Multiple Sclerosis and Its Symptoms

LEARNING OBJECTIVES
Upon completion of this module, the subscriber will be able to:

1. Recognize who is affected by multiple sclerosis (MS) along with the disease process and risk factors for MS.
2. Describe the common symptoms of multiple sclerosis.
3. Define clinical isolated syndrome (CIS) and subtypes of multiple sclerosis.
5. List the generic and brand name, route of administration, and common side effects associated with medications used in the management of multiple sclerosis.

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Managing Multiple Sclerosis and Its Symptoms

Introduction to Multiple Sclerosis: “What is it and who is affected?”

Multiple sclerosis (MS) is an incurable, chronic, progressive, inflammatory neurodegenerative disorder of the central nervous system (CNS). In other words, MS is a lifelong disorder that worsens over time and is characterized by inflammation, destruction and death of neuronal cells of the brain and the spinal cord (spine) (Figure 1A). There is currently no cure. Commonly affected areas of the brain are the optic nerves, cerebellum, brain stem, and cerebral cortex. The term “multiple sclerosis” was derived from two hallmark characteristics of this disorder: 1) “multiple” affected areas of the brain and spine that produce “multiple” different symptoms and disability, and 2) highly characteristic “sclerosed” areas (scar-forming) in the brain and spine, also called lesions or plaques, that can be seen in individuals with MS using different imaging techniques. These lesions or plaques are areas of inflammation, swelling, injury and destruction of neuronal cells.

MS currently affects about 2.5 million people worldwide and is reported in all ethnic/racial groups. It appears more frequently in Caucasians than in Hispanics or African Americans and is relatively rare in Asians and most other ethnic groups. Currently there are over 400,000 people in the United States (US) living with MS. It is estimated that every week there are about 200 newly diagnosed cases in the US. A person is usually diagnosed with MS between the ages of 20 and 50. The average age of onset is 30 years old and the most common age at onset is between 23-24 years old. There are only a small number of cases that are first diagnosed in persons under 20 or over 60 years of age. Caucasians of Northern European descent (Finnish, Norwegian, Danish, Swedish and Icelandic) have higher rates of the disease compared to other Caucasian populations. There is a clear sex-based difference with females being two times more likely to develop MS compared to males. Females tend to experience MS symptoms earlier with onset being an average of five years younger compared to males.

Impact of Multiple Sclerosis: “What is the impact of MS on the quality of life of an individual?”

MS is a very heterogeneous and multifaceted disorder. This means that the course of MS, symptoms, severity and level of disability are highly variable and unpredictable. It is very important to keep in mind that each patient might...
be affected in different ways. Patients may experience different symptoms, different symptom intensity, different disease severity and different disabilities. The extent of damage that occurs in the CNS usually correlates with the level of disability that a patient experiences. The damage to the brain and spine due to MS can eventually lead to a loss of neuronal connections between different parts of the CNS and the rest of your body. This leads to neurological disability by affecting basic human functions such as the ability to walk, the ability to coordinate hands and fingers, the sense of touch, bowel movement and urination, mood, and even cognition (thinking/knowledge).

MS is the most common non-traumatic cause of neurologic disability among young and middle-aged adults. In addition, MS is a leading cause of disability among young women of childbearing age and the second leading cause of disability among young men. Disability in individuals with MS can range from minimal (mild) to severe. With increased time living with the disease, there is typically more accumulated damage to the brain and spine and thus more neurological disability. Within 15-20 years, patients might have problems with walking and will need to use different devices for assistance such as crutches, canes, or walkers. Some persons, even when treated appropriately, may experience severe disability and may be confined to a chair or bed; have difficulty or be unable to speak; and even have difficulty swallowing foods, liquids or their own saliva (dysphagia). Therefore it is very difficult to predict the impact of MS on an individual and every MS case should be managed as such.

Because affected individuals usually experience some level of disability during their most productive years, the economic and emotional toll of this disease can be enormous for patients, their families and society. Lifespan for persons with MS is only marginally shortened (by 6-7 years) compared with the general population. Unfortunately, suicide is a significant problem and has a negative impact on the reported survival rate. This means that patients and their families should be well-educated on multiple sclerosis because, despite the fact that it is an incurable disease associated with cumulative (increasing) disability, there is an effective treatment available for managing the majority of MS symptoms. This treatment has also been shown to be effective in slowing down disease progression and associated disability in the majority of patients with MS. This is very different from other CNS disorders such as Lou Gehrig's disease (amyotrophic lateral sclerosis), where lifespan expectancy is shortened significantly and individuals typically survive only 2-5 years after they are diagnosed.

Pathogenesis and Etiology: “What is happening in the brain and spinal cord of an individual with MS and what is causing it?”

The cells affected by MS are two specific types of neuronal cells, neurons and oligodendrocytes, located in the brain and spinal cord. Oligodendrocytes are located only in the CNS; however, neurons are present in both the CNS and the peripheral nervous system (PNS, the nervous system located outside of the brain and spine). It needs to be noted that the previously-mentioned neuronal cells, only located in the CNS, are affected in MS. In order to explain what is happening in the brain and spinal cord of persons suffering from MS, it is very important to understand something about the structure and function of a neuron and explain what an oligodendrocyte is and what its function is.

A neuron is a building block of the CNS. It is a cell specialized to carry “messages” or neuronal impulses through an electrochemical process using electric current and chemical molecules called neurotransmitters (i.e., dopamine, acetylcholine, norepinephrine, and serotonin). Neurons communicate with each other through these electrochemical processes and this enables communication between different parts of the brain, spine and other parts of the body outside of the CNS such as muscles and organs. Therefore, neurons play a very important role in shaping who we are and how we function including: movement; muscle strength and coordination; sensation; memory; and emotions, among other things. A typical neuron is composed of different parts (Figure 2), each fulfilling a specific role.

The cell body, also called soma, contains the nucleus with genes and other organelles such as mitochondria, the Golgi apparatus, and the endoplasmic reticulum. A single neuron has only one cell body which is responsible for basic processes such as protein synthesis, energy production and toxin elimination in order to maintain the life of the neuron. A neuron is the only human cell that has specialized cell parts called dendrites and axons. Dendrites are short fibers that extend from the cell body, branch like a tree, and act like message receivers. A single neuron usually has multiple dendrites receiving information from adjacent neurons and bringing messages into the cell body. A neuron has usually only one axon, a long thin fiber that can be up to 1 meter long. This specialized structure acts as a signal conductor. The message from adjacent cells, received via dendrites, is then moved from the cell body along the axon to the dendrites of an adjacent cell or cells.
In this way, the message is moved, for example, from one part of the brain to another or from the brain to the spinal cord.

There is another important component necessary for a well-functioning neuron and effective message conduction. This component is called myelin or myelin sheath. Myelin is a whitish substance primarily composed of fatty substances (lipids) and a small amount of protein that forms multiple, thin layers around the axons (Figure 1B). Myelin is present in both the CNS and the PNS, but MS affects only the myelin in the brain and spine. Myelin in the brain and spine is a product of other specific neuronal cells called oligodendrocytes which are specific CNS myelinating cells. A single oligodendrocyte can provide myelin layers for many different axons. A myelin sheath that is about 1 micron thick has multiple different functions. First, it acts as insulation and is necessary for effective conduction of nerve impulses via the axon. If we would compare an axon to an electrical wire and nerve impulse to electricity, the myelin sheath acts like the insulation around the wire. Therefore, an axon with damaged and uneven layers of myelin can be compared to a corroded electric wire where, without insulation, the electricity would not be conducted in an appropriate and controlled manner to a specific location. Second, myelin acts as a physical and chemical protective barrier for the thin and vulnerable axon. It protects the axon from the outside environment including different chemicals and other cells.

So what is happening in the brain and spinal cord of a patient with MS? In a patient with MS, the myelin sheath surrounding the axons, located in the brain and spinal cord, are damaged. This leads to loss of the myelin (Figure 1C). As the disease progresses, the axons may be damaged, and the patient’s brain might shrink (brain atrophy) due to death of myelinated neurons. All these are prominent pathologic features of different MS lesions in the CNS. Importantly, axonal damage might be closely correlated with progression (advancement) of disability in MS patients.

The loss of myelin in the CNS neurons is a process called demyelination. The demyelination leads to several consequences: 1) axons are no longer protected and are exposed to the surrounding environments and chemicals that can negatively impact the well-being of these cells, and 2) axons are no longer insulated. This slows down or impairs message conduction between the axon of one cell and the dendrites of another cell. In addition, eventual axon damage and loss of myelinated neurons can lead to complete loss of connection between different cells in the brain and spinal cord, and complete hinderance of message conduction. This will significantly impact the communication between the brain, spine and other parts of the body such as the eyes or muscles of legs, arms or bladder.

Is MS contagious? Newly diagnosed patients and their families are often wondering whether MS is contagious and if they can be infected with this disease or potentially infect others. MS is not a contagious disease and there is no risk to acquire the disease by interacting with affected individuals.

