



National  
Multiple Sclerosis  
Society

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# Clinical Bulletin

Information for Health Professionals

## Overview of Multiple Sclerosis

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### INTRODUCTION

Multiple sclerosis (See [www.nationalmssociety.org/ClinicalBulletins](http://www.nationalmssociety.org/ClinicalBulletins) for detailed discussion of symptoms) (MS) is a chronic, often disabling disease of the central nervous system (CNS)—the brain, spinal cord, and optic nerves. It is thought to be an autoimmune disease in which the body's defense system mistakenly attacks the myelin, the insulating substance that surrounds the nerve fibers (axons) in the CNS. (Poser, 1972). Damaged myelin (demyelination) forms scar tissue (sclerosis), giving the disease its name. In addition to the myelin, the axons themselves can be damaged or destroyed. When the myelin sheath or nerve fiber is damaged, nerve impulses transmitted to and from the brain and spinal cord are distorted or interrupted, producing a variety of symptoms.

Most people are diagnosed between the ages of 20 and 50, but MS can appear in young children and teens as well as much older adults. MS is significantly more common (at least 2–3 times) in women than men. Approximately 400,000 people are living with MS today—with 200 more people diagnosed every week. Worldwide, MS is thought to affect more than 2.1 million people.

### ETIOLOGY AND EPIDEMIOLOGY

The etiology of MS is unknown, but decades of research indicate that MS may be the result of an abnormal autoimmune response to some infectious or environmental trigger in a genetically susceptible individual. Each of these factors—immunologic, environmental, infectious, and genetic—is the subject of intensive ongoing research.

- ◆ MS occurs more often in countries with a moderate, cool climate than in warmer countries. People who live closer to the equator are exposed to greater amounts of sunlight year-round and tend to have higher levels of naturally-produced vitamin D, thought to have a beneficial impact on immune function. This may offer protection against autoimmune diseases, including MS (Ascherio & Munger, 2007).

- ◆ MS occurs in most ethnic groups, including African-Americans, Asians and Hispanics/Latinos, but is more common in Caucasians of northern European ancestry, who also tend to live in more temperate climates. Some ethnic groups, such as the Inuit, Aborigines and Maoris, have few if any documented cases of MS regardless of where they live. These variations that occur even within geographic areas with the same climate suggest that geography, ethnicity, and other factors interact in some complex way (Rosati, 2001).
- ◆ Migration data suggest that exposure to an environmental agent or agents occurring before puberty may predispose a person to develop MS. Studies of migration patterns have shown that people born in areas that are farther from the equator (with a high risk of MS) who move to an area with a lower risk before the age of 15, acquire the risk of their new area (Kurtzke, 2000).
- ◆ Since viruses are well recognized as causes of demyelination and inflammation, it is possible that a virus or other infectious agent is the trigger in MS. More than a dozen viruses and bacteria—including measles, canine distemper, human herpes virus-6, Epstein-Barr, and Chlamydia pneumonia—have been or are being investigated to determine involvement in the development of MS, but none have been definitively proven to trigger MS (Serafini et al., 2007).

Scientists also study MS clusters—defined as higher-than-expected numbers of cases of MS that have occurred over a specific time period and/or in a certain area. Clusters may provide clues to environmental (such as industrial toxins, diet, or trace metal exposures) factors that might cause or trigger the disease. To date, cluster studies have not produced clear evidence for the existence of any triggering factor or factors in MS.

MS is not directly inherited, but genetics play an important role. While the risk of developing MS in the general population is 1/750, the risk rises to 1/40 in anyone who has a close relative (parent, sibling, child) with the disease. Even though identical twins share the same genetic makeup, the risk for an identical twin is only 1/4—which means that some factor(s) other than genetics are involved (Ebers et al., 2004).

## DIAGNOSTIC CRITERIA

To establish a diagnosis of MS clinicians must:

- ◆ Find evidence of damage in at least two separate areas of the CNS, **AND**
- ◆ Find evidence that the damage occurred at two separate points in time, at least one month apart, **AND**
- ◆ Rule out all other possible diagnoses (Polman et al., 2005; Polman et al., 2010)

MS can be difficult to diagnose, since there are no definitive symptoms, physical findings or laboratory tests that can, by themselves, make the diagnosis. The diagnosis is a clinical one, requiring:

