Multiple Sclerosis: Disease and Treatment Modality Overview

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives.
At the conclusion of this article, the participant should be able to:
1. Identify signs and symptoms associated with multiple sclerosis and describe tests to determine a differential diagnosis of MS
2. Describe each of the categories of MS and be able to classify a patient into a specific clinical course
3. Identify medications used in the treatment of MS, and describe their mechanism of action, administration, side effects, and special considerations
4. Describe methods of symptom management for MS

Multiple Sclerosis

Epidemiology. It is estimated that about 400,000 people in the United States are living with MS. The disease most commonly effects people in Europe, the United States, Canada, Australia, and New Zealand. It appears as though incidence and prevalence increase the farther you get from the Equator. Women tend to be affected 1.5-2.5 times more than men. Peak onset in patients is usually between the ages of 25 and 35, with a sharp increase after adolescence and a shallow decline after the peak age. Genetics play a strong role in multiple sclerosis. It is estimated that one’s risk for MS is 30 times higher if you have a sibling with MS. Other environmental factors are thought to contribute include sunlight exposure, infections, vaccines, tobacco, nutrition, and xenobiotics, but no association has been confirmed.

Pathophysiology. In the normal neuron, the electrical signal is ensured to be fast and strong due to the protection of the myelin sheath around the neuron. In MS, this sheath is attacked through inflammatory processes. The initial trigger of multiple sclerosis is not known. This unknown trigger initiates both the adaptive and innate immune systems. Regulatory T cells are activated to produce inhibitory cytokines like IL-10 and TGF-β. CD4+ cells begin to differentiate into TH1, TH2, or TH17 types. Once differentiated, these cells secrete cytokines. TH1 cells secrete interferon γ (proinflammatory), TH2 cells secret IL-4 and IL-13 (both anti-inflammatory), and TH17 cells secrete a host of proinflammatory cytokines. Treg cells, which control TH1, TH2, and TH17 cells, appear to have reduced function in patients with MS. CD8+ T cells can inactivate CD4+ T cells, but also can kill glial cells, which exposes the axon. CD8+ cells can also transect axons, increase vascular permeability, and activate the death of oligodendrocytes, all of which present in MS lesions. B cells, known for their production of antibodies, have also been
implicated in MS pathogenesis. Antibodies have been found in the cerebrospinal fluid of MS patients, although their target is not known. Products of B cells, including lymphotoxin and TNF-α, are proinflammatory cytokines, contributing to the inflammation. These inflammatory processes then attack the myelin sheath putting large areas of scarring, or lesions, on it. When the myelin has been destroyed enough, the signal loses strength and speed as it travels down the neuron. This results in the symptoms that patients experience.

**Clinical Presentation.** Table I lists common signs and symptoms with which patients may present.

<table>
<thead>
<tr>
<th>Primary Signs &amp; Symptoms</th>
<th>Secondary Symptoms</th>
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<tbody>
<tr>
<td>Visual Complaints</td>
<td>Incontinence</td>
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<tr>
<td>Fatigue</td>
<td>Poor nutrition</td>
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<tr>
<td>Gait problems and falls</td>
<td>Osteoporosis</td>
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<td>Ataxia</td>
<td>Respiratory infections</td>
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<td>Paresthesias</td>
<td>Tremor</td>
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<td>Speech difficulty</td>
<td>Depression</td>
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<td>Paresis</td>
<td>Cognitive changes</td>
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<td>Spasticity</td>
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<td>Recurrent UTI</td>
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<tr>
<td>Urinary calculi</td>
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<tr>
<td>Decubiti and osteomyelitis</td>
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**Diagnosis.** MS is diagnosed using a set of criteria called the McDonald Criteria. The McDonald Criteria were developed by the International Panel on the Diagnosis of Multiple Sclerosis in 2001. The criteria were updated in 2005 and again in 2010. The current criteria are listed in Table II.