So what is causing demyelination and injury and destruction of myelinated cells? The precise cause of MS and the origin of inflammatory reactions and subsequent death of myelinated neurons remain unknown; however, it is most likely multifactorial. Pathologically, MS is characterized by the presence of areas of demyelination and specific white blood cells causing inflammation in the brain.
and spine.\textsuperscript{2-3} It is believed that an abnormal immune reaction in MS initiates an attack on the myelin and axons resulting in lesions and brain damage. The complex and abnormal immune response is carried by inappropriately stimulated immune system components and cells, such as complement, white blood cells called T-cells and B-cells (antibody-producing cells), and engulfing cells that act like vacuums for damaged cells and parts (macrophages), that will travel to different areas of the brain and spinal cord.\textsuperscript{10-11} The complex interplay of a variety of cells, antibodies, and other immune-related substances leading to localized damage to oligodendrocytes, stripping the myelin sheaths around CNS axons and axon destruction, remains to be elucidated.

One of the proposed immune theories suggests that MS starts as an inflammatory autoimmune disorder.\textsuperscript{12} This theory suggests that the patient’s own immune system attacks myelinated cells and oligodendrocytes in the CNS because the immune system does not recognize CNS myelin as a normal part of their own body. It will start to attack myelin as it would attack any foreign agent such as bacteria. As an example, the presence of bacteria in the brain would lead to an activation of T-cells and macrophages that would travel to the brain and start to destroy the bacteria in order to protect the brain against this invader. Unfortunately, in the case of MS, the myelin in the brain and spine is a normal and necessary component of the CNS and its destruction by the immune system causes harm. One needs to keep in mind, however, that there is still not sufficient evidence to know without a doubt that an autoimmune response triggers MS.

Risk Factors:

\textit{“Is there anything that can predispose an individual to MS?”}

Currently, the precise cause of MS is unknown, but it appears to involve a combination of genetic predisposition (genetically-susceptible individuals) and non-genetic triggers/factors. Various factors have been linked to an increased risk for

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Test Your Knowledge #1:
Name the parts of the neuron.

1. ___________________________________________
2. ___________________________________________
3. ___________________________________________
4. ___________________________________________
5. ___________________________________________

\textit{Figure reproduced with permission from Mayo Foundation}

Test Your Knowledge #2:
Pair the number (description) with the letter (term). Only 1/term.

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ____ Fat substance providing axon insulation</td>
<td>A. inflammation</td>
</tr>
<tr>
<td>2. ____ Term that describes loss of myelin</td>
<td>B. myelin</td>
</tr>
<tr>
<td>3. ____ Part of the neuron that receives a message from other neurons</td>
<td>C. lesion</td>
</tr>
<tr>
<td>4. ____ Part of the neuron that conducts a signal to other neurons</td>
<td>D. dendrites</td>
</tr>
<tr>
<td>5. ____ Brain area of demyelination and inflammation</td>
<td>E. demyelination</td>
</tr>
<tr>
<td>6. ____ Immune reaction in MS characterized by over-activated lymphocytes in the CNS</td>
<td>F. axon</td>
</tr>
</tbody>
</table>
developing MS and/or worsening of the disease. These factors can be broadly divided into sex, genetic factors, and environmental factors. As shown in Figure 3, there is an interplay among different factors that is necessary for a patient to develop MS. It requires genetically-susceptible individuals to be exposed to a set of environmental factors which subsequently can trigger the inappropriate immune response seen in the brain and the spinal cord of a person with MS. In the future, these factors may help us to determine the exact triggers and causes for MS and to develop more effective ways to treat or even cure MS. As mentioned previously, females are at least twice as likely to be affected by MS compared to men. Therefore, being female can be one of the risk factors for MS.

**So does it mean that if I’m a woman I will develop MS?** No. It only means that being female increases your risk for MS. However, as mentioned above, the interplay of genetic susceptibility and other environmental factors needs to happen before an individual will develop MS.

Genetic susceptibility to MS is suspected based on the widely differing prevalence of MS in different ethnic/racial populations. The highest risk for MS is among Caucasians, especially in those of Northern European descent, while the risk is lower for Asians and Eskimos. Different genes, usually those associated with immune system function, have been linked with an increased risk for MS. For example, genetic variations of the gene coding for class I and II of major histocompatibility complex (MHC), also known as human leukocyte antigen (HLA), were linked with risk for MS. These proteins help the immune system distinguish the body’s own particles from foreign invaders such as viruses and bacteria. It is clear that variation in an individual’s genetic material (genes) alone is not capable of causing MS and that other factors need to be present. It needs to be noted that MS is not a purely genetic disorder. Recent studies suggest a strong environmental component because no straightforward inheritance pattern can fully explain the incidence of MS and only a small portion of patients with MS have a known relative with MS. Having a first-degree relative with MS can increase someone’s risk for developing the disease by 20-fold. This means that if your sibling or at least one of your parents has MS, you have an increased risk for MS compared to the general population.

The environmental factors/agents with the strongest supporting evidence are geographic location, lifestyle or behavior, vitamin D levels, smoking, and obesity. In addition, there is some evidence that lifetime experience of infection with the Epstein-Barr virus (EBV) can be potentially linked to an increased risk for MS.

**Geographical mapping of MS worldwide revealed a possible relationship between the risk for MS and location.** MS is rare in the tropics and increases in frequency as distance from the equator increases. Areas with cold climates such as the northern US, Canada, and the northern part of Europe have high reported incidences of MS. Interestingly, migration studies suggest that the risk for acquiring MS is related to the location in which one has lived before puberty (age less than 15 years). Individuals migrating from high to low risk areas early in life can decrease their risk for the development of MS. On the other hand, migration from low to high risk areas increases the risk for the development of MS. These data suggest that exposure before puberty to some environmental agents/factors in these geographic locations may increase the risk for developing MS later on. There is currently no known explanation for this.
There is increasing evidence that vitamin D may play a role in MS. Recent studies indicate that higher serum levels of vitamin D correlate with a decreased risk for MS.\textsuperscript{20,21} It is however currently unclear whether dietary changes or supplements high in vitamin D alter the risk for MS development. Interestingly, vitamin D levels and the risk of vitamin D deficiency for MS can also be one of the proposed explanations for the possible association of colder climates (distance from equator) with the risk for MS. In humans, natural vitamin D is synthesized (created) in the skin from a precursor that is activated by ultraviolet (UV) radiation from sunlight. Sunlight exposure is a major source for natural vitamin D and therefore people living in warmer climates and residing closer to the equator are more commonly exposed to sunlight and thus produce higher levels of naturally-synthesized vitamin D. Potentially, this means that judicious exposure to sunlight can be protective against MS because of vitamin D synthesis.\textsuperscript{15} However, it could also mean that UV radiation may be protective against MS alone or may simply modify some additional factor or agent involved in MS. In addition to risk for MS, higher vitamin D levels have been reported to be associated with a lower acute (sudden) attack risk in persons already diagnosed with MS.\textsuperscript{21}

There is also evidence suggesting there is an association between smoking and MS. Multiple studies found a higher risk for MS in smokers compared to non-smokers.\textsuperscript{22} Smoking is also a potential risk factor for MS progression.\textsuperscript{23,24} Based on current evidence, it is important to counsel MS patients on the importance of smoking cessation. In addition, excess body weight has been reported to be associated with an increased risk for MS.\textsuperscript{25}

Because the pathogenesis of MS is thought to involve the immune system, it has been hypothesized that a stimulus of the immune system by an agent such as a virus or immunization may trigger the disease. There is no current evidence suggesting an association between vaccinations and MS risk. In the general population that does not have MS, vaccinations against hepatitis B, influenza, tetanus, measles, mumps and rubella are not associated with an increased risk for MS.\textsuperscript{26-27} It is very important to communicate this information to our patients, relatives and friends since the media or other unreliable sources might promote otherwise. Another potential immune system stimulator that has received much attention is Epstein-Barr virus (EBV). This is a small virus that causes infectious mononucleosis. This virus is extensively discussed in the literature as a possible cause or trigger for MS. Several studies have demonstrated an increased risk for MS in individuals after infectious mononucleosis.\textsuperscript{28-30} These findings do not confirm that EBV is an etiologic (causing) agent, but they are suggestive and warrant further study at this time.

Note: In the rest of the text of this training we will be following a single individual who is suffering from MS. Every time this icon \includegraphics[width=1em]{icon-smiley.png} appears in the text, it is a continuation of our case.

Test Your Knowledge #3:
Based on geographical locations and the information below, which of the following individuals (case 1 or case 2) decreased their risk for MS?

<table>
<thead>
<tr>
<th>Yes/No</th>
<th>Case 1: An 8-year old female who was born in Rochester, MN relocated to Miami, FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td>Case 2: A 22-year-old female born in Rochester, MN who relocated to Miami, FL</td>
</tr>
</tbody>
</table>

Multiple Sclerosis Case
“MEET CHARLOTTE”: Part 1

Charlotte is a thin, 24 year-old Caucasian female who visits her primary care physician with complaints of sudden blurred vision in her left eye and gradual onset of weakness in her left leg over the course of the past three days. The leg weakness is accompanied by walking difficulty and the blurred vision makes it impossible for her to drive, study or attend lectures.