- ◆ A careful medical history looking for past and present indicators of neurologic impairment as well as information about birthplace, family history and places traveled that might provide further clues.
- ◆ A complete neurological examination to evaluate the functioning of the cranial nerves; strength, balance and coordination; sensation; and mental state.
- ◆ Laboratory tests to help confirm the diagnosis and rule out other conditions:
  - ◆ Magnetic resonance imaging (MRI) to look for evidence of new disease activity as well as signs of more chronic damage. Although MRI is a very useful diagnostic tool, a normal MRI of the brain does not rule out the possibility of MS. About 5% of people who are confirmed to have MS do not initially have brain lesions on MRI.
  - ◆ Evoked potential testing (EP) to look for evidence of slowed nerve conduction caused by demyelination along nerve pathways. Of the three types of EPs used by neurologists—visual, auditory, and somatosensory—visual evoked potentials (VEPs) have been found to be the most helpful in the diagnostic process.
  - ◆ Lumbar puncture (LP) to analyze the spinal fluid for certain immune system proteins and the presence of oligoclonal bands, which indicate an immune response within the CNS. Oligoclonal bands are found in the spinal fluid of about 90–95% of people with MS.

Because permanent neurologic damage can occur even in the earliest stages of MS, it is important that a confirmed diagnosis is made so that the appropriate treatment(s) can be initiated early in the disease process (Coyle, 2008).

## THE FOUR DISEASE COURSES

Four disease courses have been identified in MS (Lublin & Reingold, 1996):

- ◆ **Relapsing-remitting RRMS:** Episodes of acute worsening of neurologic function, with some amount of recovery (the most common form) and no progression in between. About 85% of people are diagnosed with RRMS initially.
- ◆ **Secondary-progressive SPMS:** Following an initial relapsing-remitting course, the disease transitions in many people to a steadily progressive form with increased loss of function. Of the 85% who start with RRMS, more than 50% will develop SPMS within 10 years and 90% within 25 years.
- ◆ **Primary-progressive PPMS:** Continuing worsening of disease from onset, without distinct relapses. Approximately 10% of people are diagnosed with PPMS.
- ◆ **Progressive-relapsing PRMS:** Progressive disease from onset, with occasional acute relapses and continuing disease progression. About 5% of people appear to have PRMS at diagnosis.

**Note:** *About 10% of the MS population experience a benign course of MS, but this can only be determined retrospectively.*

## MULTIPLE SCLEROSIS TREATMENT STRATEGIES

The progressive nature of MS, the unpredictability and variability of its symptoms, and the emotional and social changes it can cause, combine to create a complex clinical challenge for healthcare professionals from a range of disciplines, including the neurologist, urologist, nurse, physical therapist, occupational therapist, speech/language pathologist, neuropsychologist, and psychotherapist. Treatment strategies in MS fall into five general categories:

- ◆ Treatment of acute exacerbations
- ◆ Symptom management
- ◆ Disease modification
- ◆ Rehabilitation (to enhance and maintain physical function)
- ◆ Psychosocial support

### Treatment of Acute Exacerbations

Exacerbations (flares, flare-ups, relapses, attacks) of MS are caused by inflammation in the CNS that causes damage to the myelin and slows or blocks transmission of nerve impulses. A true exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. However, most exacerbations last from a few days to several weeks or even months. Exacerbations can be mild or severe enough to interfere with a person's ability to function at home and at work. Severe exacerbations are most commonly treated with intravenous, high-dose corticosteroids to reduce the inflammation, although comparable doses of oral steroids may be used (Frohman et al., 2007). Steroids decrease acute inflammation in the CNS, but have no long-term benefits.

Intravenous immune globulin (IVIG) and plasmapheresis are sometimes used to treat exacerbations when patients can't tolerate or don't respond to steroids.

Another option for the treatment of acute exacerbations is ACTH (H.P. Acthar Gel [repository corticotropin injection]).

**Symptom Management** (See [www.nationalMSSociety.org/ClinicalBulletins](http://www.nationalMSSociety.org/ClinicalBulletins) for detailed discussion of symptoms)

Because the damage to myelin in the CNS is apparently random, no two people have exactly the same symptoms, and each person's symptoms can change or fluctuate over time. Most of these symptoms can be managed very effectively with medication, rehabilitation, and other management strategies (Schapiro, 2005).

Primary symptoms are the direct result of damage to the myelin and nerve fibers in the CNS. Primary symptoms include the following:

- ◆ **Fatigue:** One of the most common symptoms, occurring in about 80% of people
- ◆ **Management strategies:** Rehabilitation, including energy management (work simplification; naps; use of assistive devices); moderate aerobic exercise; cooling strategies/

devices; medications (amantadine [Symmetrel]; modafinil [Provigil]; armodafinil [Nuvigil]; fluoxetine [Prozac])