If the criteria are met, the patient is diagnosed with MS if there is no better explanation for the symptoms. If the criteria are not fully met, the patient is diagnosed with “possible MS.” If another diagnosis arises during testing and workup, the patient is not diagnosed with MS. In diagnosing patients, MRI brain studies are completed to find damage in the brain and CNS that may indicate MS plaques. Brain atrophy may be a symptom as well. Lesions which enhance after gadolinium injection indicate new lesions and disruption of the blood-brain barrier – a sign of early conversion in MS patients. The cerebrospinal fluid (CSF) is evaluated to look for IgG levels. In MS patients, IgG appears to be increased in the CSF while serum IgG levels remain normal. Using evoked potentials, physicians can determine areas were demyelination has occurred but isn’t appearing in relapses. This last test is not diagnostic alone, but only indicated to help a formal diagnosis.
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data needed for Diagnosis</th>
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<tbody>
<tr>
<td>≥2 attacks; objective clinical evidence of ≥2 lesions or 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None</td>
</tr>
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</table>
| ≥2 attacks; objective clinical evidence of 1 lesion                                    | Dissemination in space:  
≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, spinal cord)  
-OR-  
await a further clinical attack implicating another CNS region |
| 1 attack; objective clinical evidence of ≥2 lesions                                   | Dissemination in time:  
Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing 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 |
| 1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)      | Dissemination in space:  
≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS  
-OR-  
Await a second clinical attack implicating another CNS region  
Dissemination in time:  
Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing 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 |
| Insidious neurological progression suggestive of MS (PPMS)                            | 1 year of disease progression (retro- or prospectively determined plus 2 of the following 3 criteria:  
1. Evidence of dissemination in space in the brain based on ≥ T2 lesions in the MS-characteristic regions  
2. Evidence of dissemination in space in the spinal cord based on ≥2 T2 lesions in the cord  
3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) |
Classification System. The clinical course of multiple sclerosis is divided into four types.

Relapse-remitting MS. Patients experiencing relapse-remitting MS (RRMS) have only relapses and remissions.\(^7\) New symptoms generally last at least 24 hours and remissions last at least 30 days, regardless of whether they are complete or incomplete.\(^4\) Approximately 85% of patients begin their disease course with RRMS.\(^7\)

Secondary-progressive MS. Secondary-progressive MS (SPMS) begins with an RRMS phase, which eventually transitions into a progressive phase where the patient never fully returns to baseline after each episode. During the progressive phase, patients may or may not continue to experience acute exacerbations of their MS.\(^9\)

Primary-progressive MS. In primary-progressive MS (PPMS), patients do not begin with relapses, but rather with the slow progressive decline. Patients with PPMS will not experience relapses over their progression. Approximately 15% of MS patients experience PPMS.\(^7\) These patients tend to have a worse prognosis and tend to be diagnosed later in life.\(^4\)

Progressive-relapsing MS. Progressive-relapsing MS (PRMS) is characterized by a mixture of both progression and relapses.\(^7\) Patients have suffered with the progressive phase since diagnosis yet have relapses superimposed over their progression.\(^7\)

Pharmacologic Treatments

Interferon $\beta_{1b}$ (Betaseron®, Extavia®) and Interferon $\beta_{1a}$ (Avonex®, Rebif®)

**Indications.** Both interferon $\beta_{1b}$ and $\beta_{1a}$ are indicated in patients with relapsing forms of MS to decrease the frequency of clinical exacerbations.\(^8,9\) Interferon $\beta_{1a}$ is also indicated to slow the accumulation of physical disability.\(^8\)

**Mechanism of Action.** Interferons are proteins produced by the body, usually upon the onset of an infection. Their many actions are mediated by their binding with receptors. The specific mechanism in MS is not fully known, but believed to be related to interleukin-10 (IL-10) interactions.\(^8,9\) IL-10 is increased in MS due to the increased activity of T<sub>reg</sub> cells as a result of the inflammatory processes in the disease.\(^1\)

**Dosing and Administration.** Interferon $\beta_{1b}$ (both Betaseron® and Extavia®) is a 0.25mg subcutaneous injection every other day, titrated over six weeks from 0.0625mg per dose up to the full 0.25mg dose.\(^9\) Avonex® is 30mcg injected intramuscularly once weekly.\(^8\) Rebif® is injected subcutaneously as a 22mcg or 44mcg dose three times per week. The initial dose is 20% of the final dose, which is then titrated up over a four week period to the final dose.\(^8\)

**Warnings, Adverse Reactions, Contraindications.** Reports of increased depression and suicide ideation have occurred in patients receiving all products of interferon $\beta$. Patients should be advised to report any new-onset depression or suicide ideation to their healthcare provider.\(^8,9\) Some patients taking interferon $\beta_{1b}$ have experienced necrosis of injection sites, occurring at either single or multiple injection sites. If lesions occur, the area should be avoided with future
injections and appropriate therapy initiated.\textsuperscript{9} Patients taking interferon $\beta_{1a}$ should be monitored for pancytopenia and thrombocytopenia as well as autoimmune disorders, including idiopathic thrombocytopenia, hyper- and hypothyroidism, and hepatitis. Appropriate therapy should be initiated should patients develop any of these disorders.\textsuperscript{8} Cardiac side effects have been observed in some patients with cardiac disease receiving interferon $\beta_{1a}$; these patients should be closely monitored.\textsuperscript{8} Some patients receiving Avonex® in clinical trials experienced seizures, even in patients with no prior history. Caution should be used in patients who have a history of seizure disorders.\textsuperscript{8} Elevation of liver enzymes has been detected in some patients receiving interferon $\beta_{1a}$. The medication should be discontinued if a patient develops jaundice or other symptoms of liver failure.\textsuperscript{8}

Common adverse effects experienced by patients include dizziness, headache, nausea, urinary tract infection, myalgia, sinusitis, fatigue, abdominal pain, abnormal vision, rigors, peripheral edema, insomnia, and rash.\textsuperscript{8,9} Interferon $\beta$ is contraindicated in patients with a history of hypersensitivity to the medication or human albumin.\textsuperscript{8,9}

**Glatiramer Acetate (Copaxone®)**

**Indications.** Glatiramer is a biologic response modifier approved for use in RRMS patients to reduce the frequency of relapses. Patients experiencing their first clinical episode of MS and present with MRI features resembling the disease are also eligible for treatment with glatiramer.\textsuperscript{10,12}

**Mechanism of Action.** Although the mechanism of action is not entirely known, glatiramer works on both the adaptive and innate immune systems. In the adaptive immune system, glatiramer has been shown to induce CD4$^+$ glatiramer-reactive TH2 cells. These cells mainly lie dormant, however, when myelin antigen is detected, these cells are activated to release cytokines. CD4$^+$ CD25$^-$ T$_{reg}$ cells are converted to CD4$^+$ CD25$^+$ T$_{reg}$ cells through the induction of Foxp3, a transcription factor key to the development of T$_{reg}$ cells, which is activated by glatiramer. In the innate immune system, glatiramer modifies antigen-presenting cells by inhibiting the induction of HLA proteins and the release of tumor necrosis factor (TNF) and cathepsin B by THP-1 cells. The release of other cytokines has also been shown to be inhibited by glatiramer.\textsuperscript{11}

**Dosing and Administration.** The standard dose of glatiramer is 20mg/day administered subcutaneously\textsuperscript{10}. It can be injected in the upper arms, abdomen, hips, and thighs, and is not to be administered intravenously. Patients should rotate their injection sites daily.\textsuperscript{12}

**Warnings, Adverse Reactions, Contraindications.** Some patients experienced symptoms directly after injection, including flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. Generally, these effects did not occur until after months of treatment, and were self-limited nor required medication attention during trials.\textsuperscript{10} Patients should rotate their injection site daily to avoid lipoatrophy and skin necrosis.\textsuperscript{10} Although not shown to a great extent in clinical trials, due to its mechanism of action, glatiramer could have an effect on how the immune system responds to foreign antigens, undermining its ability to detect and eliminate antigens.\textsuperscript{10}
Adverse reactions commonly seen during clinical trials include lymphadenopathy; palpitations, tachycardia, nausea and vomiting, asthenia, pain, edema, dyspnea, cough, rash, pruritis, and vasodilatation. Glatiramer is contraindicated in patients hypersensitive to glatiramer or mannitol. Glatiramer is classified as Pregnancy Category B. It is not known if glatiramer is excreted in breast milk.

Natalizumab (Tysabri®)

**Indications.** Natalizumab is a monoclonal antibody biological response modifier approved for the treatment of relapsing forms of MS to reduce the frequency of exacerbations and delay the progress of physical disability.

**Mechanism of Action.** Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins, which are present on the surface of most leukocytes (except neutrophils), preventing the binding of these integrins to their counter-receptors. One of these counter-receptors is vascular cell adhesion molecule-1 (VCAM-1), expressed on the vascular endothelium. It is believed that this interaction between the integrins and VCAM-1 allows migration of leukocytes across the blood-brain barrier, which is thought to cause the lesions known to MS. Blocking this interaction would help prevent this leukocyte migration.

**Dosing and Administration.** The dosage of natalizumab is 300mg IV infusion every four weeks. The infusion is to be completed over the course of an hour. Only providers and patients registered through the TOUCH program may administer, dispense, or receive natalizumab.

**Warnings, Adverse Reactions, Contraindications.** Some patients being administered natalizumab experienced progressive multifocal leukoencephalopathy (PML), an infection usually occurring in immunocompromised patients through the JC virus (JCV). There is no adequate treatment for PML should a patient develop it; hence Tysabri® is to be avoided in any patient who is immunocompromised. Less than 1% of patients receiving natalizumab experience a hypersensitivity reaction. Administration should be immediately discontinued and the reaction treated appropriately. Due to the immune-system modulating effects of natalizumab, patients are more at risk for opportunistic pathogens including pneumonias, gastroenteritis, and urinary tract, vaginal, and tooth infections. Patients taking other immunosuppressant medications including antineoplastics should not be treated with natalizumab. Some patients receiving natalizumab developed clinically significant liver injury. Patients with jaundice or other indication of liver injury should stop natalizumab. Tysabri® has been known to alter values of most white blood cells and nucleated red blood cells as well as hemoglobin levels.

Adverse reactions commonly seen during clinical trials include headache, fatigue, arthralgia, chest discomfort, depression, extremity pain, muscle cramps, abdominal discomfort, diarrhea, rash, irregular menstruation, vertigo, and urinary urgency/frequency. Natalizumab is contraindicated in patients who have been experienced progressive multifocal leukoencephalopathy or those with a hypersensitivity to natalizumab. It is classified as a Pregnancy Category C. The drug is excreted into breast milk.
Mitoxantrone

**Indications.** Mitoxantrone is an anthracenedione antineoplastic agent approved for use to minimize neurologic disability and relapse frequency in secondary progressive, progressive relapsing, or worsening relapsing-remitting MS.

**Mechanism of Action.** Mitoxantrone inhibits DNA and RNA by binding to the DNA strands and inhibiting topoisomerase II. B cell, T cell, and macrophage proliferation have been shown to be inhibited by mitoxantrone as well as interferon gamma, TNFα, and IL-2 secretion.

**Dosing and Administration.** Mitoxantrone is administered 12mg/m² intravenous infusion over five to fifteen minutes. Patients receive an infusion every three months.

**Warnings, Adverse Reactions, Contraindications.** Only physicians who have experience with chemotherapy should administer mitoxantrone due to the risk of severe myelosuppression. Appropriate laboratory, monitoring, and support services must be available while the patient is myelosuppressed. Patients who have previously been treated with anthracyclines, prior mediastinal radiotherapy, or who have cardiovascular disease are at increased risk for left ventricular ejection fraction (LVEF) reduction and irreversible congestive heart failure. Regular LVEF monitoring should be performed while the patient is on this medication. Some multiple sclerosis patients being treated with mitoxantrone have developed secondary acute myelogenous leukemia, especially if taking other cytotoxic drugs concurrently.

Adverse reactions commonly experienced by patients in clinical trials included nausea, hair loss, menstrual disorder and amenorrhea, arrhythmia, diarrhea, constipation, back pain, sinusitis, and headache. Mitoxantrone is contraindicated in patients who have previously experienced a hypersensitivity reaction to the medication. Mitoxantrone is a pregnancy category D. Patients of childbearing age should take precautions to avoid becoming pregnant.

Dalfampridine (Ampyra®)

**Indications.** Dalfampridine is indicated to improve walking speed in patients with multiple sclerosis.

**Mechanism of Action.** Although the mechanism in MS is not fully known, dalfampridine is a broad-spectrum potassium channel blocker that has been shown to increase the action potential conduction in demyelinated axons in animals.

**Dosing and Administration.** Ampyra® comes in a 10mg tablet which is to be taken twice daily. It can be taken with or without food, and doses should be taken about 12 hours apart.

**Warnings, Adverse Reactions, Contraindications.** Patients who have a history of seizures should not take Ampyra®. The medication displayed an increased incidence of seizures in clinical trials. If a patient experiences a seizure while on Ampyra®, the medication should be discontinued and not restarted. Dalfampridine is primarily excreted through the kidneys unchanged. In patients
with a creatine clearance $\leq 50\text{mL/min}$, the risk of seizures increases. Since no strength smaller than 10mg is available, dalfampridine should not be used in these patients.\textsuperscript{20}

Adverse effects commonly reported in clinical trials include urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, constipation, and dyspepsia.\textsuperscript{20} Dalfampridine use is contraindicated in patients with a history of seizure or moderate or severe renal impairment.\textsuperscript{20}

**Fingolimod (Gilenya\textsuperscript{®})**

*Indications.* Fingolimod is indicated to reduce the frequency of clinical exacerbations and delay the increase in physical disability in patients with relapsing forms of MS.\textsuperscript{22}

*Mechanism of Action.* After metabolism by sphingosine kinase to fingolimod-phosphate, the active form, the medication binds with high affinity to sphingosine 1-phosphate receptors, specifically 1, 3, 4, and 5. The active drug blocks lymphocytes from leaving lymph nodes, reducing the number of lymphocytes in the periphery. Although not entirely known, it is believed that fingolimod also has a similar reaction with lymphocyte transport into the central nervous system.\textsuperscript{22}

*Dosing and Administration.* Gilenya\textsuperscript{®} is taken by mouth once daily at a dose of 0.5mg. It can be taken with or without food.\textsuperscript{22}

*Warnings, Adverse Reactions, Contraindications.* Patients who begin fingolimod tend to develop a decreased heart rate. Patients should be monitored for signs and symptoms of bradycardia for 6 hours after first administration. An electrocardiogram should be obtained if one has not been recently obtained, especially in patients taking anti-arrhythmics including beta-blockers and calcium channel blockers.\textsuperscript{22} Due to its mechanism of action reducing peripheral lymphocytes, patients taking fingolimod have an increased risk of infection. A CBC should be taken before initiating.\textsuperscript{22} Some patients taking fingolimod have experienced an elevation in liver enzymes. Patients who develop symptoms of liver dysfunction should have their liver enzymes checked, and fingolimod stopped if severe damage is presumed.\textsuperscript{22} Fingolimod may cause harm to a developing fetus. Women of childbearing age should use effective methods of contraception to prevent pregnancy while on and for two months after stopping fingolimod due to its relatively long half-life.\textsuperscript{22} Fingolimod can remain in the body for up to two months following discontinuation. Lymphocyte counts return to normal within these two months, but patients need to be aware of residual immunosuppression until lymphocyte count does return to normal.\textsuperscript{22}

