CME

An update on managing patients with multiple sclerosis in primary care

Paula Hardeman, MPAS, PA-C

ABSTRACT

Multiple sclerosis (MS) is an immune-mediated inflammatory condition of the central nervous system causing periods of recurring inflammation and ultimately progression of symptoms over time. MS is a common cause of disability in younger patients. Evidence-based treatment for patients with MS early in their disease course prevents relapses and delays progression. Early treatments for MS were classified as immune-modulating; newer developments that suppress the immune system are more effective in preventing future relapses and progression but carry risks. The increased use of immunosuppressant therapies for patients with MS makes it imperative for clinicians to understand potential risks, benefits, and serious adverse reactions related to these therapies.

Keywords: multiple sclerosis, sphingosine-1-phosphate, natalizumab, cladribine, anti-CD20, alemtuzumab

Learning objectives

- Identify the characteristics and key features of MS.
- Describe the typical clinical disease course of MS.
- Describe the typical presentation of MS.
- List the diagnostic criteria for MS.
- List the long-term treatment modalities for MS and their effectiveness.

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease mainly affecting young adults, in which the immune system attacks myelin and the oligodendrocytes that form myelin in the central nervous system (CNS). The prevalence of patients with MS is increasing, and treatment has changed to focus on earlier aggressive interventions. This article describes MS pathophysiology and treatment, when to refer patients to MS specialists, and how to care for patients taking medications for MS.

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Characteristics of MS include demyelination, gliosis, neuro-axonal damage, and inflammation of the CNS. Despite substantial research, the mechanisms that drive these changes are not completely understood.[1] However, MS is thought to be an autoimmune disease involving a genetic predisposition and environmental factors. The autoimmune response is directed toward CNS self-antigens in susceptible patients.

Neurodegeneration is another key feature of MS and is a strong driver in the pathogenesis of the disease. Researchers initially believed that an inflammatory phase preceded a neurodegenerative phase in patients with MS; however, growing evidence from imaging studies and neuropathologic assessments suggests that neurodegenerative processes are present at the onset of MS.[2] The loss of axons in MS is a characteristic feature and is associated with disease progression and neurologic disability. Early signs of axonal dysfunction are seen pathologically and are worsened by sustained inflammation and impaired remyelination. Thus, over time, the axons degenerate, are lost, and contribute to CNS atrophy and worsening of the disease.[3] Clinically, this neurodegeneration is associated with important features of MS, including cognitive impairment, fatigue, and depression.[3] As a result, newer medications for MS are designed to prevent clinical relapses and neurodegeneration.[4,5] Drugs that initially were approved for MS are not as effective in preventing relapses or delaying disease progression, although they

Paula Hardeman is lead advanced practice provider in the ambulatory clinic of the Department of Neurology at UT Southwestern Medical Center in Dallas, Tex. The author has disclosed no potential conflicts of interest, financial or otherwise.

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Key points

- MS has four clinical courses: CIS, relapsing-remitting, secondary progressive, and primary progressive.
- Diagnosis involves a clinical history suggestive of a CNS inflammatory event, MRI findings, and evaluation for mimics of MS.
- Long-term management includes disease-modifying therapies aimed at preventing relapses and limiting progression, and symptom management.

have a safer drug profile.[4] Current treatment algorithms recommend starting with more effective drugs, especially in patients with large disease burden and spinal cord involvement at diagnosis.[4-6] The goal is to achieve no evidence of disease activity—that is, no clinical relapses, no sustained disability progression, no brain atrophy, and no new changes on MRI.[4-6]

CLINICAL DISEASE COURSE

MS has four clinical courses: clinically isolated syndrome (CIS), relapsing-remitting, secondary progressive, and primary progressive. CIS, recognized as the first clinical presentation of MS, refers to an inflammatory demyelinating event in the CNS that is highly likely to progress to clinically definite MS if a second event occurs.[7]

The most common clinical course of MS is relapsing-remitting, found in 85% of patients.[7] Relapsing-remitting MS is characterized by episodes of new neurologic symptoms or acute worsening of neurologic symptoms, usually over 24 hours without an infection or metabolic changes and with total or partial recovery.[8]