- ◆ **Psychosocial implications:** Inability to carry out activities at home and at work; fatigue of this magnitude is depressing; invisible symptom that is easily misinterpreted by others
- ◆ **Vision problems:** A common first symptom of MS—may include *optic neuritis* (temporary loss or disturbance of vision, often accompanied by pain; may also cause a “blind spot” [scotoma] in center of vision); *diplopia* (double vision); *nystagmus* (rhythmic jerkiness or bounce in one of both eyes)
  - ◆ **Management strategies:** High-dose corticosteroids; clonazepam (Klonopin), if necessary, for nystagmus; training in visual compensation; environmental modifications; adaptive equipment
  - ◆ **Psychosocial implications:** Visual symptoms can threaten independent functioning, increase fatigue, and interfere with activities at home and at work
- ◆ **Ambulation problems:** Walking, balance, coordination
  - ◆ **Management strategies:** Rehabilitation, mobility aids, and medication (dalfampridine [Ampyra]) to improve walking speed
  - ◆ **Psychosocial implications:** Resistance to use of mobility aids; impaired self-esteem; perceived by others as being less competent or intelligent
- ◆ **Spasticity:** Feelings of stiffness and a wide range of involuntary muscle spasms. Spasticity can range from relatively mild to quite severe, and treatment is approached in a step-wise fashion. **Note:** *Some degree of spasticity may be required to support weakened limbs.*
  - ◆ **Management strategies:** Rehabilitative PT; oral medications (baclofen [Lioresal]; tizanidine [Zanaflex]; diazepam [Valium]); intrathecal baclofen pump; onabotulinumtoxinA for upper limb spasticity; surgery
  - ◆ **Psychosocial implications:** Oral medications increase fatigue and weakness, surgical implantation of pump in abdomen can be frightening, severing of tendons is irreversible.
- ◆ **Bladder dysfunction:** Occurs in at least 80% of people with MS
  - ◆ **Failure to store** (urgency, frequency, incontinence, nocturia)
    - ◆ **Management strategies:** Anticholinergic/anti-muscarinic agents (oxybutynin [Ditropan] oxybutynin transdermal system [Gelnique]; tolterodine [Detrol]; trospium chloride [Sanctura]; solifenacin succinate [Vesicare] fesoterodine fumarate [Toviaz]); pelvic floor exercises
    - ◆ **Psychosocial implications:** Fear of drinking liquids; anxiety over loss of control; increased fatigue due to interrupted sleep

- ◆ **Failure to empty** (urgency, hesitancy, double voiding, feelings of incomplete emptying)
  - ◆ **Management strategies:** Antispasmodic medications (baclofen [Lioresal]; tizantidine [Zanaflex]) and sympatholytics (tamsulosin [Flomax]; terazosin [Hytrin]; doxazosin [Cardura]; silodosin [Rapaflo]; alfuzosin [UroXatrol]; prazosin [Minipress]); intermittent self-catheterization (ISC); may require indwelling catheter; dietary changes to increase acidifying urine
  - ◆ **Psychosocial implications:** Anxiety about loss of control; fear of ISC
- ◆ **Combined failure to store/failure to empty**
  - ◆ **Management strategies:** Combination of the above
  - ◆ **Psychosocial implications:** Same as above
- ◆ **Bowel dysfunction:** Constipation and loss of bowel control
  - ◆ **Management strategies:** Bowel training; high-fiber diet; exercise; medication (e.g., softeners, mild laxatives, mini-enemas); manual disimpaction of fecal impaction
  - ◆ **Psychosocial implications:** Discomfort; loss of control; anxiety about leaving home; embarrassment
- ◆ **Sensory problems/pain:** Including numbness, tingling, and neuropathic pain in the face, body, or extremities caused by demyelination
  - ◆ **Management strategies** (differ by type of pain): Medications: carbamazepine (Tegretol), gabapentin (Neurontin), phenytoin (Dilantin), duloxetine (Cymbalta), baclofen (Lioresal), high-dose IV steroids, topical Capsaicin cream; surgery: radiofrequency rhizotomy, radiofrequency electrocoagulation, glycerol rhizotomy
  - ◆ **Psychosocial implications:** Medications increase fatigue; steroids can affect mood; chronic pain is debilitating and depressing
- ◆ **Cognitive dysfunction:** Approximately 50% of people with MS will develop problems with high-level functions
  - ◆ **Functions commonly affected:** Working memory; attention/concentration; information processing speed; visuospatial relations; executive functions; word-finding
  - ◆ **Management strategies:** Cognitive rehabilitation, including retraining exercises to restore functions (with only limited benefit for daily activities) and compensatory strategies (e.g., memory aids, organizational tools) to enhance function in everyday activities
  - ◆ **Psychosocial implications:** Anxiety; loss of self-esteem/self-confidence; loss of employment; interpersonal strain; impact on treatment adherence
- ◆ **Depression:** More than 50% of people with MS will experience a major depressive episode; more common in MS than in the general population or in other equally disabling chronic illnesses