Charlotte is a second-year medical student at the University of Minnesota and lives in Duluth, MN where she was born and raised. She is otherwise healthy with no history of neurological or vision problems. She has a history of vitamin D deficiency and her current serum vitamin D levels are below normal (vitamin D deficiency). She began smoking at age 17 (10-15 cigarettes/day) but quit a year ago to be a better example for her future patients.
Charlotte is the only daughter of Danish parents who relocated to the United States 30 years ago from Copenhagen, Denmark. Her father is healthy and her mother was diagnosed with MS at the age of 22.

Clinical Presentation of Multiple Sclerosis:
“What clinical symptoms does a patient with MS usually experience?”

There are a number of MS symptoms, with some being more disabling or bothersome than others. These symptoms are the result of the positions of lesions within the brain and the spinal cord and thus are highly variable. In addition, the intensity of symptoms is usually related to the amount of damage. Therefore, MS symptoms vary widely among different individuals and no two people will experience exactly the same symptoms, severity, frequency or duration. There are no specific symptoms that are only characteristic of MS; however, some of them are very common and quite typical for MS. It is when these symptoms are bothersome that a person usually seeks medical help which may eventually lead to the diagnosis of MS. However, some patients might experience only very weak symptoms that disappear in a few days or weeks and have no other reason to suspect they might be sick. This will delay a diagnosis of MS.

The most common early symptoms of MS are:31-32
1) problems with vision such as blurred vision or double vision;
2) problems with the sensory system including numbness, tingling or pain in parts of the body;
3) weakness in one or more limbs;
4) muscle spasms;
5) clumsiness or lack of coordination;
6) fatigue;
7) dizziness or vertigo; and/or
8) bladder problems

A person with MS may experience one or more of these symptoms at the onset of MS. These symptoms are commonly experienced early in the disease and come and go later during the course of the disease.

Visual problems are very commonly reported in persons with MS. The most common problem is optic neuritis and double vision. It is estimated that almost 70 percent of MS patients have at least one episode of optic neuritis during their lifetime and that it is frequently one of the first symptoms experienced.32 Optic neuritis is an inflammation of the optic nerve and is associated with sudden blurred vision and eye pain, as well as with graying of colors and temporary loss of vision (blindness), usually in one eye at a time.33 It is very uncommon that both eyes would be affected at the same time. The optic nerve is responsible for transmission of messages from the eye into the brain (Figure 4, page 10). These symptoms might resolve without treatment, but there is the risk that if inflammation of the optic nerve is left untreated, it may lead to permanent damage to the optic nerve and result in permanent and/or severe loss of vision. Double vision is a symptom that is usually associated with inflammation and a lesion in the cerebellum which is another part of the brain.

Persons with MS often report problems with sensation such as tingling, numbness, and even painful itching and burning in different parts of the body such as the legs, arms, trunk, and face. Tingling or pricking is usually reported as “pins and needles,” an “electric-like” sensation following the spine or a “crawling” sensation. Loss of sensation, as well as loss of feeling in the extremities (numbness), are also reported and can affect walking and dexterity of an individual. Problems with sensation can be experienced anytime during the course of the disease, however about one third of persons with MS will present initially with sensory disturbances involving their limbs. One of the sensory symptoms experienced in MS is electric shock radiating into the arms and legs or down the spine that is precipitated (caused) by turning the neck or

Test Your Knowledge #4:
From this case, identify all the risk factors for MS development that are present for Charlotte.

1. ________________________________________ 5. ________________________________________
2. ________________________________________ 6. ________________________________________
3. ________________________________________ 7. ________________________________________
4. ________________________________________
head. This is associated with a lesion or lesions in the spinal cord. Other symptoms commonly associated with muscles and coordination include: clumsiness and difficulty standing; difficulty in performing coordinated motions with the arms; walking; or even difficulty speaking. The parts of the body typically affected are the arms and legs with the leg(s) being most commonly affected. Due to the damage of specific neurons (motor neurons) in the brain and spine that are responsible for bringing information from the CNS to the muscles, the control of skeletal muscle movement can be lost. Depending on the location of neuronal damage and the amount of damaged neurons, only one muscle or entire groups of muscles may be affected. As an example, you might see a patient with MS who reports weakness in one leg (as our patient Charlotte), in one arm, in both legs, or in all extremities. General muscle weakness is associated with low muscle tone and coordination making it very hard for someone to walk if either leg is affected. On the other hand, spasticity is an increased tone of muscles due to inappropriate muscle stimulation by the CNS that is also referred to as an unusual “tightness,” “stiffness,” or “pull” of muscles. The muscles may tighten (spasticity) and/or contract spontaneously (spasm). Spasticity might range from mild stiffness to strong, painful muscle spasms. It can negatively impact someone's ability to move; make it harder to walk or write; and can also lead to painful muscle spasms. The most common area affected by spasticity is the legs. Both muscle weakness and spasticity involve problems with muscle coordination. However, the muscles themselves are not damaged. In addition to muscle weakness and spasticity, problems with gait and balance are common in MS and may cause a person to sway or stagger, and might result in the need for a walking aid to help prevent falls and to facilitate walking. Another symptom that can affect someone's ability to stand or walk is dizziness or lightheadedness. Some patients experience vertigo which is a more severe type of dizziness associated with a feeling of “spinning” motion. A person typically reports the sensation that objects in the environment are moving and that the person is also moving. In addition, vertigo can be associated with nausea and vomiting. Dizziness can be associated with the risk for falls and can dramatically affect a person's ability to stand and/or walk. Almost 90 percent of all persons with MS will experience some level of bladder problems. Bladder problems are usually associated with either feeling the need to urinate often during the day or night, or trouble emptying the bladder fully. This can cause a person distress and significantly affect his/her quality of life. The urgent need to urinate during the night can affect both the quantity and quality of sleep and may contribute to tiredness and fatigue during the day due to a lack of sleep. Frequent urgency to urinate during the day can lead to constant visits to the bathroom, increased hesitancy of an individual to leave the house due to a constant need to use the bathroom, and even lead to incontinence (loss of bladder control). Bladder problems can also lead to an increased rate of urinary tract infections (UTIs). What other symptoms can persons experience while living with MS? Something that is a very typical feature of MS is sensitivity to heat. This means that persons become intolerant to increased temperature accompanying increased activity (exercise) or external sources such as hot weather, hot baths and showers, pools, saunas and hot tubs. An increase in body temperature can worsen MS symptoms or even produce new ones. This occurs because
Managing Multiple Sclerosis and Its Symptoms

Elevated body temperature slows nerve message conduction in the axons; axons that already have poor conductivity due to damaged myelin. Simply speaking, any symptoms that a person experiences due to brain and/or spinal cord lesions can become much worse in the heat. The good news is that these worsening or heat-related symptoms are only temporary and are generally rapidly reversed when the heat-inducing factor returns to normal. These events do not produce permanent nerve damage. Sometimes persons might experience new symptoms in the heat which is the result of a lesion in a corresponding area of the brain or spinal cord that was small enough that it did not cause any symptoms that could be noticed. For instance, blurred vision can be experienced as a result of heat exposure in those persons with MS who have a small lesion on the optic nerve but never had major symptoms of optic neuritis, and who may even be unaware that they ever had it. Due to this sensitivity, persons need to be cautious about spending time in hot weather, rigorous exercise, drinking warm beverages, and using hot tubs, saunas and pools (with water warmer than 85°F). Therefore, careful planning of outdoor activities, especially during warm months, needs to occur. For some people, heat intolerance can be debilitating enough that they are unable to function well at even slightly elevated temperatures. These individuals may need to consider moving to a cooler geographic location. **Table 1** lists possible strategies that can help to manage heat intolerance.