Secondary progressive MS is diagnosed retrospectively based on the history of gradual worsening neurologic function in a patient with relapsing-remitting MS.[7] The transition from relapsing-remitting MS to secondary progressive MS is gradual, and no clear clinical findings or diagnostic criteria identify the transition.[7,9] Based on research data, transition occurs about 19 years after the diagnosis of relapsing-remitting MS.[10] Risk factors associated with transition include male sex, older age at diagnosis of relapsing-remitting MS, and spinal cord involvement.[8]

About 10% of patients are diagnosed with primary progressive MS, which is characterized by a lack of a relapsing-remitting course and ongoing neurologic progression from onset.[11] In addition, the mean age of onset is older (ages 40 years and older).[12]

Radiologically isolated syndrome (RIS) is not a distinct clinical course for MS but describes radiographic changes suggestive of a demyelinating process in patients without clinical symptoms.[7,13] Factors that increase the likelihood of MS include asymptomatic spinal lesions, gadolinium-enhancing lesions, or positive cerebrospinal fluid markers.[14]

EPIDEMIOLOGY AND RISK FACTORS

MS primarily occurs in young adults, with an incidence that peaks at age 30 years.[15] Wallin and colleagues estimate the prevalence of MS in US adults at 362 cases per 100,000, or about 914,000 cases.[16] The study also reported a 3:1 ratio in women compared with men that was similar to previous estimates of 2.3-3:1.[16-18]

The prevalence of MS is increasing globally: Current estimates are that 2.8 million patients worldwide have MS.[16,19] The mean age of patients with relapsing-remitting MS ranges from 25 to 29 years, and the mean age of those with primary progressive MS ranges from 39 to 41 years.[17] With a few exceptions, the global distribution of MS generally increases the farther one is south or north of the equator.[20] Pockets of high rates of MS have been seen in specific regions such as Sardinia, Italy, and in the Orkney and Shetland Islands in the United Kingdom.[21] Between 3% and 10% of patients with MS present before age 16 years, which is known as pediatric MS (also referred to as pediatric-onset, early-onset MS, or juvenile MS) and also is increasing in incidence.[22]

PATHOGENESIS

MS is an abnormal immune response that results in the pathologic hallmarks of inflammation with demyelination, astroglial proliferation, and neurodegeneration.[4,6] The two main immune cells involved in MS pathogenesis are T and B cells.[23] From animal studies, the pathogenesis of MS begins in the periphery when T cells become activated and migrate into the CNS.[23] Once in the CNS, activated T cells are reactivated and activate B cells and other immune cells, triggering an inflammatory cascade that destroys the myelin, axons, and the cells that make myelin.[23]

The exact cause of MS is unknown; however, environmental, lifestyle factors, infections, and genetic factors may contribute to its development.[24] Several observational studies have demonstrated that patients with low serum vitamin D levels are at increased risk of developing MS.[25] Cigarette smoking, obesity early in life, or having symptomatic Epstein-Barr virus also are associated with an increased risk of developing MS.[6,25,26] Patients who carry the *HLA-DR1*15:01* allele—the genetic factor most frequently associated with MS—have an increased risk of developing MS.[6,25,26]

CLINICAL PRESENTATION

In most patients, the clinical presentation of MS depends on the specific areas of the CNS that are affected by the disease. MS commonly presents as unilateral optic neuritis (eye pain associated with blurry vision), partial myelitis (sensory changes and weakness in the torso and extremities and/or ataxia), focal sensory disturbance (limb paresthesia), or brainstem syndromes (sixth nerve palsy, facial sensory changes).[4,24] Symptoms may present over hours to days and gradually improve over weeks to months.[4,6] Symptoms

can be severe at onset or begin insidiously.[4] Findings on neurologic examination may include afferent pupillary defect, impaired sensation, motor weakness, ataxia, and gait impairment (often with hyperreflexia).[4] A clinical attack suggestive of MS is a single clinical event with symptoms and objective clinical findings localized to the CNS, developing acutely or subacutely, with a duration of at least 24 hours in the absence of infection or fever.[24] If MS is suspected, promptly refer the patient to an MS specialist.

