELAPSE RISK AFTER DELIVERY

The rate of MS relapse increases after delivery. One study observed that a rapid increase in the number of interferon-γ-producing T-cells may be responsible for the increased risk of relapse [271]. Women with higher Expanded Disability Status Scale scores and higher relapse rates before pregnancy tend to have a greater risk of relapse during the postpartum period [272].

BREASTFEEDING

As with all women, the rate of breastfeeding among women with MS varies widely and depends upon various factors. Several studies have demonstrated a possible beneficial effect of breastfeeding on postpartum relapse rates, but the higher risk of relapses during the postpartum period may make breastfeeding difficult or impossible, especially if adequate treatment with immunomodulatory or immunosuppressive agents is indicated [273]. Studies have found an increased risk of relapse in the first three months postpartum, with disease stability prior to pregnancy considered a primary factor in reducing this risk. However, a 2020 study found no increased relapse rate in the postpartum period and suggests that exclusive breastfeeding may contribute to this reduced risk [274]. There is insufficient information regarding the levels of many MS drugs in human milk.

CONCLUSION

MS is a relatively uncommon disease, but the effects can be devastating for patients. Unfortunately, a cure is elusive, and the cause is still unknown. Different MS subtypes are being described, and healthcare providers should stay abreast of the different clinical presentations, effective management, and progression of the disease. There is also a need for healthcare providers to be able to communicate with and educate patients regarding important treatment options available and disease prognosis. At every follow-up visit, healthcare professionals should encourage their patients to participate actively in decision-making and self-management. Although a variety of specialists is often involved in the care of individuals with MS, the primary care team has a pivotal role in the overall management of these patients. Rapid strides have been made in the understanding MS, and without a doubt one can say that the future holds better prospects for patients with this debilitating disease.

RESOURCES

National Multiple Sclerosis Society
https://www.nationalmssociety.org/For-Professionals/Professional-Resource-Center

American Academy of Neurology
https://www.aan.com/Guidelines/home/Search?topic=MultipleSclerosis

National Institute of Neurological Disorders and Stroke
https://www.ninds.nih.gov

Multiple Sclerosis Foundation
https://msfocus.org

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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