<table>
<thead>
<tr>
<th>Table 1. Strategies to Overcome the Effect of Heat on MS and Its Symptoms[^36]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What can a person with MS do about the heat?</strong></td>
</tr>
<tr>
<td>• Avoid extreme temperatures (hot baths, showers, saunas)</td>
</tr>
<tr>
<td>• Stay in an air-conditioned environment during extreme heat and humidity</td>
</tr>
<tr>
<td>• Use cooling aids (cold packs, moistened vest, bandana) during exercise and outdoor activities</td>
</tr>
<tr>
<td>• Wear lightweight and breathable clothes that are well ventilated and moisture-wicking</td>
</tr>
<tr>
<td>• Drink cold beverages such as slushes or iced coffee or consume cold foods (e.g. popsicles) for temporary relief while in warmer environments or climates</td>
</tr>
<tr>
<td>• Use oscillating fans in rooms without air-conditioning or during outdoor activity</td>
</tr>
<tr>
<td>• Do not take hot showers or baths</td>
</tr>
<tr>
<td>• Exercise in a cool pool with a temperature below 85°F</td>
</tr>
</tbody>
</table>

Other symptoms that are common in MS but may not be seen initially are fatigue; sexual dysfunction; mild tremor or shaking of extremities and (occasionally) head; depression; and/or stress.[^32,^36] As the disease progresses, some persons might also experience problems with memory, attention and concentration, and inappropriate outbursts of crying and laughing (pseudobulbar affect). In the most severe cases, persons might lose the ability to stand, walk, speak clearly or swallow.[^32]

One of the major complaints typical of a person with MS is **fatigue**[^32]. Almost every single person with MS will report it. It is a result of demyelinating pathological processes and damage in the CNS and is usually a long-term problem. Fatigue specific to MS, also known as MS-related fatigue or primary fatigue, is quite unique and can be differentiated from other types of fatigue (see Table 2). This occurs nearly every day, might be present in the morning even after a good night’s sleep, is described as physical exhaustion that is not directly related to increased activity, and usually worsens in the late afternoon. It can be worsened by humidity and heat and is quite severe and bothersome. Fatigue has a direct impact on the quality of life for persons with MS due to its interference with daily activities such as working, cleaning, and cooking. In addition, fatigue slows down movement and thinking processes, reduces energy and endurance for everything, and affects mood and the ability to cope. Persons usually report difficulty even meeting their own basic needs such as hygiene or eating due to an overwhelming tiredness that makes everything very difficult. When a person with MS is asked about the most bothersome symptoms, many persons consider fatigue to be the worst MS symptom. What can be very troublesome for persons with MS is that MS-related fatigue is quite a

<table>
<thead>
<tr>
<th>Table 2. Characteristics of MS-Related Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What makes MS-related fatigue unique?</strong></td>
</tr>
<tr>
<td>• Usually occurs every day</td>
</tr>
<tr>
<td>• Occurs even with sufficient sleep during the previous night</td>
</tr>
<tr>
<td>• Overwhelming tiredness that is not directly related to increased activity (lassitude)</td>
</tr>
<tr>
<td>• Worsens in the late afternoon</td>
</tr>
<tr>
<td>• Worsens and is aggravated by heat and humidity</td>
</tr>
<tr>
<td>• Develops suddenly</td>
</tr>
<tr>
<td>• Generally more severe than normal fatigue</td>
</tr>
<tr>
<td>• Interferes with normal daily life (ie., working, cleaning, cooking, speed of thinking and movement)</td>
</tr>
</tbody>
</table>
debilitating symptom affecting normal daily life and quality of life that is invisible to others. Thus it is quite difficult for family members, friends and employers to understand. Importantly, this severe fatigue is actually one of the major reasons for unemployment among persons with MS.

In addition to fatigue caused by the disease itself, fatigue in MS patients can also be due to other problems such as lack of sleep due to night urges to urinate, insomnia, pain, muscle cramps, spasticity or depression; and also due to the sedative side effects of common medications used to treat MS such as muscle relaxants and steroids.32,36

Sexual dysfunction occurs in about 70 percent of persons with MS. Both females and males may be affected by it and it is characterized by low responsiveness to touch, decreased libido (sex drive) and trouble reaching orgasm. Females may also report severe vaginal dryness. Males may report erectile dysfunction. Sexual dysfunction can be worsened by fatigue, side effects of antidepressants, decreased sensation, depression and even spasticity.32

About half of all persons with MS may have some level of difficulty with concentration, attention, slowed mental processing (thinking), and remembering recent information/events (short-term memory). In only a small percentage of cases (5-10%), these cognitive problems can be so severe that they significantly impair the ability to carry out activities of daily living and may result in severe dementia. However, slowed mental processing, lack of concentration, challenges with reasoning, and memory difficulties can affect the person’s productivity at work or may even lead to unemployment.32

Psychiatric manifestations can also be common. Approximately half of all persons with MS will experience an episode during the course of their illness. Depression in MS can be the result of various factors: 1) the disease itself when parts of the brain that are responsible for emotional control are damaged; 2) the result of difficult situations due to MS complications and disability; and 3) side effects of drugs used for treatment of MS such as steroids and disease-modifying treatments.32 Not only can depression be associated with depressed mood or feeling down, but it can also be associated with a lack of interest in seeking pleasure; difficulty sleeping; lack of appetite; fatigue; and worsening cognition. Since depression can worsen other types of MS symptoms, it should be recognized and treated to improve the quality of life of individuals with MS. In addition, it needs to be noted that people with MS are at a higher risk for suicide compared to the general population.8 Healthcare providers should have an awareness regarding the increased risk of suicide in persons with MS. Another psychiatric problem associated with MS is the pseudobulbar affect (PBA). This is characterized by episodes of uncontrollable laughing and/or crying. Currently it is estimated that about 10 percent of persons may experience PBA.37 This emotional condition is caused by a lesion or lesions in a specific part of the brain that controls emotions. Someone might have severe emotional outbursts that are inappropriate for the current situation. This is beyond their control. For example, a person may laugh uncontrollably, even at a funeral, while inner feelings may be sadness.

Types of Multiple Sclerosis:
“Based on disease progression what type of MS can a patient experience?”

MS is usually classified into four subtypes (Figure 5) based on disease progression of disability and the presence of relapses or acute attacks: 1) relapsing-remitting multiple sclerosis (RRMS), 2) secondary progressive multiple sclerosis (SPMS), 3) primary progressive multiple sclerosis (PPMS), and 4) progressive-relapsing multiple sclerosis (PRMS).1,38

RRMS is the most common form of the disease, affecting about 85 percent of all MS patients.1,39 RRMS is characterized by alternating periods of relapses and remissions, when these symptoms improve or completely resolve. Relapse, also known as acute exacerbation, flare-up, or attack, is defined as the development of new or recurring symptom(s) which last(s) at least 24 hours and is/are at least 30 days after the previous attack. It is caused by acute inflammation that occurs when the immune system attacks the myelin surrounding the nerves in the brain or spinal cord. Symptoms experienced by the patient result directly from this acute inflammation in the CNS and represent the formation of a new lesion or lesions. Different neurologic symptoms may develop suddenly or over a few days such as fatigue, arm or leg weakness, or blurred vision. A person might experience one or more symptoms during this time. These attacks/relapses are remarkably unpredictable and very heterogeneous. The patient never knows what symptom or symptoms might appear or when. A relapse can eventually resolve on its own and usually a person will return to the original level of functioning or will experience a significant improve-
Managing Multiple Sclerosis and Its Symptoms

The progression of disability due to MS is highly variable. The level of disability can be measured by using the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS provides a total score on a scale from zero to 10 with a higher number being associated with greater disability. The first levels (1.0 - 4.5) refer to people with a high degree of ambulatory ability (mobility). Subsequent levels (5.0 - 9.5) refer to loss of ambulatory ability. In general, RRMS progresses slowly and disability accumulates over 10-20 years. Patients tend to be ambulatory (a score of 4.5 or less) for a very long period after diagnosis.

After an average of 27 years from the disease onset, they will reach EDSS 6 when a cane is needed for walking. Persons affected by SPMS usually have a score of six or higher, meaning that some form of assistance is needed to walk. Generally, at this time, persons will need constant walking assistance with canes, crutches or leg braces and, as the disease progresses and more disability accumulates, may eventually need a wheelchair or scooter and later be chair- or bed-bound with very limited mobility. In the most advanced state, a person is no longer able to communicate, move, swallow or eat and eventually will pass away.

About 10-15 percent of people will be diagnosed with PPMS that is very disabling and is associated with a steady progression with no relapses or symptom remission. PRMS is a rare type of MS reported in only about 5 percent of those diagnosed with MS. Symptoms continue to worsen gradually from the onset of the disease, with occasional exacerbations of worsening symptoms. There are no periods of symptom remission or disease/symptom stabilization.

Figure 5. Subtypes of Multiple Sclerosis.
Four major types of MS have been proposed based on MS classification developed by a consensus of MS experts.
Diagnosis and Disease Course of Multiple Sclerosis:
“How do we know that someone has MS and what tests might be helpful to support this diagnosis?”

Multiple sclerosis can be difficult to diagnose due to the complexity of the disease. There are no clinical symptoms or findings unique to MS and other diseases can have similar symptoms. Some clinical findings such as optic neuritis, onset between the ages of 15-50 years, electric sensation projecting down the spine or to the extremities upon neck turning, and persistent fatigue can be highly characteristic of MS. In addition, some symptoms might not be sudden or dramatic and might not interfere with normal daily life and thus might not even be noticed by the patient. Usually patients seek medical help when moderate to severe symptoms interfere with daily life.

MS is a clinical diagnosis. Clinical diagnosis means that a disease is diagnosed solely based on the various clinical findings such as review of a patient’s symptoms, the patient’s history, a physical exam and family history. Importantly, there is no single diagnostic test that can be utilized to diagnose a patient with complete certainty. In comparison, diabetes or high blood pressure can be easily and rapidly diagnosed using a single diagnostic test such as fasting plasma glucose or glycosylated hemoglobin A1C for diabetes, and blood pressure readings for high blood pressure (hypertension). It is far less simple and straightforward to arrive at a diagnosis of MS.