TABLE 1. 2017 McDonald criteria for the diagnosis of MS

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Two or more clinical attacks and objective clinical evidence of two or more lesions on MRI
- Additional criteria: none

Two or more clinical attacks and objective clinical evidence of one lesion on MRI
- Additional criteria: DIS demonstrated by
  - One or more T2 lesion on MRI in at least two of four MS-typical regions (periventricular, juxtacortical, infratentorial, or spinal cord)

  OR
  - Wait for another clinical attack affecting a different CNS location

One clinical attack and objective clinical evidence of two or more lesions on MRI
- Additional criteria: DIT demonstrated by
  - Simultaneous presence of 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 timing to baseline scan

  OR
  - Wait for a second attack

  OR
  - The presence of CSF oligoclonal bands

One clinical attack and objective clinical evidence of one lesion on MRI
- Additional criteria: DIS and DIT
  - DIS demonstrated by
    - One or more T2 lesions on MRI in at least two of four MS-typical regions (periventricular, juxtacortical, infratentorial, or spinal cord)

    OR
    - Wait for another clinical attack affecting a different CNS location

  AND
  - DIT demonstrated by
    - Simultaneous presence of 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 timing to baseline scan

    OR
    - Wait for a second attack

    OR
    - The presence of CSF oligoclonal bands

DIAGNOSIS

The diagnosis of MS is based on a combination of clinical symptoms and findings, laboratory findings, and imaging criteria known as the revised McDonald criteria of 2017 (**Table 1**).[27] Two or more areas of the CNS must be involved at different points in time (dissemination in space and time), along with exclusion of other conditions such as other CNS inflammatory conditions, systemic inflammatory conditions, hereditary conditions, vascular conditions, infections, nutritional deficiencies, and neoplastic processes (**Table 2**).[24,27,28] Given the wide differential diagnosis of MS, primary care providers (PCPs) should obtain bloodwork to evaluate for other causes of the patient's symptoms.[29] If a workup for conditions that mimic MS is negative, refer the patient to an MS specialist.

Dissemination in space (DIS) refers to the optic nerve, brain, and spinal cord lesions associated with multiple clinical attacks, multiple T2 hyperintense lesions on MRI, or both.[27] *Dissemination in time* (DIT) refers to the development of new lesions over time. The presence of simultaneous gadolinium-enhancing lesions in conjunction with nonenhancing lesions at one time or the development of a new T2 lesion on follow-up MRI will satisfy DIT.[27] In patients with a single clinical attack, the presence of oligoclonal bands in the cerebrospinal fluid meets the criterion for DIT.[27]

MANAGEMENT

The management of MS includes long-term management with disease-modifying therapies (DMTs) aimed at preventing relapses and stopping progression, acute management of relapses, and symptomatic management to reduce daily symptoms associated with MS.[6,24] DMTs are available for administration orally or by injection or infusion. DMTs are classified as immune-modulating or immune-suppressing, with the latter being highly effective treatments. Historically, MS was treated with low-risk, less effective drugs until patients had a relapse or continued progression, when treatment was escalated to more effective and riskier drugs.[6]

LONG-TERM MANAGEMENT

Injectables (interferons and glatiramer acetate) Interferon-beta was the first approved medication for MS in 1993.[30,31] Four formulations are approved for MS treatment and vary in frequency—every other day or three times per week SC, weekly IM, or every 2 weeks SC. Interferon-beta reduces relapses by 18% to 32% compared with placebo.[31] The mechanism of action of interferon-beta is not well understood. However, interferon-beta is produced when the immune system is exposed to viruses, and increased levels reduce T-cell activation and increase anti-inflammatory cytokines, leading to a decrease in proinflammatory

cytokines.[30] Flu-like adverse reactions (low-grade fever, myalgia, arthralgia, and chills) lasting for hours are common, and can be mitigated with acetaminophen or nonsteroidal anti-inflammatory medications.[31] Interferons have been associated with hepatotoxicity, leukopenia, thrombocytopenia, and infections at the injection site.[31] The patient's liver function and complete blood cell (CBC) count should be checked annually.[31]

Glatiramer acetate is a subcutaneous injection given daily or three times per week. Glatiramer acetate reduces relapse by 29% compared with placebo.[31] The mechanism of action is not understood but clinical trials have proven efficacy.[30] Injection-site reactions are the most reported adverse reactions. Prolonged use can cause lipoatrophy at the injection site.[31] Glatiramer acetate does not interact with other medications and no routine laboratory testing is recommended.[31]