- ◆ **Management strategies:** Antidepressant medication; psychotherapy; exercise
- ◆ **Psychosocial implications:** Interferes with self-care and wellness, adherence to MS treatment, performance at work, and relationships with others
- ◆ **Sexual dysfunction:** Caused by demyelination; includes impaired arousal, sensory changes, reduced vaginal lubrication, erectile dysfunction
  - ◆ **Management strategies:**
    - ◆ **Men:** Oral medications (sildenafil [Viagra]; vardenafil [Levitra]; tadalafil [Cialis]); injectable or insertable medication (alprostadil [Prostin VR, MUSE]); prosthetic devices
    - ◆ **Women:** Lubricating substances; enhanced stimulation
  - ◆ **Psychosocial implications:**
    - ◆ **Individual:** Significant impact on gratification, self-esteem; embarrassing to discuss with healthcare providers
    - ◆ **Interpersonal:** Significant impact on intimate relationships—easily misunderstood by long-term partner; causes embarrassment with new partners
    - ◆ Complicated by other MS symptoms (e.g., fatigue, spasticity, weakness) and medications (e.g., anticholinergics, antidepressants)
- ◆ **Dizziness and vertigo:** Lightheadedness or feeling off-balance
  - ◆ **Management strategies:** Oral medication (meclizine [Antivert]); IV fluids and high-dose corticosteroids if nausea prevents the use of oral medications
  - ◆ **Psychosocial implications:** Impaired functioning at home and work
- ◆ **Speech/swallowing problems**
  - ◆ **Dysarthria** (poorly articulated, slurred, or low-volume speech)
    - ◆ **Management strategies:** Exercise program; training with augmentative or alternative communication devices, if needed
    - ◆ **Psychosocial implications:** Slurring can be misinterpreted as drunkenness or lack of intelligence. Slow, slurred speech interferes with communication
  - ◆ **Dysphagia** (difficulty in swallowing that can lead to aspiration and/or inadequate nutrition)
    - ◆ **Management strategies:** Exercise program; postural recommendations; modified diet; non-oral feeding strategies, if needed
    - ◆ **Psychosocial implications:** Loss of enjoyment/social interactions surrounding food and mealtimes

- ◆ **Tremor:** Involuntary movements of the arms, legs, or head; tremor can be the least treatable and most debilitating symptom of MS
- ◆ **Management strategies:** Rehabilitation—balance/coordination exercises; weights on limbs or utensils; medications—propranolol; clonazepam (Klonopin); primidone (Mysoline); isoniazid (Laniazid); buspirone (BuSpar); ondansetron
- ◆ **Psychosocial implications:** Fear of loss of control; major threat to independence; medication can increase fatigue

Secondary symptoms are the complications that can arise as a result of the primary symptoms. Secondary symptoms such as pressure sores caused by immobility or decreased bone density due to inactivity can be addressed and treated, but the goal is to prevent them from happening in the first place.

## **Disease Modifying Treatments**

Since 1993, the U.S. Food and Drug Administration (FDA) has approved eight drugs for use in multiple sclerosis. For the first time, we have the ability to reduce disease activity for many people with MS. These drugs do not cure MS or provide relief from current symptoms—in fact, the effects on the disease may not be immediately apparent. However, each of these drugs has been shown in phase III clinical trials to provide significant long-term benefit for people with relapsing forms of MS. Unfortunately, no medications have yet been approved for the treatment of primary-progressive MS. *And none of these medications are recommended for use by women who are pregnant or trying to become pregnant, or who are breastfeeding. Women should be encouraged to discuss all of their medications with their physician and/or nurse prior to trying to conceive.*

The most current information about the disease-modifying medications can be found on the Society's Web site at [www.nationalMSSociety.org/Treatments](http://www.nationalMSSociety.org/Treatments). Ongoing clinical trials are listed at [www.nationalMSSociety.org/ClinicalTrials](http://www.nationalMSSociety.org/ClinicalTrials). Since new trials are announced periodically, and additional information becomes available as trials are completed, it is important to check these sites on a routine basis.

Five of the approved medications are delivered by injection; one is oral; and two are delivered by intravenous infusion. The injectable and oral options are considered first-line treatment options, meaning that the FDA does not require that any other medication be tried before prescribing one of these. The remaining two options are recommended for individuals who have not received sufficient benefit from one or more of the first-line options.

### ***First-Line Medications***

Five of the first-line medications are delivered by injection and one is taken orally. The five injectable therapies include two different formulations of interferon beta-1a (Avonex and Rebif), one formulation of interferon beta-1b that is marketed under two brand names (Betaseron and Extavia), and glatiramer acetate (Copaxone).

## ◆ Interferon Beta Medications

Interferon beta has a variety of effects on the immune system, including a reduction in those immune responses that attack the myelin and nerve fibers in MS. The four interferon beta medications that have been approved by the FDA are Betaseron (Bayer HealthCare Pharmaceuticals Inc.) and Extavia (Novartis Pharmaceuticals, Corp.), which are the identical formulation of interferon beta-1b distributed by two different companies; and Avonex (Biogen Idec) and Rebif (Serono/Pfizer, Inc.), which are different formulations of interferon beta-1a. All are manufactured through the use of recombinant DNA technology.

All of the interferon medications should be used with caution by any person with a history of depression, liver or heart problems, epilepsy, thyroid problems or blood problems. Because of the potential of the interferon medications to affect the functioning of the liver and thyroid gland, and to alter the levels of white blood cells, red blood cells, and platelets in a person's system, blood tests are recommended at regular intervals.

### ◆ Interferon beta-1b (Betaseron; Extavia)

**Approval by the U.S. Food and Drug Administration (FDA):** Betaseron (Bayer HealthCare Pharmaceuticals Inc.) and Extavia (Novartis Pharmaceuticals, Corp.) are both approved to reduce the rate of relapses in people with relapsing forms of MS. In addition, Betaseron and Extavia are approved for use by individuals who have experienced their first clinical episode and have MRI-detected brain lesions consistent with MS (clinically-isolated syndrome) but have not yet met the criteria for a definite MS.

**Clinical Outcomes:** Interferon beta-1b has been shown in clinical trials to reduce the frequency of relapses and the number of new lesions on MRI, and to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in those with clinically-isolated syndrome. Betaseron received FDA approval in 1993. Because Extavia is identical to Betaseron, the FDA did not require new clinical trials in order to approve Extavia in 2009.

**Route of Delivery and Side Effect Profile:** Both Betaseron and Extavia are injected subcutaneously every other day, with the most frequent side effect being flu-like symptoms that gradually diminish over time. Some patients also experience injection site reactions consisting of pain, redness, inflammation, and occasionally tissue breakdown.

### ◆ Interferon beta-1a (Avonex)

**Approval by the FDA:** Avonex (Biogen Idec) is approved by the FDA for the treatment of relapsing forms of MS. In addition, Avonex is approved for people who have experienced their first clinical episode and have MRI-detected brain lesions consistent with MS (clinically-isolated syndrome) but have not yet met the criteria for a definite MS diagnosis.

**Clinical Outcomes:** Avonex has been shown in clinical trials to reduce the number of relapses and the number of new lesions on MRI, as well as to slow the progression of disability. Avonex has also been shown to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in people with a clinically-isolated syndrome.

**Route of Delivery and Side Effect Profile:** This medication is given by intramuscular injection once a week. The most common side effects of Avonex are flu-like symptoms that gradually diminish over time. Injection site reactions were rare.

◆ **Interferon beta-1a** (Rebif)

**Approval by the FDA:** Rebif (Serono/Pfizer) is approved by the FDA for the treatment of relapsing forms of MS.

**Clinical Outcomes:** Rebif has been shown to reduce the number of relapses as well as the number of new lesions on MRI. It has also been shown to delay the time to a second clinical episode (and therefore a confirmed diagnosis of MS) in people with a clinically-isolated syndrome, and the company has applied to the FDA for approval of this use of the medication.

**Route of Delivery and Side Effect Profile:** This medication is given by subcutaneous injection three times per week, with the most frequent side effect being flu-like symptoms that gradually diminish over time. Some patients also experience injection site reactions consisting of pain, redness, inflammation, and occasionally tissue breakdown.

◆ **Glatiramer Acetate**

◆ **Glatiramer acetate** (Copaxone)

Copaxone (Teva Neuroscience) is a synthetic compound made up of four amino acids (the building blocks of protein) that are found in myelin. This drug seems to block myelin-damaging T-cells through a mechanism that is not completely understood.

**Approval by the FDA:** Copaxone is approved by the FDA for the treatment of relapsing-remitting MS and for people who have experienced a first clinical episode and have MRI features consistent with MS.

This medication is also approved in Canada.

**Clinical Outcomes:** Copaxone has been shown to reduce the frequency of MS relapses, as well as the number and volume of brain lesions on MRI.

**Route of Delivery and Side Effect Profile:** This medication is delivered daily by subcutaneous injection. Injection site reactions, including pain, redness, inflammation, and occasionally tissue breakdown, are the most common side effect of Copaxone. On rare occasions, some people taking Copaxone also experienced a brief post-injection reaction involving shortness of breath, flushing, and chest tightening that subsided spontaneously after a few moments. This post-injection reaction is thought to have no lasting consequences.

◆ **Fingolimod**

◆ **Gilenya** (fingolimod)

Gilenya (Novartis) is a new class of medication called a sphingosine 1-phosphate receptor modulator, which is thought to act by retaining certain white blood cells (lymphocytes) in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into

the central nervous system (CNS). Preventing the entry of these cells into the CNS reduces inflammatory damage to nerve cells.

**Approval by the FDA:** Gilenya was approved by the U.S. Food and Drug Administration (FDA) in 2010 for adults with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.

**Clinical Outcomes:** Gilenya has been shown to reduce relapses, the risk of disability progression, and brain lesion activity on MRI. In a one-year head-to-head trial with interferon beta-1a (Avonex), Gilenya was more effective in reducing relapses and disease activity.

**Route of Delivery and Side Effect Profile:** Gilenya is a capsule that is taken once daily. The most common side effects in the clinical trials of Gilenya were headache, influenza, diarrhea, back pain, abnormal liver tests, and cough. Gilenya may also cause a slowed heart rate, particularly after the first dose; an increased risk of infections; swelling of the macula in the eye.

**Managing the Risks Associated with Gilenya:** Prior to starting treatment, the physician may do blood work to determine the person's white blood cell count, test for antibodies to the varicella zoster virus (chicken pox) and provide the vaccination if the person is antibody-negative, and test the person's vision and repeat the testing after 3-4 months of treatment or any time the person reports vision changes. The FDA has also recommended that the patient's heart rate be monitored in the doctor's office for six hours after the initial dose.

Additional information about Gilenya (including results from clinical trials) can be found on the Society's Web site at [www.nationalMSSociety.org/Gilenya](http://www.nationalMSSociety.org/Gilenya). Since new information is announced periodically, it is important to check these resources on a routine basis.

## *Additional Treatment Options*

### ◆ **Natalizumab**

#### ◆ **Natalizumab** (Tysabri)

Tysabri (Biogen Idec/Elan Pharmaceuticals) is a laboratory-produced monoclonal antibody that is designed to hamper the movement of potentially damaging immune cells from the bloodstream, across the blood-brain barrier, and into the brain and spinal cord. The drug inhibits this movement by attaching to alpha 4-integrin, a protein on the surface of immune T-cells that normally enables them to adhere to and pass through the blood-brain barrier. Because of this mode of action, Tysabri is called a selective adhesion molecule inhibitor (or "SAM").

**Approval by the FDA:** Tysabri is approved for all relapsing forms of MS. However, because of the risks associated with Tysabri, the FDA has recommended that it only be used by someone who has not received sufficient benefit from the first-line, injectable medications

or has been unable to tolerate their side effects. The FDA further recommends that Tysabri should not be used in combination with any of the injectable medications.

**Clinical Outcomes:** Tysabri has been shown to reduce the risk of progression of disability, the number of clinical relapses, and the development of new lesions on MRI.

**Mode of Delivery and Side Effect Profile:** Tysabri is delivered by monthly intravenous infusion at approved infusion centers. The most common side effects associated with the monthly infusions include headache, pain in the extremities, fatigue, urinary tract infections, lung infections, vaginitis, joint pain, depression, diarrhea, and pain in the stomach area. Tysabri also increases a person's risk for a rare brain infection called progressive multifocal leukoencephalopathy (PML), that usually results in death or severe disability. The primary risk factors for PML are: prior exposure to the JC virus (antibody-positive on the blood serum test); prior immunosuppressant therapy; on Tysabri for more than two years.

**Managing the Risks Associated with PML:** Because of the risk of PML, Tysabri is available only through a special distribution program called the TOUCH Prescribing Program. The medication can only be prescribed and delivered by physicians, infusion centers, and pharmacies that are registered with the program. And only those patients who are enrolled in the program, and meet all the conditions set by the program, can receive this medication. Prior to starting treatment with Tysabri, and before each infusion, people will be evaluated at the infusion center to ensure that they are still appropriate candidates for this medication.

Additional information about Tysabri (including results from clinical trials) can be found on the Society's Web site at [www.nationalMSSociety.org/Tysabri](http://www.nationalMSSociety.org/Tysabri). Since new information is announced periodically, it is important to check these resources on a routine basis.

## ◆ Mitoxantrone

### ◆ Mitoxantrone (Novantrone)

Novantrone (Serono), an immune suppressant, acts by slowing the division of cells and altering other immune cells and substances.

**Approval by the FDA:** Novantrone is approved by the FDA to reduce neurologic disability and/or the frequency of clinical relapses in patients with secondary-progressive MS (with or without relapses), progressive-relapsing MS, or worsening relapsing-remitting MS. It is not approved for use in primary-progressive MS, nor is it commonly used as an initial treatment.

**Clinical Outcomes:** Novantrone has been shown to slow progression of disability, reduce frequency of relapses, and reduce accumulation of new brain lesions as shown on MRI.

**Mode of Delivery and Side Effects Profile:** Novantrone is administered via intravenous (into the vein) infusion, once every three months. The short-term side effects, including nausea, hair loss, urinary tract infections, and menstrual disorders, are manageable and reasonably well tolerated. Novantrone also increases a person's risk of heart damage and

secondary acute myelogenous leukemia (AML). The risk of AML is higher for those people who have previously been treated with certain types of chemotherapy drugs.

**Managing the Risks Associated with Novantrone:** Because of its potential long-term impact on cardiac function, the FDA cautions that the drug should only be used in those with normal heart function, and that cardiac monitoring should continue for the duration of the treatment. It is further recommended that the total lifetime dose of Novantrone be limited to avoid cardiac problems. As a result, most people will receive a maximum of 8 to 12 doses over two to three years.

Additional information about Novantrone (including results from clinical trials) can be found on the Society's Web site at [www.nationalmssociety.org/Treatments](http://www.nationalmssociety.org/Treatments). Since new information is announced periodically, and additional information becomes available as trials are completed, it is important to check these resources on a routine basis.

### *Other Treatments for Progressive Disease*

Although none have been approved for use in MS, other immunosuppressive agents, including azathioprine (Imuran), cladribine (Leustatin), cyclophosphamide (Cytoxan), and methotrexate are also used to treat progressive disease. Although the dosages used in MS are significantly lower than those used for cancer treatment, the short-term side effects (e.g., nausea, hair loss) and the long-term side effects (e.g., sterility, cardiotoxicity, liver toxicity) are valid concerns.

### **Rehabilitation**

Although we now have disease-modifying therapies available to help slow the progression of multiple sclerosis, most people with MS will continue to have limitations. Rehabilitation in MS involves the intermittent or ongoing use of multidisciplinary strategies to promote functional independence, prevent complications, and enhance overall quality of life. It is an *active* process directed toward helping the person recover and/or maintain the highest possible level of functioning and realize his or her optimal physical, mental, and social potential given any limitations that exist.

Rehabilitation specialists (including physiatrists, physical therapists, occupational therapists, and speech/language pathologists) target the following impairments in their work with individuals with MS: fatigue, weakness, spasticity, cognitive impairments, imbalance, sensory loss, ataxia/tremor, pain, paraparesis, speech and swallowing problems, visual disturbances, and bowel and bladder problems. The goal of these rehabilitation interventions is to reduce "disablement," as defined by the World Health Organization (WHO) in the International Classification of Impairments, Activities, and Participation: A Manual of Dimensions of Disablement and Health (ICIDH-2). Although rehabilitation interventions cannot reverse the neurologic damage caused by MS, they can reduce disablement by:

- ◆ Minimizing the impact of existing impairment(s) on day-to-day functioning
- ◆ Enhancing the person's ability to carry out daily activities and participate to the fullest extent possible in all of his or her life roles

The Society's Expert Opinion Paper entitled *Rehabilitation: Recommendations for Persons with Multiple Sclerosis* can be downloaded from the website at [http://www.nationalmssociety.org/pdf/forpros/ExpOp\\_Rehab.pdf](http://www.nationalmssociety.org/pdf/forpros/ExpOp_Rehab.pdf).

## Psychosocial Support

Psychosocial support is the fifth major category of treatment in MS, encompassing:

- ◆ Disease-related education (more recently termed *psychoeducation*—a supportive educational process designed to enhance people's understanding of the disease, adaptive coping strategies, and available resources)
- ◆ Diagnosis/treatment of emotional and/or cognitive problems
- ◆ Family interventions designed to support family members' efforts to cope with the intrusion of MS into the household
- ◆ Support for people's efforts to remain productively employed as long as they are able and interested, and to transition out of the workforce when, and if, it is necessary to do so
- ◆ Helping individuals with MS and their families to access available resources

## Health and Wellness

In addition, promoting a healthy overall lifestyle helps the person with MS to achieve a sense of emotional and physical well-being. Choosing a balanced, low fat, high fiber diet is an important step in maintaining an appropriate weight and facilitating mobility, bowel function and proper nutrition. Regular approved exercise helps maintain cardiac health, stamina, and mood, and helps manage fatigue, weakness, and bladder and bowel difficulties (Petajan et al., 1996). Stretching exercises can relieve stiffness and improve flexibility and mobility. Preventative health maintenance and establishing prudent habits (regular checkups, using seat belts, and not smoking) are of utmost importance to everyone, but particularly to a person with a chronic condition. Of special interest to people with MS, links between smoking and brain tissue damage have been observed on MRI (Zavidinov et al., 2009) and investigators have found that MS disability progresses more quickly in smokers (Healy et al., 2009).

## RECOMMENDED READINGS

- Ascherio A, Munger K. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Ann Neurol* 2007; 61: 504–513.
- Cohen BA, Rivera VM. PRISMS: The story of a pivotal clinical trial series in multiple sclerosis. *Curr Med Res Opin* 2010 Apr; 26(4): 827–838.
- Cohen JA, Cutter GR, Fischer JS, et al.; IMPACT Investigators. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002 Sep 10; 59(5): 679–687.
- Comi G, Martinelli V, Rodegher M, et al.; PreCISe study group. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome

- (PreCISe study): A randomised, double-blind, placebo-controlled trial. *Lancet* 2009 Oct 31; 374(9700): 1503–1511. Epub 2009 Oct 6.
- Coyle PK. Early treatment of multiple sclerosis to prevent neurologic damage. *Neurology* 2008; 71: S3–S7.
- Ebers GC, Reder AT, Traboulsee A, et al.; Investigators of the 16-Year Long-Term Follow-Up Study. Long-term follow-up of the original interferon-beta1b trial in multiple sclerosis: Design and lessons from a 16-year observational study. *Clin Ther* 2009 Aug; 31(8): 1724–1736.
- Ebers GC, Sadovnick AD, Dymont DA, et al. Parent-of-origin effect in multiple sclerosis: Observations in half-siblings. *Lancet* 2004 May 29; 363: 641–649.
- Frohman EM, Shah A, Eggenberger E, et al. Corticosteroids for multiple sclerosis: I. Application for treating exacerbations. *Neurotherapeutics* 2007 Oct; 4(4): 618–626.
- Goodin DS. Disease-modifying therapy in multiple sclerosis—Update and clinical implications. *Neurology* 2008; 71: S8–S13.
- Goodin DS, Cohen BA, O'Connor P, et al. Assessment: The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review). *Neurology* 2008; 71: 766–773.
- Healy BC, Eman NA, Guttman CRG, et al. Smoking and disease progression in multiple sclerosis. *Arch Neurol* 2009 July; 66(7): 858–864.
- IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993 Apr; 43(4): 655–661.
- Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000 Sep 28; 343(13): 898–904.
- Johnson KP, Brooks BR, Ford CC, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. *Mult Scler* 2000 Aug; 6(4): 255–266.
- Kappos L, Radue EW, O'Connor P, et al.; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010 Feb 4; 362(5): 387–401. Epub 2010 Jan 20.
- Kurtzke JF. Epidemiology of multiple sclerosis. Does this really point toward an etiology? Lectio doctoralis. Neuroepidemiology Section (127), Veterans Affairs Medical Center, 50 Irving Street, NW, Washington, DC 20422, USA. *Neurol Sci* 2000; 21: 383–403.
- Lublin F, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* 1996; 46: 907–911.
- Neuhaus O, Kieseier BC, Hartung H-P. Immunosuppressive agents in multiple sclerosis neurotherapeutics. *J Am Soc Exp NeuroTherapeutics* 2007 Oct; 4: 654–660.

- Noseworthy JH. Management of multiple sclerosis: Current trials and future options. *Curr Opin Neurol* 2003 Jun; 16(3): 289–297.
- Petajan JH, Gappmaier E, White AT, et al. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996 Apr; 39(4): 432–441
- Polman CH, O'Connor PW, Havrdova E, et al.; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006 Mar 2; 354(9): 899–910.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011 Feb; 69(2): 292–302. doi: 10.1002/ana.22366
- Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald" criteria. *Ann Neurol* 2005; 58: 840–846.
- Poser C. Recent advances in multiple sclerosis. *Symp Neurology Med Clinics North America* 1972 Nov; 56(6): 1343–1362.
- Rosati G. The prevalence of multiple sclerosis in the world: An update. *Neurol Sci* 2001 Apr; 22(2): 117–139.
- Sawcer S, Lander ES, Daly MJ, et al. Risk alleles for multiple sclerosis identified by a genome-wide study. *N Engl J Med* 2007 Aug 30; 357(9): 851–862. Epub 2007 Jul 29.
- Schapiro RT. Managing symptoms of multiple sclerosis. *Neurol Clin* 2005 Feb; 23(1): 177–178.
- Schapiro RT. The symptomatic management of multiple sclerosis. *Ann Indian Acad Neurol* 2009 Oct–Dec; 12(4): 291–295.
- Serafini B, Rosicarelli B, Franciotta D, et al. Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. *J Exp Med* 2007 Nov 26; 204(12): 2899–2912. Epub 2007 Nov 5.

## RECOMMENDED RESOURCE

National MS Society's Professional Resource Center ([www.nationalMSSociety.org/PRC](http://www.nationalMSSociety.org/PRC);  
[healthprof\\_info@nmss.org](mailto:healthprof_info@nmss.org))

- ◆ Information
- ◆ Professional publications
- ◆ Clinical consultations
- ◆ Comprehensive library services

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