The 2010 McDonald diagnostic criteria incorporate clinical exam and supportive tests’ findings for diagnosis, and allow an earlier and often accurate diagnosis based on history of attacks and myelin destruction in more than one area of the CNS. Quite simply, MS is diagnosed clinically through the demonstration of the CNS lesions disseminated across SPACE: the presence of at least two different lesions in the CNS (two lesions in different areas of the brain; or one lesion in the brain and one lesion in the spinal cord; or two different lesions in the spine), and TIME: experience of at least two different episodes or acute attacks involving one or more MS symptoms. This means that MS is diagnosed on the basis of two or more relapses involving two or more areas of the CNS over time. These revised criteria enable earlier diagnosis and thus earlier treatment to preserve brain tissue and slow progression of the disease.

The most useful and sensitive test that can aid in the diagnosis of MS is magnetic resonance imaging (MRI) of the brain (Figure 6) and spinal cord. Simply put, an MRI is a procedure to scan or visualize the inside of the body. An MRI machine looks like a long tube with a strong, circular magnet that uses a magnetic field and radio waves to create detailed structural images. An MRI is capable of detecting new and old lesions in the CNS. Not only can we see the size and number of lesions but we can also identify their locations. Importantly, MRI is painless and non-invasive (no entry into the body) and there is little or no preparation for this procedure. The patient is usually asked to change into a gown and to remove any metal objects. The patient lies down on the table, is positioned within the tube, and needs to remain still for a period of time. The coil with the magnet then moves to the specific area that is to be investigated. For MS, an MRI is useful to find any evidence of affected brain areas, or lesions, in the CNS. In this case, we are only interested in obtaining...
Managing Multiple Sclerosis and Its Symptoms

Prior to a definitive MS diagnosis (discussed above), individuals with a single acute attack (exacerbation) may often be diagnosed with a clinically isolated syndrome (CIS). A CIS is defined as a single acute exacerbation with neurologic dysfunction due to inflammatory demyelination in the spinal cord and/or brain that is followed by at least partial resolution in someone experiencing this for the first time. Common first symptoms associated with neurologic dysfunctions include optic neuritis, sensory disturbances such as tingling, muscle weakness in extremities, urinary urge, and problems with balance and coordination. MRI imaging of the spine and brain may reveal a single or multiple lesions. At this time, it is usually difficult to confirm dissemination in time or space. If the patient does not have a previous episode with MS symptoms or evidence from an MRI that would indicate prior lesion or lesions on the spine or brain, definitive diagnosis of MS cannot be confirmed and the individual is diagnosed with CIS. All patients with CIS are followed closely. So, how is CIS related to MS? Patients presenting with CIS are at increased risk for developing MS. Those individuals with CIS and an abnormal MRI readings that reveal lesions in the brain and/or spine are at increased risk. About 80 percent of patients with CIS and abnormal MRI will eventually develop MS, typically within 7-14 years, compared to 20 percent of those with CIS and a normal MRI. It is important to identify all patients who are experiencing CIS and especially those with high risk for MS development so that we may initiate specific treatments in those patients to prevent or further delay myelin and axonal damage in the CNS and delay disability due to damage.

So what happens if a patient with CIS develops a second attack with MS symptom(s)? A person who was previously diagnosed with CIS who experiences another relapse or acute exacerbation or a new lesion identified by a follow-up MRI can be diagnosed with MS.

To summarize the section on MS diagnosis, a typical person with MS presents as a young adult with two or more clinically-distinct attacks (relapses, exacerbations, flare-ups) associated with various MS-related symptoms such as numbness, tingling, urinary urgency, optic neuritis or impaired balance. An MRI will detect two or more lesions in different parts of the CNS. Presenting symptoms may
be either consistent with a single CNS lesion or consistent with more than one lesion. Based on the location of the lesion(s) or size of the lesion(s), the person might experience a single symptom (such as optic neuritis in the left eye that is associated with a lesion in the optic nerve of the left eye) or multiple symptoms associated with lesions in different parts of the brain and/or spine such as tingling and bladder problems or optic neuritis. In this way all requirements for MS diagnosis are fulfilled and there is evidence of lesion dissemination across time and space.

Charlotte was referred to a neurologist who evaluated her thoroughly and also ordered an MRI of her spinal cord and brain. The MRI scans reveal several new CNS lesions: one lesion in the brain (optic nerve) and one lesion in the spine.

Based on physical findings and the MRI results, Charlotte is diagnosed with optic neuritis and a clinical isolated syndrome (CIS). The neurologist suggests a follow-up visit in one month to repeat the MRI. In one month, no new lesion is identified and Charlotte has fully recovered from the optic neuritis.

**Teaching Points:**
1) In our case, Charlotte’s clinical presentation is consistent with a clinically isolated syndrome (CIS). She has neither prior history of any neurologic problems or disorder, nor any previous attack (exacerbation) with MS symptom(s). She is experiencing her first neurologic episode, also known as attack or exacerbation associated with optic neuritis characterized by blurred vision in her left eye and muscle weakness in her left leg. Both symptoms are very characteristic as early signs of CIS and MS. In addition, her MRI reveals two distinct lesions, one in the brain and one in the spine. At this time we are only able to provide evidence of dissemination across space by MRI but we are not able to provide dissemination across time since no previous symptom(s) or attack was reported.

2) Due to CIS and an abnormal MRI that shows two distinct lesions in the brain and spine, Charlotte has a very high risk, around 80 percent, to eventually develop MS within the next 7-14 years.

5 years later, Charlotte is experiencing bladder urgency and severe vertigo. An MRI reveals three new lesions in different parts of the brain.

**Teaching Points:**
1) At this time Charlotte is diagnosed with MS since we now have evidence of lesion dissemination across time and space as evidenced by MRI images and at least two acute exacerbation/relapses.

**Current Treatment Therapies for Multiple Sclerosis:**

“What can we do to help individuals with MS?”

There is no cure available for MS at this time. Management of MS can be divided into three basic types of treatments/strategies:

1) Treating relapses or acute exacerbations of symptom(s)
2) Disease-modifying treatment
3) Management of symptoms associated with MS

(1) Treatment of Relapses or Acute Exacerbations

Acute symptomatic exacerbations or relapses (when a patient is experiencing new symptoms or worsening symptoms) may be treated with a high dose of corticosteroids. Relapse or acute exacerbation is caused by an acute inflammation in different parts of the CNS and steroids are effective for rapid suppression of the immune system’s response and thus are capable of treating inflammation. The mechanism of action behind this effect is unclear, but it may involve inhibition of T-cells and preventing immune cells from entering the CNS. The corticosteroid treatment usually significantly shortens the duration of the most severe symptoms allowing for a faster return to normal activities. The decision is made to treat a relapse based on how much disability the symptoms are causing and how much they interfere with daily activities, especially symptoms increasing disability or impairment in vision, strength, mobility and coordination. Not every symptom of MS needs to be treated with steroids during a relapse. A patient who is experiencing mild tingling in the left foot that does not interfere with normal functioning may not need treatment since acute symptoms usually improve on their own in a matter of days or weeks. However, a patient who experiences numbness in the leg which interferes with walking, driving or other activities needs to be treated.
Corticosteroids are the mainstay in the treatment of acute relapses/exacerbations and are only used for short-term (a few days) treatment. They are not effective in changing the disease course or in decreasing the frequency of acute attacks or exacerbations and they do not impact any long-term outcomes of the disease. Their role is simply to treat the symptoms during relapses or acute exacerbations. The most common treatment is methylprednisolone (SoluMedrol) which is administered intravenously (IV) as 1,000 mg over 60 minutes daily for 3-5 days. If the patient is experiencing severe disability due to symptoms, s/he might be hospitalized. The duration of methylprednisolone therapy can be longer (up to 10 days), based on the judgment of individual clinicians. The response to this therapy is usually seen within five days of initiation. In addition, large doses of oral steroids might have comparable results to the intravenous route. Some patients might initially receive oral prednisone (Deltasone) in an equivalent therapeutic dose to IV methylprednisolone. Typically it is a 10-day treatment course consisting of five doses of 1,250 mg of oral prednisone administered every other day. It is important to understand this because a patient can appear in the pharmacy with a prescription for an unusually high dose of prednisone tablets. Oral therapy can avoid discomfort, inconvenience, as well as expense of IV therapy.

The most common side effects of short-term treatment with corticosteroids are: irritability; water retention (bloating) which can be associated with weight gain and swelling; metallic taste; increased appetite; and difficulty sleeping. In some patients, oral corticosteroids can also cause increased blood pressure, nausea, vomiting, diarrhea, peptic ulcers, and heartburn. Water retention and increases in blood pressure can be minimized during therapy by minimizing salt intake. If ankle swelling appears, it is recommended to wear compression stockings and elevate the feet. These symptoms should disappear after the completion of therapy.