Adverse effects commonly reported in clinical trials include bronchitis, sinusitis, gastroenteritis, headache, dizziness, paresthesia, migraine, diarrhea, back pain, weight loss, cough, dyspnea, depression, and hypertension.\textsuperscript{22} Gilenya\textsuperscript{®} does not have any contraindications listed at this time.\textsuperscript{22}
Preferred Therapy

The American Academy of Neurology has made some recommendations for therapy for multiple sclerosis.

Interferon β has been shown to reduce the attack rate in patients with MS. In a randomized, double blind, controlled study, RRMS patients who received interferon β_{1b} showed a clinical relapse rate decreased by 34% over placebo. The number of active lesions was also reduced by 83% in these patients. A multicenter, randomized trial of interferon β_{1a} showed a reduction of 37% versus placebo in RRMS patients’ extended disability status scale (EDSS) progression rate. Interferon β_{1b} was tested in SPMS patients in a randomized, double-blinded placebo controlled study. Patients receiving interferon β_{1b} showed a reduced EDSS progression rate (by 22%) and 31% lower clinical attack rate. Based on these and other studies, interferon β should be used in patients who already have RRMS or SPMS.²³

Glatiramer acetate has been demonstrated to reduce the MS attack rate in patients with RRMS. A large multicenter, randomized, double blind, placebo controlled trial showed glatiramer reduced patients’ clinical attack rates by 29%. A short duration trial examining MRI results showed that the glatiramer group had a 35% reduction over placebo in the number of enhancing lesions. Therefore, glatiramer acetate therapy can be considered in any patient who has RRMS.²³

Mitoxantrone has been shown in studies to have a beneficial effect on the progression of the disease in patients who are deteriorating. In a randomized, double blind, placebo control trial in patients with RRMS, mitoxantrone provided a 68% decrease in exacerbations per patient. A phase III multicenter, double-blind, controlled trial in patients with RRMS or SPMS showed that mitoxantrone reduces the number of patients who have a deterioration on the EDSS scale by 64%.²⁴ Recent studies have become concerned with safety, however, as in one trial, 2.2% of patients taking mitoxantrone developed asymptomatic left ventricular ejection function loss. Other studies have shown 0.81% of patients in clinical trials develop leukemia.²⁵ Based on this evidence, mitoxantrone can be used in patients who have failed other therapies but with caution due to toxicity concerns.²⁴,²⁵ Only physicians experienced in administering cytotoxic agents should administer mitoxantrone.²⁴

Natalizumab has been shown to reduce measures of clinical activity and improve measures of severity in trials. Trials showed that MRI activity measures were significantly reduced with natalizumab administration when compared to placebo or placebo with other disease-modifying agents. Aggregate data of the studies indicate MRI activity suppression by 80-90% and clinical activity reductions of 50-70%. Natalizumab therapy should be reserved for patients with RRMS who have failed other therapies due to risk of PML. The combination of interferon β and natalizumab also present a problem with PML, and should not be used.²⁶

Fingolimod and dalfampridine have not yet been evaluated for inclusion in the guidelines, and should be considered second-line at this time.
Nonpharmacologic Treatments

Some patients who prefer alternative medicine to treat MS alter their diet or use supplements. Some agents such as vitamins A, C, and E, α-lipoic acid, coenzyme Q10, grape seed, pine bark extracts, mangosteen, and acai may be effective to help MS. Most of these agents are antioxidants, with the end effect of stimulating the immune system. Since MS is based off an immune system response, this may prove counterproductive.4

Some patients choose to use electrical therapy to help relieve symptoms. Stimulating the muscles with electrical current works to reduce fatigue and weakness in MS patients, as well as improve the voluntary movement of muscles. Korkmaz and associates completed a study looking at the improvement of muscle strength and fatigue in MS patients treated with high voltage pulsed galvanic stimulation (HVPGS). Patients were treated with proprioceptive neuromuscular facilitation (PNF) or HVPGS. Strength and fatigue were found to improve after therapy in both treatment groups.27

All patients should receive the influenza vaccine yearly. The live attenuated intranasal vaccine, Flumist®, is not recommended, however, due to patient’s immunosuppressive therapy.4

Symptom Management

Since there is no cure for MS, it is important that pharmacists seek to improve the patient’s quality of life through management of the symptoms of MS.

Gait Difficulties and Spasticity. Baclofen is often recommended at 10mg doses taken three times daily due to its GABA-ergic activity. Patients are then titrated upward to effect. Diazepam in small doses (0.5-1 mg) is sometimes added if baclofen does not obtain optimal response. The α-adrenergic agonist tizanidine increases presynaptic inhibition of motor neurons to reduce spasticity. Patients generally start out with 4mg at bedtime and titrate up slowly to effect. Diazepam, clonazepam, dantrolene, gabapentin, tiagabine, and pregabalin may also prove effective. Sometimes botulinum toxin type A can be used, but only in smaller muscles, as the amount required for larger muscles is too large to inject.4

Tremors. Propranolol, primidone, and isoniazid can help treat cerebellar symptoms leading to tremor.4

Bowel and Bladder Symptoms. Anticholinergic agents, such as oxybutynin, tolterodine, hyoscymine and dicyclomine have all been used to treat mild symptoms of incontinence, urgency, frequency, and nocturia. Tricyclic antidepressants such as imipramine and amitriptyline have also been used. Patients may need to be catheterized if large residual volumes exist postvoid. These patients are at higher risk for urinary tract infections, and may need prophylactic therapy. Appropriate medications include sulfamethoxazole/trimethoprim, cephalexin, and nitrofurantoin. Dietary fiber and hydration will help constipation, the primary bowel complaint.4
Major Depression. Patients with MS tend to be more prone to depression, especially when receiving biologic response modifier therapy. These patients should be evaluated and treated appropriately.  

Sensory Symptoms. Patients who have numbness and paresthesia, both normal complaints in MS, may not need to be treated. If the patient develops acute or chronic pain, such as trigeminal neuralgia or painful dysesthesias, treatment is indicated. Carbamazepine is the preferred agent at doses between 400mg and 1200mg per day. Tricyclic antidepressants, gabapentin, pregabalin, and duloxetine can also be used.  

Sexual Dysfunction. Male patients complaining of sexual dysfunction may be treated with sildenafil, tadalfil, vardenafil, or alprostadil injection or suppository. The use of sildenafil in females suffering from sexual dysfunction with MS is currently being studied.  

Fatigue. Treatment of fatigue in MS patients is often not considered. Methylphenidate, dextroamphetamine, and modafinil have all been commonly used. Fluoxetine can be used to alleviate both fatigue and depressive symptoms.  

Overview and Summary  

Multiple sclerosis is a lifelong disease usually caused by inflammation. Its course can be classified into four categories, and patients typically complain of weakness, fatigue, paresthesias, and sensory problems. Biologic response modifiers are the mainstay of treatment, mediating the immune attack on the neurons. Since there is no cure, symptom management is key to maintaining patients’ quality of life. As very accessible healthcare professionals, pharmacists can help patients manage their symptoms through monitoring and medication recommendations. Pharmacists can also help reduce patient’s cost by recommending the most cost-effective therapy to help manage their disease state.  

References  

22. Gilenya (fingolimod) [product information]. East Hanover (NJ): Novartis; September 2010.

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