Oral medications Fumarates such as dimethyl fumarate and diroximel fumarate are taken orally and dosed twice daily. Their mechanism of action in MS is not completely understood, but they seem to inhibit and suppress proinflammatory pathways.[30] Fumarates reduce relapses by 44% to 53% compared with placebo.[31] The most common adverse reactions to fumarates are skin flushing and gastrointestinal disturbances (nausea/vomiting and diarrhea). Taking fumarates with a meal or 81 mg aspirin can help mitigate skin flushing. Hepatotoxicity also is a risk.[31]

Rare complications of fumarates include lymphopenia and progressive multifocal leukoencephalopathy (PML), a demyelinating disease caused by the John Cunningham virus.[30,32] The estimated incidence of PML in patients treated with fumarates is 0.02 per 1,000 patients.[32] Prolonged lymphopenia is the main risk factor for developing PML while on a fumarate.[30] Periodic monitoring of CBC count with differential and liver function testing is recommended.[31]

Teriflunomide is taken once daily and is available in two dosages—7 mg and 14 mg.[33] Teriflunomide blocks a key enzyme in the pyrimidine synthesis of rapidly dividing lymphocytes, reducing the proliferation and function of activated T and B cells.[33] Relapses are reduced by 30% to 36% compared with placebo.[31,33]

Elevation of alanine aminotransferase is a common adverse reaction to teriflunomide, and monthly hepatic testing is required for the first 6 months of treatment.[24] Other common adverse reactions associated with teriflunomide are hair thinning, diarrhea, nausea, and peripheral neuropathy.[32,33] Tuberculosis (TB) was seen in the clinical trials of teriflunomide, so patients should have a negative TB screening before starting this drug.[24,30]

The sphingosine-1-phosphate (S1P) receptor modulators, fingolimod, siponimod, ponesimod, and ozanimod, are administered orally and taken daily. These drugs modulate the S1P receptors, causing sequestration of lymphocytes in the lymph nodes and reducing lymphocyte migration into the CNS.[34] S1P receptors have five subtypes found on lymphocytes, cardiac tissue, smooth muscle, neurons, and endothelial cells.[34] S1P receptor modulators reduce annualized relapse rates by 38% to 55%.[31,34]

TABLE 2. Differential diagnosis for MS

Inflammatory CNS conditions:
- Acute disseminated encephalomyelitis
- Neuromyelitis optica spectrum disorders
- Transverse myelitis
- Susac syndrome
- Primary cerebral vasculitis
- Idiopathic optic neuritis
- Myelin oligodendrocyte glycoprotein antibody disorder
- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
- Hashimoto encephalopathy

Vascular disorders:
- Stroke or transient ischemic attack
- Cerebral small vessel disease
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome
- Dural arteriovenous fistula
- Cerebral vascular malformations
- Ischemic optic neuropathy

Systemic inflammatory conditions that also can affect the CNS:
- Small and medium vasculitis
- Behçet syndrome
- Neurosarcoidosis
- Sjögren syndrome
- Systemic lupus erythematosus
- Antiphospholipid syndrome
- Paraneoplastic conditions

Metabolic/toxic diagnoses:
- Vitamin B12 deficiency
- Copper deficiency
- Heavy metal poisoning
- Alcohol
- Malnutrition
- Nitrous oxide toxicity
- Serotonin syndrome

Infections:
- Syphilis
- Human T-cell lymphotropic virus type I
- HIV
- Lyme disease
- West Nile virus
- Herpes simplex virus
- Cat scratch fever
- Toxoplasmosis
- Cytomegalovirus
- Epstein-Barr virus
- Neurobrucellosis
- *Cryptococcus*

Neoplasms:
- Lymphoma
- Glioma
- Metastatic tumor

Fingolimod, which binds to four of the five S1P receptor subtypes, was the first S1P receptor modulator approved for treating MS.[6] Later-developed S1P receptor modulators are more specific and reduce the potential adverse reactions observed with fingolimod. Siponimod and ozanimod are selective modulators and bind to $S1P_1$ and $S1P_5$. Ponesimod is selective and binds only to $S1P_1$.

Bradycardia or atrioventricular heart block are the main risk factors associated with this drug class, which depend on the binding affinity for the S1P subtypes.[26] Because of this risk, fingolimod requires a first-dose observation.[31] Before starting drugs from this class, the patient's medications are reviewed for concomitant use of drugs such as beta-blockers or calcium channel blockers that could cause bradycardia or conduction abnormalities.[35] S1P receptor modulators are contraindicated in patients with myocardial infarction, unstable angina pectoris, AV block type 2, transient ischemic attack, stroke, decompensated heart failure, or QT prolongation within the last 6 months.[36]

Other common adverse events of this drug class are increased liver enzymes, macular edema, and infections.[31] Monitoring for macular edema within the first year of treatment is required. Patients with diabetes or uveitis are at increased risk of developing macular edema.[31] In post-marketing clinical trials and data of S1P receptor modulators, herpes infections and rare cryptococcus infections were reported.[35,37,38] The overall risk of herpes and cryptococcus infections was similar or slightly higher than placebo, but no risk factors were identified.[38] Patients are screened for antibodies to varicella before treatment, and those with a negative antibody test should be vaccinated against varicella.[31]

> Formal recommendations for breast screening before starting ocrelizumab have not been established.

Forty cases of PML have been reported with fingolimod use, with a risk estimate of 0.13 per 1,000 patients.[37,39] Live or live-attenuated vaccines are contraindicated in patients being treated with any of the S1P receptor modulators.[31]

Cladribine, an oral synthetic purine nucleoside analog, depletes circulating lymphocytes. The cumulative dose of cladribine is 3.5 mg/kg over two treatment courses separated by at least 43 weeks.[31] Cladribine is recommended after a suboptimal response to another treatment.[31] Treatment with cladribine causes a temporary reduction in lymphocytes followed by a repopulation of lymphocytes.[40] Cladribine reduced the annualized relapse rate by 58% compared with placebo.[41]

Adverse reactions include infections, lymphopenia, and malignancies.[40] Before starting cladribine, patients should be screened for infections, including human immunodeficiency, TB, hepatitis B, and hepatitis C.[31] Patients who are antibody-negative to varicella should be vaccinated before treatment.[31] Patients with a lymphocyte count of less than 200 cells/mL should receive antiherpes prophylaxis.[31] Live or live-attenuated vaccines should be administered 4 weeks before therapy. These vaccines are contraindicated during treatment.[31]

Monoclonal antibodies Natalizumab prevents circulating lymphocytes from entering the CNS.[31] It targets the alpha4-chain integrin subunit, the pathway that lets lymphocytes cross the blood-brain barrier. Natalizumab reduced the annualized relapse rate by 67% compared with placebo.[32] The drug is administered monthly as an infusion, and infusion-related adverse reactions have been reported, as well as elevated liver enzymes and anaphylaxis.[30,42]

The most concerning risk of natalizumab is PML in the brain.[43] Factors that increase the risk of developing PML while on natalizumab include positive anti-John Cunningham virus antibody testing, previous immunosuppressant therapy, and more than 24 months of exposure to natalizumab.[30] Live or live-attenuated vaccines are not recommended during treatment.[31]

Ocrelizumab and ofatumumab are humanized monoclonal antibodies that target anti-CD20 on B cells, which causes depletion of B cells.[44] Precursor B cells are not affected, thus preserving humoral immunity.[44] Ocrelizumab reduced the annualized relapse rate by 46% and 47% in clinical trials. Ofatumumab reduced the annualized relapse rate by 51% and 59%.[31] Ocrelizumab is given as an infusion every 6 months. Ofatumumab is a monthly subcutaneous injection.

Before starting patients on either of these drugs, screen for hepatitis B and C, varicella-zoster virus, and TB.[6,26] Adverse reactions to these drugs include infusion-related or injection-site reactions, infections, hepatitis B reactivation, and malignancies.[35,37,45] Patients can be treated with corticosteroids, antihistamines, and antipyretics before receiving ocrelizumab to prevent infusion-related reactions.[44] Cases of PML have been reported with anti-CD20 B cell-depleting drugs, but the overall risk of developing PML is low.[35,43] Decline of immunoglobulins can occur with anti-CD20 B cell-depleting drugs.[44] In clinical trials of ocrelizumab, a higher incidence of breast neoplasms was observed.[31] However, formal recommendations for breast screening before starting ocrelizumab have not been established.[44] Vaccinations with live or live-attenuated vaccines should be given 4 weeks before treatment with either drug.[31]

Alemtuzumab targets the CD52 antigen on leukocytes, including T and B lymphocytes, monocytes, and granulo-

cytes, causing prolonged depletion of CD52-expressing cells.[46] T and B cells repopulate at different rates; B cells usually repopulate in 3 to 6 months, and T cells repopulate in 9 to 12 months.[37,46] Alemtuzumab reduced the annualized relapse rate by 49% and 55%.[31] The infusion is given daily for 5 days and can be repeated (daily for 3 days) 12 months after the initial infusion.[31] This drug causes a release of cytokines, which can cause headache, rash, pyrexia, and non-anaphylactoid hypotension.[31,35] Patients are premedicated with corticosteroids, antihistamines, and antipyretics before each alemtuzumab infusion to lessen the severity of these reactions.[24]

Secondary autoimmune conditions have been reported; typically, autoimmune thyroid disease was seen in 16% to 18% of patients after 2 years and in 30% of patients with longer follow-up.[37] Also, idiopathic thrombocytopenia, hemolytic anemia, and glomerulonephritis have been reported.[37] Because of these risks, patients will need CBC counts with differential, serum creatinine levels, urinalysis, and thyroid testing every 3 months for 48 months after the last dose.[31]

Herpes and listeriosis infections have been reported in patients receiving alemtuzumab.[37,42] Patients should be counseled on properly heating foods that could contain sources of listeria and to avoid dairy products made with unpasteurized milk.[35] Patients starting alemtuzumab should be placed on anti-herpes prophylaxis and remain on this until their CD4 count is above 200 cells/mm^3.[31]

PROGRESSIVE MS MANAGEMENT

Ocrelizumab is the only drug that is FDA-approved for primary progressive MS.[12] All DMTs indicated for relapsing-remitting MS also are indicated for active secondary progressive MS, which is defined as occasional clinical relapses and MRI changes in a patient with secondary progressive MS.[12] Thus, the management of progressive patients should focus on symptoms and psychosocial needs.[12] A multidisciplinary approach that includes primary care, physical therapy, occupational therapy, urology, social services, counseling, and pain management is recommended.[12]

TREATING ACUTE RELAPSES

Patients may present to their PCP complaining of worsening symptoms. When evaluating a patient diagnosed with MS for a relapse, the first step is determining if the patient has a true relapse or a pseudorelapse. A pseudorelapse worsens existing symptoms in an external factor such as a fever, infection, increase in core body temperature (exercise), or stress.[47] Pseudorelapse typically has a fluctuating pattern.[47] If a pseudorelapse is suspected without obvious triggers, assess the patient's CBC count and urinalysis to rule out infection, electrolytes, and liver function tests. High-dose corticosteroids are not indicated for patients with pseudorelapse, and the goal of treatment is to treat the external factor or cause. However, if the workup does not identify an alternative reason for the patient's symptoms, evaluation by an MS specialist is warranted.

An MS relapse is a single clinical event with symptoms and objective clinical findings localized to the CNS, developing acutely or subacutely, and lasting at least 24 hours without infection or fever.[24] Symptoms of an MS relapse evolve over hours to days, followed by a gradual and variable recovery that can last weeks to months.[47] A true relapse is confirmed with evidence of gadolinium-enhancing lesion on MRI.[47] Most MS relapses will improve over time without treatment, so if the patient's symptoms are not interfering with function, symptom monitoring is acceptable.[47] The goal of acute treatment of MS is to accelerate recovery, but acute treatment may not lead to a pre-relapse baseline.[27,47] Acute management of MS relapses involves using high doses of corticosteroids—typically, 500 mg of oral methylprednisolone for 3 days or 1,000 mg of methylprednisolone IV for 3 to 5 days.[27,47] Following treatment with high-dose corticosteroids, a taper is not necessary.[47]

SYMPTOM MANAGEMENT

Patients with MS can experience many symptoms depending on the part of the CNS affected, including fatigue, depression/anxiety, cognitive impairment, bladder, sexual dysfunction, sensation changes or pain, gait abnormalities, imbalance, muscle spasticity, and weakness.[48] A multidisciplinary team approach is needed to manage symptoms.