For those patients who cannot tolerate a high dose of steroids or who are allergic to them, there are a few alternatives such as corticotropin injection (purified form of pig or cow adrenocorticotropic hormone or ACTH [H.P. Acthar Gel]). This medication is administered subcutaneously (beneath the skin; Sub-Q) or intramuscularly (into the muscle; IM) and can be self-injected. It stimulates the production of natural corticosteroids by the adrenal gland. The usual dose is 80 units daily for one week followed by a tapering schedule over the second week with 40 units daily for four days followed by 20 units daily for three days.

In our case, Charlotte is experiencing her first acute exacerbation with two symptoms: 1) numbness in her left leg and 2) optic neuritis in her left eye. Since both symptoms are severe and interfere with daily functioning, she will be treated with methylprednisolone 1,000 mg administered by IV infusion over 60 minutes each day for 3 days. The medication will be administered in the physician's office. This treatment will not prevent any other relapses or acute exacerbations that Charlotte might experience in the future but will treat the acute inflammation in the CNS and thus will speed up her recovery and provide for more rapid symptom improvement.

(2) Disease-Modifying Treatment (DMT)

Disease-modifying treatment (DMT) simply alters or modifies the course of the disease, decreasing the severity and/or number/frequency of acute exacerbations/relapses and also reduces the number of new CNS lesions as detected by MRI. As such, everyone diagnosed with MS should begin DMT. Selected DMT approved for treatment of CIS can delay the occurrence of a second attack and thus delay the onset of MS for up to five years. There are currently 10 DMT agents available in the US approved for MS (Table 3, page 18). Currently, all DMT agents are approved for use only in RRMS with only mitoxantrone (Novantrone) also approved for the treatment of secondary SPMS and PRMS. There is currently no treatment for PPMS. In addition, several DMT agents are recommended for use in CIS in those patients with a high risk for future development of MS. This treatment is quite expensive. The approximate cost per month is between $3,000-4,400 (wholesale acquisition cost) depending on the agent used. There are patient assistance programs available through manufacturers to help some people who qualify and cannot afford the medication.

Current MS disease-modifying therapies are based on the abnormal immune response and the presence of inflammation in the CNS. In general, they are capable (in different ways) of modifying the abnormal immune reaction in MS that play roles in axon demyelination and axon destruction in the spine and brain. DMT medications include beta interferons (Avonex, Betaseron, Rebif and Extavia), glatiramer acetate (Copaxone), fingolimod (Gilenya), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), natalizumab (Tysabri) and mitoxantrone (Novantrone). The various DMTs currently available in the US for treatment of MS have unique management and safety considerations. These are included in Table 3. It needs to
be noted that none of the ten currently available disease-modifying medications are recommended for use during pregnancy or breastfeeding. In general, it is recommended to discontinue DMT prior to conception or once a pregnancy is known. Women with MS who are contemplating pregnancy should discuss their plan to become pregnant with their prescribing physician/neurologist. Effective contraception is required for all women of childbearing potential during DMT to prevent the risks to the fetus associated with potential drug toxicity. In addition, a negative pregnancy test is required for all women of childbearing potential while on teriflunomide and before each dose of mitoxantrone.

**Beta Interferons (Avonex, Betaseron, Rebif, and Extavia)**

Interferon beta-1a and interferon beta-1b are considered a first-line therapy for RRMS and CIS as well as other relapsing types of MS. All are available in a self-injectable form and include the following.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Indication</th>
<th>Route</th>
<th>Dose</th>
<th>Important Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>interferon beta-1a</td>
<td>Avonex</td>
<td>Relapsing MS and CIS</td>
<td>IM, Sub-Q</td>
<td>30 mcg weekly</td>
<td>Flu-like symptoms, injection site reactions (less common for IM formulation), depression, liver abnormality</td>
</tr>
<tr>
<td></td>
<td>Rebif</td>
<td></td>
<td></td>
<td>44 mcg 3 times weekly</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1b</td>
<td>Betaseron</td>
<td>Relapsing MS and CIS</td>
<td>Sub-Q, Sub-Q</td>
<td>0.25 mg every other day</td>
<td>Flu-like symptoms, injection site reactions, depression, liver abnormality</td>
</tr>
<tr>
<td></td>
<td>Extavia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td>Copaxone</td>
<td>Relapsing MS and CIS</td>
<td>Sub-Q</td>
<td>20 mg daily</td>
<td>Injection site reactions, transient immediate post-injection reaction</td>
</tr>
<tr>
<td>teriflunomide</td>
<td>Aubagio</td>
<td>Relapsing MS</td>
<td>PO</td>
<td>7-14 mg daily</td>
<td>Hair loss/thinning, liver abnormality, liver toxicity*, GI side effects, infection.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pregnancy Category X</td>
</tr>
<tr>
<td>fingolimod</td>
<td>Gilenya</td>
<td>Relapsing MS</td>
<td>PO</td>
<td>0.5 mg daily</td>
<td>Headache, diarrhea, influenza, back pain, liver abnormality, macular edema and decreased HR and BP associated with first dose (requirement of first-dose observation)</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td>Tecfidera</td>
<td>Relapsing MS</td>
<td>PO</td>
<td>120-240 mg BID</td>
<td>Flushing, GI side effects</td>
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<tr>
<td>natalizumab</td>
<td>Tysabri</td>
<td>Relapsing MS</td>
<td>IV</td>
<td>300 mg IV over 60 minutes every 4 weeks</td>
<td>PML*, suppression of immune system, infections</td>
</tr>
<tr>
<td>mitoxantrone</td>
<td>Novantrone</td>
<td>Worsening forms of relapsing MS and SPMS</td>
<td>IV</td>
<td>12 mg/m² over 5-15 minutes every 3 months for 2-3 years (Maximum life dose 140 mg/m²)</td>
<td>Blue-green urine 24 hours after infusion, nausea, hair loss, menstrual disorders, cardiotoxicity*, liver toxicity, suppression of immune system (leukopenia=low white blood cells*), leukemia*, infections</td>
</tr>
</tbody>
</table>

Abbreviations: clinically isolated syndrome (CIS); intramuscular (IM); subcutaneous (Sub-Q), oral (PO); intravenous (IV); progressive multifocal leukoencephalopathy (PML); gastrointestinal (GI), heart rate (HR); blood pressure (BP)  *FDA Black box warning
formulation (see Table 3). Interferon beta-1a is available as Avonex, a weekly intramuscular formulation (administered into the muscle), and Rebif, a subcutaneous formulation administered three times weekly (below the skin). Interferon beta-1b is available only in a subcutaneous formulation as Betaseron and Extavia, administered every other day. Interferons beta are naturally occurring immune molecules that are secreted by immune cells and have anti-inflammatory properties. The precise mechanism of action of beta interferon in MS is poorly understood but may be related to reducing transport/migration of specific white blood cells to the CNS and reducing lesion proliferation.

All formulations of interferon beta are associated with flu-like symptoms such as headache, fatigue/tiredness, muscle aches, fever and chills; and occur in about 60 percent of patients receiving these medications. These symptoms may dissipate over time with the use of medication. There are a few things that can be done or suggested to the patient to alleviate the flu-like symptoms: 1) medications should be administered in the evening; 2) increase the dose slowly; and 3) use of pre-medication with oral acetaminophen (Tylenol) or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin). As these symptoms usually disappear after longer use of these medications, some patients might not be able to tolerate them and will need to switch to a different therapy.

In addition, all interferon beta formulations are associated with injection site reactions presenting as redness, swelling, pain and itching at the injection site; however, they are less common with intramuscularly administered interferon beta 1a (Avonex). There are few prevention strategies that can be utilized in order to reduce this: 1) injected medication should be at room or body temperature; 2) injection site should be iced for 15 minutes before and after injection; 3) massage injection site before and after injection; 4) injection site should be rotated and medication should not be injected in the same location; 5) use autoinjectors similar to an insulin pen that can be obtained free of charge from the manufacturer; and 6) use hydrocortisone 1% cream on the site for a short period of time if severe itching occurs.

Patients treated with any of the interferons beta are at risk for depression and worsening of depressive symptoms, liver function abnormalities, thyroid disease, and both white and red blood cell count abnormalities (anemia and leukopenia). Therefore, before and after initiation of these medications, there is a need for laboratory testing and regular follow-up. Liver function tests and complete blood count (count of all cells in blood: red, white and platelets) should be performed upon initiation of medication and one, three and six months after initiation as well as periodically while on therapy.

Importantly, treatment with any of the beta interferon medications can result in the generation of neutralizing antibodies. Neutralizing antibodies are antibodies that are synthesized by a person’s immune system and can reduce beta interferon’s clinical effectiveness. If these antibodies are found in a patient, the medication needs to be switched to some other medication that does not belong in the same class. The next usual step would be initiation of glatiramer acetate.

Glatiramer acetate (Copaxone)

Glatiramer acetate is a first-line therapy for MS and CIS which is administered daily as a subcutaneous self-injection (Table 3). It can also be appropriate for those patients who have either developed neutralizing antibodies in response to interferon beta or those who cannot tolerate interferon beta due to limiting flu-like symptoms, depression or liver toxicity. Glatiramer acetate is a mixture of four amino acids that mimics the basic myelin protein found in the myelin sheath around axons in the CNS. Its mechanism of action is distinct from that of interferon beta, therefore a patient may respond differently to this drug. It is believed that glatiramer acetate stimulates the specific white blood cells that suppress the immune attack on myelin, however its precise effect in MS is poorly understood.

The common side effects associated with subcutaneous injection of glatiramer acetate are injection site reactions similar to those seen with interferon beta injections. Similar prevention strategies may be used for this medication in order to prevent injection site reactions. Unlike interferon beta, glatiramer acetate is not associated with depression, flu-like symptoms, liver dysfunction or blood abnormalities, and no laboratory monitoring is needed. A common side effect unique to glatiramer acetate is its associated temporary reaction, often referred to as a transient immediate post-injection reaction, that is reported in about 16 percent of patients. It is characterized by flushing and/or chest tightness and accompanied by shortness of breath, anxiety and heart palpitations. This is a benign (self-limiting) reaction that only lasts about 15 minutes and resolves without any other complications and generally occurs after the first few months of treatment. It may
occur more than once in a given individual. It is important to inform patients about this since it can lead to a fear of heart attack or other conditions, and may lead the patient to discontinue treatment prematurely.

**Fingolimod (Gilenya)**

Fingolimod is the first orally-available DMT for the treatment of RRMS. It is given as a 0.5 mg capsule once daily (Table 3). It blocks the release of white blood cells from lymph nodes and thus decreases their migration to the CNS. The most common side effects associated with fingolimod include headache, influenza, liver function abnormalities, diarrhea and back pain. First dose monitoring needs to be done when fingolimod is initiated for the first time because it has been reported to be associated with a significant drop in heart rate (bradycardia) and blood pressure (hypotension). A patient should receive his/her first dose in the doctor's office or in another medical facility where the patient's blood pressure (BP) and heart rate (HR) can be monitored for a period of six hours. Before initiation, BP, HR and ECG should be performed followed by hourly monitoring of HR and BP and a second ECG conducted at the end of the six-hour observation period.

If heart rate and blood pressure is normal, patients can be released and continue treatment with the medication. Ocular abnormality (swelling in the eye) has been reported with this medication and thus baseline and periodic ophtalmic monitoring is recommended. This medication should not be administered to those without documentation of, or vaccination for, chicken pox (varicella zoster virus). Because use of this medication can be associated with liver abnormalities and reduction in white blood cell count (leukopenia), specific blood tests are recommended prior to starting treatment and periodically thereafter.

**Teriflunomide (Aubagio)**

Teriflunomide is the second oral agent approved for RRMS which inhibits T-lymphocyte activation. It is usually not used as a first-line treatment but rather as second-line treatment when first-line therapy fails. It is administered as a 7 or 14 mg tablet given once daily (Table 3). Common side effects are temporary hair loss/thinning that seem to wane after six months; diarrhea; influenza; liver abnormality; infections; and increased blood pressure. This medication is strictly contraindicated in pregnancy because it has been reported to cause fetal abnormalities and deformities (Pregnancy Category X). Women capable of becoming pregnant should have a negative pregnancy test prior to initiation and use reliable contraception in order to avoid pregnancy while on this medication. In addition, teriflunomide is also secreted into the semen, thus both men and women who wish to conceive a child should discontinue teriflunomide and undergo an accelerated drug elimination procedure using cholestyramine or activated charcoal. Because of teriflunomide's potential to weaken the immune system, it is important to rule out the possibility of having tuberculosis (TB) so a TB skin test or TB blood test should be done prior to initiation of this medication. All live vaccines such as MMR vaccine, shingles vaccine, and intranasal influenza vaccine should be avoided during therapy and for at least six months after discontinuation of therapy. Various laboratory tests are needed prior to initiation and thereafter while on this therapy.

**Dimethyl Fumarate (BG-12, Tecfidera)**

This is the third and most recently approved oral medication for RRMS that has anti-inflammatory and potentially neuroprotective properties. It is currently approved for twice daily administration as 120 mg and 240 mg delayed-release capsules (Table 3). It can be taken with or without food and the capsule should not be crushed, opened or chewed and must be swallow whole. An important fact is that this medication needs to be stored in its original container and discarded 90 days after the original container is opened. The most common side effects are flushing, abdominal pain/discomfort, diarrhea, and nausea. Side effects, especially flushing, usually dissipate after the six weeks of treatment. Taking medication with food may alleviate flushing and gastrointestinal discomfort. In addition, administration of aspirin prior to dimethyl fumarate can be used to blunt the flushing effect.

**Natalizumab (Tysabri)**

Natalizumab is an intravenous therapy which is not recommended as first-line therapy for RRMS due to serious side effects. It is usually reserved for severe cases when first-line treatment is not effective and when the patient is still experiencing very frequent relapses and continued disease progression (Table 3). It is administered intravenously over 60 minutes every four weeks. Its use is associated with infections, nausea, allergic reaction and progressive multifocal leukoencephalopathy (PML). PML is a life-threatening brain infection caused by the opportunistic John Cunningham virus (JCV) causing damage to neurons and is associated with a high risk of death or severe disability. The risk of PML increases the longer the patient takes the medication, has presence of JCV antibodies, or has a suppressed immune system. Due to this risk, the patient, pharmacy and prescribing physician have to enroll...
in the Tysabri Outreach: Unified Commitment to Health (TOUCH®) prescribing program. Before initiation of natalizumab, an MRI and laboratory test for the presence of anti-JCV antibodies need to be done.\textsuperscript{59,71-72}

**Mitoxantrone (Novantrone)**

Mitoxantrone is an intravenous therapy administered every three months (Table 3) which suppresses the activity of immune cells that are believed to damage myelin in MS. Blue-green urine is observed about 24 hours after the infusion and the patient should be informed regarding this effect. It is not used as first-line therapy for MS and is reserved for patients with rapidly advancing MS (worsening RRMS or SPMS) or those for whom other treatment options have failed.\textsuperscript{58} This medication is very effective in the prevention of relapses, however it is associated with very serious cardiac and liver toxicity, therefore it is rarely used. The risk of cardiotoxicity increases with cumulative dose. It has a lifetime cumulative dose of 140 mg/m\textsuperscript{2} and treatment should not exceed 2-3 years of therapy.\textsuperscript{58, 73}

How long will someone with MS need to be on DMT medication? Treatment with disease-modifying medications is life-long. It is very important to start DMT early and emphasize to patients the need for medication adherence. For treatment success and to achieve the best health outcomes for MS patients, it is important to establish realistic expectations and stress the need for adherence. Upon diagnosis of MS or CIS in patients who are prescribed any DMT for the first time, their physician, trained nurse or pharmacist should educate them about MS, medications, and what can be expected. One of the major counseling points is that these medications do not cure MS but might decrease the number and severity of relapses and disease progression. Patients still may experience occasional relapses as well as some symptoms while taking these medications as prescribed. This is very important so that the patients have realistic expectations about the effect of treatment and are not discouraged or think that the medication does not work if they still experience an occasional attack or symptom. DMT medications are associated with a 30-70\% reduction in relapses depending on the DMT medication.\textsuperscript{62} Untreated patients may experience a relapse every six months, while those treated and compliant with DMT may experience an attack every 2-5 years. This is not ideal, but it is a significant reduction. It is imperative that a patient is compliant with this treatment and patients should be educated that it will not work unless s/he is taking it as instructed.

In our case, Charlotte is diagnosed first with CIS and has a high risk for developing MS in the next 7-14 years. Charlotte should be counseled on CIS and MS. Disease-modifying treatment should be recommended to her due to the high risk for MS development. First-line treatments that are approved for CIS are interferon beta formulations (Avonex, Betaseron, Rebif and Extavia) and glatiramer (Copaxone). Charlotte should be educated about the importance of adherence (following dosing instructions), common side effects, and what to do to alleviate them, as well as what to expect from this therapy. After consulting with the neurologist, Charlotte decided to start intramuscular interferon beta-1a. She experienced minor flu-like symptoms that disappeared over a few weeks of therapy. Overall, she was tolerating the medication well and was symptom and relapse free for the next five years.

Five years later, after her first acute exacerbation, she experienced a relapse and was finally diagnosed with MS. Charlotte was compliant with the medication which was well tolerated and no neutralizing antibodies were detected against interferon beta-1a. The neurologist recommended that she continue with her current DMT.