Fatigue is common in patients with MS, and the cause usually is multifactorial.[48] Review the patient's medications for those that can cause sedation and consider less-sedating medications if possible.[48] Screen patients for depression and, if warranted, obtain a sleep study to evaluate for sleep apnea and other sleep-related disorders that can cause fatigue.[48] Physical therapy and exercise can help improve fatigue and muscle weakness. Pharmacologic agents used for MS-related fatigue include modafinil, armodafinil, amantadine, and amphetamine compounds.[48]

The prevalence of depression is higher in patients with MS than in the general population.[48] Screen patients annually for depression and anxiety; treatment can include cognitive behavioral therapy or drugs such as selective serotonin reuptake inhibitors or serotonin norepinephrine inhibitors.[48]

Between 45% and 65% of patients with MS have cognitive impairment, such as deficits in recent memory, attention, information-processing speed, executive function, and visuospatial perception.[48] Assess patients for tobacco use, polypharmacy, depression, fatigue, and sleep disruptions.[48] Counsel patients on strategies to help improve cognition, such as using notepads and calendars, regular physical exercise, and regular social contact.[48]

Neurogenic bladder dysfunction in patients with MS is characterized by urinary frequency, urinary retention, or

a combination of both.[48] Assess patients for constipation, which could exacerbate their urinary symptoms.[48] Obtain a urinalysis and postvoid residual ultrasound of the bladder—consider intermittent catheterization if the patient's postvoid residual volume is greater than 100 mL.[48] Otherwise, anticholinergic medications such as oxybutynin can be prescribed. Advise patients to limit fluids at night, schedule voiding, and avoid bladder irritants such as caffeine, tobacco, alcohol, carbonated beverages, chili peppers, citrus fruits, and vitamin C supplements.[48] Patients who do not respond to anticholinergic medications can be referred to a urologist for intravesical botulinum toxin injections.[48]

Sexual dysfunction can affect up to 90% of patients with MS.[48] Erectile dysfunction and ejaculatory disorders in men can be treated with phosphodiesterase inhibitors.[48] Women usually report anorgasmia, reduced vaginal lubrication, and reduced libido. Evaluate patients for medications that could exacerbate symptoms and encourage them to broaden the definition of sexual activity beyond penile-vaginal intercourse.[48] If physical limitations are contributing to sexual dysfunction, the use of cushions for positioning may be helpful.[48]

Neuropathic pain can be treated with gabapentin, pregabalin, amitriptyline, carbamazepine or oxcarbazepine, or other antiepileptic drugs.[6,48] Spasticity management should start with stretching exercises; consider baclofen or tizanidine if stretching fails to improve spasticity.[48] However, these medications could worsen fatigue, so monitor patients.[48] Patients with refractory spasms should be referred to a specialist for botulinum toxin injections or intrathecal baclofen.

Gait and balance impairment in patients with MS usually is multifactorial and caused by spasticity, weakness, fatigue, and sensory changes.[48] Physical therapy and assistive devices such as ankle foot orthotics, canes, walkers, wheelchairs, or scooters can help address gait and balance impairments.

IMPLICATIONS FOR PRIMARY CARE

Encouraging patients with MS to maintain a healthful lifestyle and screening for other comorbid conditions is an important factor in managing symptoms associated with MS.[49] Lifestyle changes include healthful eating, routine exercise, good sleep hygiene, and stress management. No diet or nutritional approach has been proven effective in MS.[49] However, increasing consumption of fresh fruits, vegetables, and whole grains; reducing consumption of processed food and refined sugars; and exercise tailored to the patient's needs have helped patients manage MS fatigue.[49] Refer patients to physical therapy for help with designing an exercise program.[49]

PCPs also can assess for tobacco use and encourage patients to stop using tobacco products, which are associated with MS progression.[49]

CONCLUSION

MS treatment has greatly improved since the first DMT was approved in 1993 and now includes drugs that are more effective in preventing disease progression and disability. Treatment algorithms are transitioning to recommending earlier use of more effective immunosuppressants to prevent relapses and slow disease progression. This makes timely diagnosis of MS vital. As the prevalence of patients with MS increases, all clinicians must know when to refer patients to MS specialists, must be aware of the potential adverse reactions to immunosuppressant drugs, and must know the appropriate safety monitoring for patients on these treatments.[5] **JAAPA**

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