(3) Symptomatic Treatment

Despite DMT's ability to reduce the frequency of relapses and slow the rate of disease progression, MS patients can have a variety of symptoms which require treatment. Certain symptoms are very common, albeit with variable frequency, regardless of treatment with DMTs. Because there is no cure for MS at this time, symptom management is critically important to improve quality of life and decrease disability among patients with MS. Symptoms are somewhat difficult to treat, but can be manageable by com-

<table>
<thead>
<tr>
<th>Test Your Knowledge #5: Pair the correct brand name (number) with generic name (letter).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAND NAME</strong></td>
</tr>
<tr>
<td>1. ____ Copaxone</td>
</tr>
<tr>
<td>2. ____ Betaseron</td>
</tr>
<tr>
<td>3. ____ Aubagio</td>
</tr>
<tr>
<td>4. ____ Tysabri</td>
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<tr>
<td>5. ____ Tecfidera</td>
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<tr>
<td>6. ____ Avonex</td>
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<tr>
<td>7. ____ Gilenya</td>
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<tr>
<td>8. ____ Novantrone</td>
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<tr>
<td>9. ____ SoluMedrol</td>
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bining non-pharmacologic and pharmacologic approaches. It is crucial, if possible, that a patient with MS receive interprofessional care in a specialized multiple sclerosis clinic that includes physicians, nurses, pharmacists, physical therapists, occupational therapists, psychiatrists/psychologists, nutritionists and social workers.

Non-pharmacologic strategies include: psychological counseling; coping strategies; physical therapy including stretching and range of motion exercise for better flexibility and mobility; balance exercise; use of walking aids such as braces, crutches, canes; and complementary medicine such as utilization of massage and yoga among other things. Pharmacologic treatments include different medications that can assist with symptomatic management of MS. The selection of medications used to treat these symptoms should be made very carefully because it can often worsen other symptoms. Therefore, the treatment should be individualized for each and every patient.

Walking difficulties such as the inability to walk fast or to walk without rest or use of a walking aid are most often reported by patients as being very disabling and debilitating. Dalfampridine (Ampyra) is a new oral medication that is approved for the symptomatic management of MS to improve walking speed in patients with any type of MS. This medication can cause seizures and thus should not be given to a patient with a reported history of seizures or epilepsy.

### Table 4. Management Strategies of Common MS Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Problems</td>
<td>• Medications for overactive bladder: e.g., tolterodine (Detrol), oxybutynin ( Ditropan), trospium (Sanctura), solifenacin (Vescicare)</td>
</tr>
<tr>
<td></td>
<td>• Applying pressure right above the bladder to assist emptying in urinary hesitancy</td>
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<tr>
<td></td>
<td>• Self-catheterization in patients with problems of bladder emptying</td>
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<tr>
<td>Depression</td>
<td>• psychological counseling</td>
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<td></td>
<td>• antidepressants: e.g., sertraline (Zoloft), fluoxetine (Prozac), venlafaxine (Effexor); bupropion (Wellbutrin)</td>
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<tr>
<td>Dizziness &amp; Vertigo</td>
<td>• Meclizine (Antivert), scopolamine patch (Transderm Scop) or anti-nausea medication, ondansetron (Zofran)</td>
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<tr>
<td>Fatigue</td>
<td>• Short period of rest</td>
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<td></td>
<td>• Planning of daily activities and energy conservation strategies</td>
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<tr>
<td></td>
<td>• Regular exercise program</td>
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<tr>
<td></td>
<td>• Cooling strategies and avoidance of hyperthermia</td>
</tr>
<tr>
<td></td>
<td>• Assistive devices</td>
</tr>
<tr>
<td></td>
<td>• Amantadine (Symmetrel)</td>
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<tr>
<td></td>
<td>• Use of antidepressant that is activating if also diagnosed with depression</td>
</tr>
<tr>
<td></td>
<td>• CNS stimulants such as modafinil (Provigil) or methylphenidate (Ritalin)</td>
</tr>
<tr>
<td>Cognitive Problems</td>
<td>• Coping strategies: keeping lists, using smartphones, pill boxes, signs</td>
</tr>
<tr>
<td></td>
<td>• Cognitive enhancers such as donepezil (Aricept), galantamine (Razadyne)</td>
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<tr>
<td>Optic Neuritis</td>
<td>• Corticosteroids (i.e. methylprednisolone 1g IV for 3-5 days)</td>
</tr>
<tr>
<td>Pseudobulbar Affect (PBA)</td>
<td>• Dextromethorphan/quinidine (Nuedexta)</td>
</tr>
<tr>
<td>Sexual Dysfunction</td>
<td>• Erectile dysfunction: sildenafil (Viagra), vardenafil (Levitra)</td>
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<tr>
<td></td>
<td>• Sexual dysfunction in females: use of a lubricant</td>
</tr>
<tr>
<td>Spasticity</td>
<td>• Stretching and exercise programs (aqua therapy, yoga; but watch core temperature since heat can worsen MS symptoms)</td>
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<td></td>
<td>• Physical therapy</td>
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<tr>
<td></td>
<td>• Use of orthotics or braces</td>
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<tr>
<td></td>
<td>• Modification of daily activities</td>
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<tr>
<td></td>
<td>• Muscle relaxants: baclofen (Lioresal) or tizanidine (Zanaflex)</td>
</tr>
<tr>
<td></td>
<td>• Both can worsen fatigue and cause drowsiness.</td>
</tr>
<tr>
<td></td>
<td>• Abrupt discontinuation of baclofen can cause seizure</td>
</tr>
<tr>
<td>Walking</td>
<td>• Exercise and physical therapy</td>
</tr>
<tr>
<td></td>
<td>• Assistive walking devices (crutches, braces, canes)</td>
</tr>
<tr>
<td></td>
<td>• Use of wheelchair and scooters</td>
</tr>
<tr>
<td></td>
<td>• Dalfampridine (Ampyra) – improvement of walking speed</td>
</tr>
</tbody>
</table>
The medication is given as 10 mg tablets orally twice daily. The most common adverse effects are UTI, insomnia, dizziness, headache and nausea.\textsuperscript{74} In addition to medications that are specifically approved for the management of MS such as DMTs and dalfampridine, there are several other medications used to treat other conditions that can also be useful for symptom management in MS (Table 4).

**Conclusion**

Living with MS is not easy and presents many daily challenges for those who are affected by this disorder as well as their families. Many aspects of a person’s life such as relationships, education, work and career, parenting, social activities and hobbies can be affected. However, with an appropriate management of multiple sclerosis, proper patient education, and the ability of an individual to learn how to cope with problems and to adapt, many challenges of this disease can be overcome and the majority of individuals are able to live full and satisfying lives. Pharmacists and pharmacy technicians play crucial roles in optimal care for patients with MS. Therefore, a pharmacy technician should be familiar with major aspects of MS in order to better assist the pharmacist and patients in the area of MS care. In addition, they can assist patients to obtain DMT medications by helping them with the prior authorization process necessary for insurance carriers to cover medications. They can also assist patients with available medication assistance programs for different manufacturers of DMTs.
An emotional problem that can be caused or worsened by the use of beta interferons.

A common early sign of MS experienced by almost every single patient with MS.

One of the most common side effects of dimethyl fumarate

The part of the neuron that acts as a message receiver from other neurons.

The generic name for an oral disease-modifying treatment for MS associated with hair loss.

Over-activation of immune cells in MS is associated with this pathological process causing demyelination.

The majority of patients with MS will experience sensitivity to this.

The brand name for glatiramer acetate.

The part of the central nervous system affected by MS.

A neurologic episode associated with the development of new or recurring symptoms that last at least 24 hours.

A long thin neuronal fiber that conducts messages to other neurons.

A lipid substance surrounding the axon.

The intravenous steroid used for the management of acute exacerbation in MS.

The abbreviation for the most common type of MS.

The risk factor associated with risk for MS.

The brand name for a disease-modifying treatment for MS that needs to stay in the original bottle.

The generic name for an intravenous disease-modifying treatment associated with progressive multifocal leukoencephalopathy (PML).

The generic name for a disease-modifying treatment requiring a first-dose observation period.

The abbreviation for the most sensitive and useful test for MS diagnosis.

The brand name for an intramuscularly administered beta interferon.

**Test Your Knowledge #6: Complete this Crossword Puzzle.**

![Crossword Puzzle Image](Image)
References


ANSWER KEY: Test Your Knowledge Exercise

Exercise #1: (1) cell body (soma); (2) nucleus; (3) dendrite(s); (4) axon; (5) myelin or myelin sheath or layer

Exercise #2: 1B; 2E; 3D; 4F; 5C; 6A

Exercise #3: Case 1. Rationale: Case 1 migrated from high to low risk area before the puberty (at age of 8). Case 2 was born and lived all 22 years in high risk area and after the puberty (at age 22) relocated to low risk area.

Exercise #4: sex (female); young age (she is 24 years old); mother with MS (first degree relative: increased risk by 20-fold compared to the rest of the population), grew-up in cold climate (geography), vitamin D deficiency (low levels of vitamin D); Caucasian with northern European descent (family from Denmark), history of smoking (she smoked for 7 years)

Exercise #5: 1C; 2D; 3E; 4H; 5F; 6A; 7B; 8G, 9I

Exercise #6: