

CHAPTER I

Optimizing Your Medical Management

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Multiple sclerosis is a complex disability. The two goals of this chapter are for you to understand your disability and gain a wider perspective on ways to manage it. You do have choices in getting a better handle on your multiple sclerosis (MS).

THE PREVALENCE OF MULTIPLE SCLEROSIS

As a person with multiple sclerosis, you are certainly aware of your own situation, but it may be helpful to know that you are not alone. In Western countries, where MS afflicts one in 1,000 people, it is the leading nontraumatic cause of neurological disability in young adults (LaRocca 2005). MS is not new and has probably existed for hundreds or even thousands of years. Perhaps the first case to have been described was that of St. Lidwina of Schiedam (1380–1433), although Charcot in France is credited with having described and established MS as a unique disease in 1877.

MS affects millions worldwide and approximately 400,000 Americans (Rosenberg 2005). Caucasians, especially those of Northern European heritage, have higher rates than other races (Rosenberg 2005). MS is rare in equatorial areas of the world and more frequent at higher latitudes both north and south of the equator (Guarnaccio and Booss 2005). This geographic gradient is also found within the U.S., where the states of Vermont and Washington have the highest prevalence rates in the country (Kurtzke 2005).

Children may be affected by MS, but the age of onset is usually between ages fifteen to fifty (Rosenberg 2005). The peak age of onset for the most common type of MS, the type called “relapsing-remitting MS,” is in the late twenties (Kraft and Cui 2004). Women are affected more than twice as often as men, a gender predilection that is found in a host of other autoimmune diseases, including rheumatoid arthritis, lupus, and Graves’ disease (Rosenberg 2005).

In the United States, MS appears to be more common in upper socioeconomic groups (Kraft and Taylor 1998). This may be related to genetic factors, unidentified environmental factors that are more common in well-to-do households, or due to the better access to medical care that affluent people have.

WHAT CAUSES MS?

The short but unsatisfying answer to the question above is “we don’t know.” Certainly, genetics play a part in determining who gets the disease. The risk of a daughter of someone with MS also acquiring the disease is about 3 percent—that’s more than tenfold higher than the risk for the general population (Hensiek, Roxburgh, and Compston 2003). The risk for an identical twin is about 30 percent (Guarnaccio and Booss 2005). Although this fact demonstrates the heritability of MS, it also indicates that MS is not purely genetic, or the risk for an identical twin of someone with MS would be about 100 percent.

If you have MS, it is a combination of genes, not one single gene, that predisposes you to getting the disease. The HLA gene group, used to match organ donors with recipients, is where some of the genes linked to MS have been found. These genes help the immune system to distinguish self from nonself. The protein products of these genes may set the stage for an immune response against the brain in MS in much the same way that they can trigger rejection of a mismatched donor organ.

Epidemiological data suggests that MS is caused or triggered by an environmental factor in people who are genetically susceptible. Whatever the trigger, it appears that it occurs years before the onset of MS (Kurtzke and Wallin 2000). We still have a long way to go before the environmental factors are well understood. For example, we’ve learned that smoking doubles the risk of getting MS, but we haven’t got a clue yet whether it is a chemical (or chemicals) in the tobacco smoke or something else in the smokers’ environment, such as lighter fluid, that may contribute to the disease.

Great efforts have been made to uncover just what in the environment might be causing MS. It could be a virus, such as the Epstein-Barr virus, but many investigations of many different viruses have been inconclusive. Vaccinations, bacterial infections, head injury and trauma, stress, cold climate, vitamin deficiency, sunlight deficiency, exposure to dogs, processed foods, and fat have all been studied, but the jury is still out as to what specific factors in the environment cause MS. We do know with some certainty that claims of toxins, dental amalgams, or food substitutes causing MS are baseless (Bowling 2001).

HOW DOES YOUR IMMUNE SYSTEM RELATE TO YOUR MS?

The immune system is vital to protecting humankind against an environment teeming with bacteria, viruses, and other pathogens (what your mother might call “germs”). It even protects us against cancer. In MS, the immune system conducts what could euphemistically be called “friendly fire.” What this means is the immune response is misdirected against elements of our own bodies, specifically the central nervous system (CNS), which is composed of the brain, brain stem, and spinal cord. Nerves running from the spine out to the limbs and muscles are not directly affected by MS.

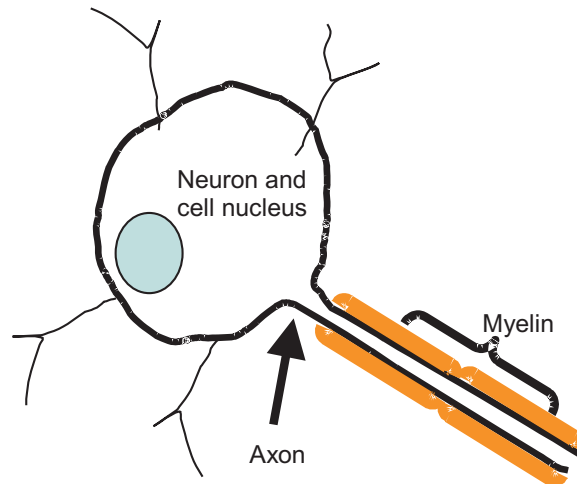


Figure 1.1: Myelin, the target of the attack.

Through very complex signaling mechanisms, white blood cells known as *T cells* (“T” because they mature in the thymus gland in the chest) become sensitized against submicroscopic particles. Once activated in the blood, they migrate across the blood-brain barrier into the brain. Once inside the nervous tissue, these white blood cells induce an immune reaction (inflammation) against *myelin*, which is a substance composed of fat and protein that functions as insulating material for nerves. The resulting myelin damage is called *demyelination*.

Nerve branches (called *axons*) and the cell bodies of neurons are also damaged as bystanders in this inflammatory process. The inflammation is usually patchy. Each patch is referred to as a *lesion*; lesions usually vary in diameter from the size of a peppercorn (3 mm) to the size of a nickel (2 cm).

Once a new lesion appears on your brain MRI (magnetic resonance image), it usually stays there permanently. This doesn’t necessarily mean that it is a lost cause. The brain has repair mechanisms to restore myelin, a process called *remyelination*. Partial or complete remyelination occurs in about half of all MS lesions. Even when MS lesions are completely remyelinated, however, the myelin is thin and doesn’t function perfectly. To keep it simple, let’s remember that “demyelination” is bad and “remyelination” is good.

THE FOUR TYPES OF MS

Multiple sclerosis is a *heterogeneous disease*, which means that it can affect you in many different ways. There are four basic types of MS, although there are several other rare variations of MS-related disease. If you have MS, it usually begins with an attack of neurological symptoms that subside partly or completely in a few weeks or months. Such attacks are called “exacerbations” or “relapses.”

1. If you have the most common type of MS, known as *relapsing-remitting MS (RRMS)*, you will have sporadic exacerbations, at an average rate of about once every seventeen months, but you are neurologically stable between exacerbations.

POP QUIZ! What do MS, rheumatoid arthritis, and juvenile diabetes mellitus have in common?

2. Over a few decades, most people with RRMS (about two-thirds) progress to a second type of MS, known as *secondary-progressive MS (SPMS)*. Rather than having a stable baseline punctuated by exacerbations, people with SPMS have a gradual, progressive decline in function while exacerbations become less frequent. The only way to get to SPMS is by first having passed through RRMS. This is a definitely difficult road to hoe, but new medications are helping us slow this progression.
3. About 10 percent of people with MS begin with progressive disease from the beginning without any sharp exacerbations or remissions. You are then said to have *primary-progressive MS (PPMS)*. With PPMS, you tend to be older at diagnosis than people with RRMS and the ratio of females to males is more equal.
4. The fourth type, *progressive-relapsing MS*, is rare; it shows progression from the beginning along with relapses.

Pathological analysis of brain specimens also has found four basic patterns of the disease that involve differences in immunological activity and cell death. These patterns, however, don't match up with the four clinical types of MS that the patients carried.

There is speculation that MS ultimately may prove to be a syndrome caused by a small number of separate diseases that may require different treatments. Incidentally, the only way to do such pathological analysis is by having a brain biopsy or an autopsy. Obviously, neither of these options is very appealing.

THE MEDICAL DIAGNOSIS OF MS

Medical diagnosis depends on the nature of the disease. If a disease is hereditary, it can now be diagnosed by testing the patient's DNA for the specific genetic marker of the disease. Infectious diseases are diagnosed by identifying the invasive organism with a microscope by isolating it *in vitro* (outside the body and in an artificial environment), or by finding antibodies produced by the host's body to fight against the organism within the host's tissues or fluids.

For all immunological diseases including MS, however, there is no genetic, bacterial, or viral test that can make the diagnosis. Immune disorder diseases are generally diagnosed by criteria that include clinical information (physical examination and symptom history) and laboratory findings (self-antibody tests and pathology results).

Answer: They are all autoimmune diseases.

In MS, magnetic resonance imaging (MRI) of the brain and spinal cord and electrical tests of nerve pathways also can help in establishing the diagnosis. When there is uncertainty about the diagnosis of MS, a lumbar puncture (also called an “LP” or “spinal tap”) may help to make or break the diagnosis by allowing inspection of the cerebrospinal fluid.

The Criteria Used to Diagnose MS

There are detailed criteria for diagnosing MS, the current standard of which is called the McDonald Criteria (McDonald et al. 2001). Here, we will provide a simplified explanation. The basic concept is that MS requires multiple abnormalities (that’s why it’s called “multiple” sclerosis) and that these abnormalities must involve the central nervous system. The most frequent initial abnormalities are, in descending order: (1) sensory (numbness and tingling of a limb or the face); (2) visual (loss or alteration of vision in one eye); (3) weakness and walking difficulty; (4) incoordination (an inability to coordinate muscular movements); (5) double vision; (6) vertigo; (7) bladder, bowel, or sexual dysfunction; (8) cognitive problems. These multiple abnormalities must occur in a pattern that fits the formula.

How the Diagnosis Is Applied

There is a very standard procedure in diagnosing MS that may be helpful for you to understand. Making the MS diagnosis boils down to the following formula: SIT + SIS + NBE. SIT stands for “Separation In Time.” The time between the onset of two abnormalities must be more than thirty days. This is an arbitrary cutoff point that was chosen to aid in diagnosis. SIS stands for “Separation In Space.” This means the abnormalities must be at different sites of the CNS. NBE stands for “No Better Explanation.” This means corroborating tests are consistent with MS (e.g., MRI shows lesions only in the white matter of the brain, lumbar puncture shows elevated or specific immune globulins in the cerebrospinal fluid compared with the serum), and tests for alternative diagnoses (e.g., viral infection) are negative.

A Short Checklist for a Diagnosis of MS

Generally, all three boxes must be checked to make the diagnosis. However, a new lesion on follow-up MRI can be taken as evidence of a second attack to establish the Separation In Time criteria.

- Two or more neurological symptoms or signs; onset separated by more than thirty days. (Separation In Time [SIT])
- Abnormalities found in two or more different sites in the central nervous system. (Separation In Space [SIS])
- Your doctor has considered other possibilities and found no evidence of another cause. (No Better Explanation [NBE])

Worksheet 1, below, will help you better understand the diagnosis process. Why don’t you try to answer the following questions before you read the answers that follow.

WORKSHEET I: HOW TO APPLY THE FORMULA FOR DIAGNOSIS

- A. Neal had an attack of arm numbness, arm weakness, imbalance, and confusion all starting one after another over a month-long period. The brain MRI shows multiple lesions in the white matter. Tests for diseases other than MS are all negative. Does Neal have MS?
- B. Tammy has had seven attacks of visual changes in the past four years. Her MRIs and evoked potential tests show lesions at both optic nerves, but no other sites in the central nervous system. Does Tammy have MS?
- C. Mary has kidney disease due to *vasculitis* (inflammation of blood vessels). She developed paraplegia from a spinal cord lesion. Four months later, she noticed double vision when she looked down or to one side. Her MRIs show one lesion in the spinal cord and another in the midbrain. Does Mary have MS?
- D. Rod has never had an “attack” of symptoms. Over five years, he has gradually noticed weakness and spasticity in his legs, bladder urgency, memory and concentration problems that interfere with his job, and fatigue that is much worse in hot weather. His MRIs show multiple lesions in the brain and spinal cord, and lumbar puncture results are positive for the changes seen in MS. There is no family history or other findings to suggest another disease. Does Rod have MS?

Answers

- A. Neal has the SIS and the NBE, but he doesn't have the SIT, because all of these symptoms occurred within one month. He cannot be diagnosed with MS until he suffers another attack. His doctors might advise treatment for MS anyway, because he is at high risk for developing the disease.
- B. Tammy cannot be diagnosed with MS because she doesn't have the SIS. Her diagnosis of MS will have to wait until she develops an abnormality other than visual loss. In the meantime, she will be treated for recurrent optic neuritis.
- C. Mary has both SIT and SIS. However, she has vasculitis that can damage the central nervous system in a way similar to MS. Her diagnosis cannot be MS, because she fails the NBE clause.
- D. Even though Rod has not had MS attacks, he still has evidence of SIT, SIS, and NBE. He could be diagnosed with primary-progressive MS.

YOUR PROGNOSIS AS A PERSON WITH MS

Over the first two years, the course of your MS predicts how you will do in the long run. If you have multiple attacks every year and significant disability by five years, you are probably not going to do as well as someone who experiences two attacks and no disability after five years. Men tend to have a worse prognosis than women. And those whose disease starts after the age of forty tend to do worse than those with earlier onset (Kraft et al. 1981).

Studies of large numbers of patients have provided a rough estimate of what can be expected. Your mild disability could mean marked involvement of one aspect of the CNS, such as sharply decreased touch sensitivity or pain sensation in one limb, or mild abnormalities in several areas of the CNS. The median time until a cane may be required is twenty years, and median time for wheelchair assistance is approximately thirty years (Pittock et al. 2000).

Based on clinical neuropsychological assessments, approximately 45 to 65 percent of individuals with MS exhibit some form of cognitive limitation (Rao 1995). These limitations, however, may or may not impair daily living activities or working. Impaired recent memory, slowing of information processing, abstract reasoning, and problem solving are the most frequent cognitive problems. (See chapter 10 for information about having your potential concerns assessed.)

With time, people with MS tend to acquire more brain lesions. As the brain lesions seen on the MRI increase, cognitive problems tend to worsen. Cognitive function does not correlate well with the physical deficits caused by MS. You may physically feel reasonably good, but be losing some ground cognitively. Even the medical community did not understand this well for years. It is, however, important for you to bear in mind that these facts are based on patient data from an era when most people were generally not treated for MS. There is good reason to believe that the prognosis will improve as medical treatment of the disease improves. Early medication intervention is now the rule.

THE RELATIONSHIP BETWEEN RELAPSES AND DISABILITY

Once you have received a diagnosis of MS, all additional attacks are called “relapses.” One group of investigators examined all of the existing U.S. clinical and historical MS data sets to test the effect of relapses on the development of disabilities. They found that each relapse carries a 42 percent chance of adding measurable residual impairment (such as an abnormal sign on physical examination) (Lubin, Baier, and Cutter 2003).

Abnormalities that persist for three months postrelapse usually become permanent. In contrast, French investigators reported that relapse rates predict the development of new disability only up to a point of mild permanent disability (Confavreux et al. 2000). At higher levels of disability, relapse rates do not seem to affect the rate of worsening neurological status. Together, these findings suggest that relapses are associated with worsening disability at the early stages of the disease, but not after marked disability has occurred. Therefore, to have an effect on disability, we say again that your treatment should be started early.

UPDATING YOUR KNOWLEDGE OF MEDICATION

We are fortunate to have several MS disease-modifying medications available for your treatment that will slow the progression of the disease. Although none of the drugs stop MS, they are designed to reduce relapse rates, reduce the number of new lesions on MRI scans, and reduce disability, thereby improving the quality of your life. Medication is selected on a case-by-case basis and determined by what is best for you. It is helpful to remember that medication research study results are based on group averages, however, and that individual responses to medication may differ.

The following medication chart reviews important points when you are selecting an MS disease-modifying medication. These points include consideration of your doctor's recommendations, your personal health, readiness to start treatment, personal choices, lifestyle, support system involvement (family and/or close friends), finances, education about MS disease-modifying medications, and responses to treatment.

If the medication you pick doesn't best meet your needs, you will want to talk with your doctor, make medication adjustments as directed, allow enough time to adjust to the revised treatment plan, and reevaluate how you think the medication is working to slow your disease. If you are having problems taking the medication or you don't like how it makes you feel, let your doctor and nurse know that. They want you to be successful in whatever treatment you choose.

Multiple sclerosis disease-modifying medications are to be taken for a lifetime unless a cure for MS is developed. Luckily, there are many research studies in progress that are giving us new information about current treatments that can lead to changes in medication protocols. Achieving the best outcomes is greatly influenced by an open and honest relationship between you and your significant others, and your doctor, nurse, and healthcare team.

In the U.S., there are currently five Food and Drug Administration (FDA) approved medications for MS. These drugs include three forms of recombinant human interferon:

- Interferon beta-1a (Avonex),
- Interferon beta-1a (Rebif), and
- Interferon beta-1b (Betaseron), and
- a synthetic copolymer glatiramer acetate (Copaxone), and
- a chemotherapeutic agent mitoxantrone (Novantrone).

These five drugs have a direct influence on the course of MS and are designed to slow its progression. Interferon beta-1a, interferon beta-1b, glatiramer acetate, and mitoxantrone are approved for relapsing-remitting MS. Mitoxantrone is also effective for secondary-progressive MS.

The following table of medications will enable you to compare the pros and cons of these medications. Although all these drugs have side effects, most people find them manageable. This table may be very worthwhile for you to review, particularly when you are at the point of deciding what your first medication should be. For a more complete review and comparison of these therapies, see Goodin et al. (2002).

Choosing What Is Best for You

Table I.1: Multiple Sclerosis Disease-Modifying Medications					
Brand-Name	Avonex	Betaseron	Rebif	Copaxone	Novantrone
Generic Name	Interferon beta-1a	Interferon beta-1b	Interferon beta-1a	Glatiramer acetate	Mitoxantrone
Administration	intramuscular injection	subcutaneous injection	subcutaneous injection	subcutaneous injection	intravenous infusion
Pre-filled Syringe	Yes	No	Yes	Yes	No
Automatic Injection Device	No	Yes	Yes	Yes	No
Frequency of Injections	Once a week	Every other day	Monday, Wednesday, Friday	Daily	Once every three months for up to two to three years only
Injection Site Reaction	Rare	Yes	Yes	Yes	No
Injection Site Necrosis (skin breakdown)	No	Possible	Possible	No	No
Flu-like Symptoms	Yes	Yes	Yes	No	No
Panic-like Reaction	No	No	No	Yes	No
Blood Tests	Yes	Yes	Yes	No	Yes
Refrigeration	Yes	No	Yes	Yes	Not applicable
Stop if Pregnant	Yes	Yes	Yes	Yes	Yes
Patient Training Kit	Yes	Yes	Yes	Yes	Yes
Financial Assistance Program	Avonex Access Program 800-456-2255	Betaseron Foundation 800-998-5777	Rebif MS Lifelines 877-447-3243	National Organization for Rare Disorders 203-746-6518	MS Lifelines 877-447-3243
Patient Support Program	Avonex Alliance 800-456-2255	Pathways 800-788-1467	MS Lifelines 877-447-3243	Shared Solution 800-887-8700	MS Lifelines 887-447-3243

Making the Right Medication Choice

If you need to make a medication choice, the following worksheet may be helpful. You may need to take into account all of the items below, including the actual cost to you of the medication, excluding financial assistance from the relevant pharmaceutical company. Now let's use the worksheet.

WORKSHEET 2: MEDICATION CHOICES

When considering your choice of medication, you need to consider the following:

Item number

Your notes/Critical observations

1. Doctor's recommendation _____

2. Personal health choices _____

3. Readiness to start treatment _____

4. Lifestyle considerations _____

5. Support concerns _____

6. My finances _____

7. Education about medication _____

8. Response to treatment _____

My top medication choice(s) are: _____

The material on this sheet can easily be discussed with your doctor or simply used as the basis for your final choice.

THE IMPORTANCE OF EARLY TREATMENT

Early treatment with *immunomodulation* (altering your immune system's responses with the use of a variety of agents) is recommended with the aim of reducing relapses and delaying disability. Research suggests the positive effects of MS disease-modifying medications are maximized if they are started soon after the initial diagnosis of MS is made. If you start taking a medication early in the course of your illness, you will respond better than those who begin treatment later. Treatments show a decrease in relapse rates for patients using the interferons, glatiramer acetate, or mitoxantrone (Goodin et al. 2002).

The National Multiple Sclerosis Society (2005, 1) states, "Initiation of therapy with an immunomodulator is advised as soon as possible following a definite diagnosis of MS with active disease . . ." You may have heard that this is not the case, but today early medication treatment is the "gold standard" in the treatment of MS. The goal of early intervention is based primarily on the fact that inflammation of the CNS (brain and spinal cord), which is characteristic of MS, may lead to irreversible *axon* destruction, sometimes early in the course of the disease. (An axon is a nerve cell extension that usually conducts impulses away from the cell body.) If you can interrupt this process, then more permanent neurological damage may be delayed. Although the MS disease-modifying medications do not reverse damage, they can decrease future damage.

You may believe that you don't have a sufficient number of MS symptoms or haven't had a sufficient number of relapses to justify starting an MS disease-modifying medication. But it is important to know that many people are unaware of the true number of relapses they have had or are still experiencing. One estimate holds that for every relapse you know about, may have had, or are still experiencing, at least five silent relapses or exacerbations have occurred that you don't know about.

IMMUNOMODULATING MEDICATIONS

In this section you'll find up-to-date information on the medications commonly used for treating MS. These include the interferons, Copaxone (glatiramer acetate), and Novantrone (mitoxantrone). These medications have become widely available only in the last decade.

Interferons

Interferons are naturally produced proteins made by different cells of the body, often in response to infection. These molecules interfere with the replication of many viruses. All interferons can cause flu-like symptoms, such as fever, chills, sweating, muscle aches, malaise, fatigue, and headaches. For most people, these flu-like symptoms lessen or disappear with time. To decrease flu-like symptoms, it is suggested you start the interferon at a reduced dose and slowly increase the dosage over several weeks.

An example would be to start the interferon at a quarter-strength dose for one to two weeks, then increase the amount by one-quarter strength dose every one to two weeks, (as tolerated), up to a full-strength dose. Flu-like symptoms can be effectively managed with acetaminophen (Tylenol), aspirin (Bufferin), or ibuprofen (Motrin) taken before and after the injection. For most people, with time, the need for this preventive medication disappears.

To further manage the flu-like symptoms, it is suggested that you take interferon at bedtime to allow yourself time to sleep through the first several hours, during which time the side effects may occur.

Interferons may cause pain or discomfort at the injection site and abnormal blood tests. It is recommended that blood tests be performed before treatment starts and every three to six months during treatment.

Avonex (Interferon Beta-1a)

Avonex became available in 1996. It is designed for relapsing-remitting forms of MS. It reduces the number of relapses or exacerbations the patient experiences. It is given by *intramuscular injection* (into the muscle) once a week. The amount is 30 mcg/6 million IU, per dose. Avonex is available in a prefilled syringe or as either a liquid or powdered form that you can mix. Because Avonex is injected deep into a muscle, rarely will you see any injection site reaction or feel any injection site discomfort. However, since Avonex is an interferon, it may cause flu-like symptoms.

If you are employed, to initially adjust to the medication, you might want to take Avonex on Friday nights because if flu-like symptoms do occur, they will not happen during a workday. It is recommended you choose the most convenient day of the week for yourself. To learn how to administer the injection yourself, it is best to be taught by a qualified doctor or nurse who is knowledgeable about MS. However, if this is not possible, training may be provided by a nurse recommended by the manufacturer of Avonex.

Avonex has demonstrated: (a) a reduction in relapse rate, (b) a slowing in the disability's functional impairing effect, and (c) a reduction in active lesions as shown on an MRI (Jacobs et al. 1996). Note that it may take several months for the Avonex to begin working.

Rebif (Interferon Beta-1a)

Rebif became available in 2002. In the United States, it is the newest interferon for MS. Rebif is nearly identical to Avonex; however, the two medications differ slightly in their manufacturing process and in the preservatives added to the final solution. Rebif is given by *subcutaneous injection* (in the tissue between the skin and muscle). The recommended dose and schedule for Rebif is 44 mcg three times a week. Ideally, you should take the medication the same three days of each week. For example, inject the Rebif every Monday, Wednesday, and Friday. It is also best to take the medication at the same time each day; preferably at bedtime.

Rebif is supplied in a prefilled syringe. It also comes with an automatic injection device that makes giving the injection easier for you. The automatic injection device also causes reduced injection site skin reactions. Because the Rebif is administered into the subcutaneous tissue, localized injection site skin reactions may last several weeks before disappearing. These reactions may be redness, swelling, itching, and pain.

One serious side effect has been reported in a small number of people using Rebif. That is injection site tissue damage or *tissue necrosis* (tissue death). The necrosis may occur at a single injection site or at multiple injection sites. If an injection site becomes very painful, swollen, or looks infected and doesn't heal within a few days, call your doctor.

There is an ongoing debate over the best Interferon beta-1a (Avonex versus Rebif) dosage and whether the higher weekly dose of Rebif results in better health outcomes. Evidence may indicate that the interferon beta formula, dose, and frequency of injection may influence patient outcomes, with the outcomes showing more favorable change toward the more intense schedules of Rebif and Betaseron (see below). Rebif has demonstrated: (a) a reduction in relapse rate and (b) a reduction in progression of the

disease and (c) a reduction in new lesions as seen on an MRI. Regular tests to monitor liver and blood counts are recommended.

Betaseron (Interferon Beta-1b)

Betaseron became available in 1993. It is designed for relapsing forms of MS. It reduces the number of relapses or exacerbations a person experiences. It is given by subcutaneous injection, at a dose of 0.25 mg/8 million IU, every other day. You can also use an automatic injection device with Betaseron. Because the medication is administered into the subcutaneous tissue, localized injection site reactions may occur, and they may last several weeks before disappearing. These reactions can be redness, swelling, itching, and pain.

A serious side effect has been reported in a small percentage of people on Betaseron. That is severe skin damage or tissue necrosis at injection sites. The necrosis may occur at a single or multiple injection sites. If one of the injection sites becomes very painful, swollen, or looks infected and doesn't heal within a few days, call your doctor. You will need to rotate injection sites regularly and use correct injection technique to reduce the chance of this problem occurring. If tissue necrosis does occur, notify your doctor immediately.

Because flu-like side effects may occur with Betaseron, take it at bedtime, with acetaminophen (Tylenol), aspirin (Bufferin), or ibuprofen (Motrin). Start the Betaseron at a reduced dose and gradually work up to taking it at full strength over several weeks.

To learn the best injection technique and how to manage the side effects of medication, we recommend again that you receive training from a doctor or nurse who is knowledgeable about MS. If this is not possible, the manufacturer of Betaseron has a nursing staff who will come to your home and provide injection training. While you are on Betaseron, your blood will need to be monitored regularly. Betaseron has demonstrated: (a) a reduction in relapse rate and (b) a reduction in active lesions as seen on an MRI. Note that it may take several months for the Betaseron to start working. Regular tests to monitor liver and blood counts are recommended.

Copaxone (Glatiramer Acetate)

Copaxone became available in 1996. It is designed for relapsing-remitting MS. It is given by subcutaneous injection every day. The dose is 20 mg per day. For the consumer's convenience, Copaxone comes in a prefilled syringe with an automatic injection device.

Copaxone is not an interferon. It is believed to work by activating anti-inflammatory regulatory T cells, which then migrate into the CNS to inhibit local immune reactions.

Compared to interferons, Copaxone has different side effects. With Copaxone, you may experience localized injection site skin reactions that last for a few days. These reactions typically consist of redness, itching, pain, swelling, and a lump under the skin at the injection site(s). These reactions are usually mild and seldom require medical treatment.

Copaxone has sometimes been associated with a wasting of the fat tissue at the injection site. Also, with this medication there is about a 10 percent chance of experiencing an immediate post-injection reaction that feels like a panic reaction. These symptoms consist of flushing (feeling warm and/or redness), sweating, chest pain or tightness, rapid heart rate, anxiety, throat tightness, and trouble breathing. Usually, this reaction is not harmful and it is not associated with a heart attack or an allergic

reaction to Copaxone. These symptoms generally occur within minutes after an injection and last for about fifteen to twenty minutes. They go away by themselves without requiring medical treatment.

If you experience this reaction, sit down, try to relax, take some deep breaths, and wait for the symptoms to pass. Because Copaxone does not cause the flu-like symptoms typical of the interferons, it can be taken at any time of the day. However, you may prefer to take the Copaxone at bedtime when you are less hurried and have more time to attend to the injection. You don't need to take blood tests while taking Copaxone.

Copaxone has demonstrated: (a) a reduction in relapse rate, (b) a reduction in time for disability to occur, and (c) a reduction in active lesions as seen on an MRI. It may take several months for the Copaxone to start working.

Taking Immunomodulating Medications: Building a Support System

It is normal to be nervous about starting an injectable medication. Your doctor and nurse will help you through this difficult period. The first injection is the hardest but it does get easier. It's always a good idea to bring someone with you for your first injection training. Two sets of ears and eyes are better than one. A family member or friend, someone who has been through the teaching, can help you with your injections. Most medication side effects are easily managed. Tell your doctor and nurse if you're having problems, especially if you're thinking about stopping the medication. The flu-like side effects of the interferons usually lessen and disappear after several months.

All MS disease-modifying medications are expensive. However, the good news is all of these medications have financial assistance programs. Speak to your doctor's office staff to find out about these programs. Ultimately, you must decide which drug will work best for you, but your doctor and nurse can help you to make this decision.

Checklist 1: Injection Tips Review

The following information will help you with your MS injections, regardless of which medication you choose. If you're using one of the medications previously discussed, please review these concerns carefully by reading the checklist below and asking yourself all of the following questions:

- _____ Before I started using MS disease-modifying medication, did I tell my doctor about all the other medications I'm already taking? (This includes prescription, nonprescription, herbal, and other naturopathic medications.)
- _____ Do I check the expiration date on the medication? (Do not use it if it has expired.)
- _____ Do I allow the medication time to warm up to room temperature before doing the injection? (Cold solution can hurt.)
- _____ If I am unable to inject the medication myself, can a family member or friend be taught the injection technique to help me?

- ___ Do I wash my hands and clean my skin before every injection to reduce the risk of infection?
- ___ Do I briefly ice my skin, before and/or after an injection to reduce injection site pain or discomfort?
- ___ Do I cleanse the injection site with alcohol, or another antiseptic solution, before giving the injection?
- ___ Do I allow time for the antiseptic solution to dry before giving the injection?
- ___ If the antiseptic solution is irritating to my skin, do I use unscented soap instead?
- ___ Do I use a dry injection needle? (Do not squirt any medication out of the syringe and onto the needle before giving the injection, because the medication can burn and irritate the skin.)
- ___ There may be small air bubbles in the prefilled syringes of some of the MS disease-modifying medications. Do I try to expel the air bubbles from the syringe before injecting? (**Note:** These air bubbles are *not* harmful and expelling them may put irritating solution on the tip of the needle, which can get on the skin.)
- ___ Do I gently swirl (not shake) the medication that comes in the liquid and powdered form that must be mixed?
- ___ Do I try to give myself my injection at the same time every day?
- ___ Do I unnecessarily pinch the skin for the subcutaneous injections? (Pinching the skin is not necessary and may bruise the site.)
- ___ Do I rotate injections to all skin sites and make sure I spread the injections out around a site? (That is, I don't always come down on the same puncture point.)
- ___ Do I avoid administering injections into skin that is reddened, bruised, infected, scarred, or hard?
- ___ If I have hives, dizziness, severe pain at an injection site, or other abnormal changes with my health, do I tell my doctor and nurse as soon as possible?
- ___ If I use Copaxone, do I avoid massaging the injection site until twenty-four hours after the injection?
- ___ Do I use an automatic injection device if one is available?
- ___ Have I had the automatic injection device adjusted for different injection site locations?
- ___ Do I lightly rest the automatic injection device on the skin? (Do not punch the skin with it.)

_____ Do I ever consider reusing needles or syringes? (**Caution:** Injection needles are for one-time use only.)

_____ Have I checked with my local public health department, doctor, nurse, or pharmacist about needle and syringe disposal? (There may be special state and/or local laws for disposing used equipment. Do not throw needles or syringes directly into the garbage or recycling container.)

_____ Do I store my medication, needles, syringes, and needle disposal container out of the reach of children?

Answer the questions below if they are applicable:

_____ Do I ever consider taking MS disease-modifying medication if I am planning on becoming pregnant, or if I am pregnant, or breast-feeding? (**Caution:** Do not use MS disease-modifying medication if planning on becoming pregnant, or you are pregnant, or breast-feeding.)

_____ If I become pregnant while taking an MS medication, I will stop and tell my doctor.

In terms of my medication and injection procedures, I need to remember the following:

NOVANTRONE (MITOXANTRONE): AN IMMUNOSUPPRESSIVE

Novantrone became available for multiple sclerosis in 2000. It is approved for worsening relapsing-remitting MS, secondary-progressive MS, and progressive-relapsing MS. It has been used as a chemotherapy medication for over ten years in the treatment of breast cancer, prostate cancer, lymphomas, and other malignancies. Novantrone is an *immunosuppressive drug*, which means it suppresses the immune system, and disrupts or kills certain cells in the immune system that play a role in destroying myelin and causing lesions in the brain and spinal cord of MS patients. Other drugs for MS (Avonex, Rebif, Betaseron, Copaxone) are not immunosuppressive, they are *immunomodulators*, which means they alter or change immune responses, they do not suppress them.

Novantrone is given by *intravenous infusion* (into a vein) once every three months for approximately two to three years. It is then stopped because of concerns about heart damage. The risk of permanent and irreversible heart damage usually does not occur until the person with MS exceeds the total lifetime maximum dose of 140 mg/m². The amount of Novantrone given for each intravenous infusion for MS is usually lower than what a cancer patient receives. In any case, your doctor will want to make sure the harmful effects from the Novantrone are avoided, so your heart will be monitored regularly during treatment and you will undergo additional laboratory tests.

The most common side effects of Novantrone are nausea (upset stomach), fatigue, hair thinning, upper respiratory or bladder infections, loss of menstrual periods, and mouth sores. The nausea is usually mild and generally lasts less than forty-eight hours. It can be managed with anti-nausea medication that is taken before and after each Novantrone treatment. Because Novantrone is a dark blue in color, your urine and the whites of your eyes may turn blue for a short time after each dose.

Tell your doctor immediately if you develop heart problems, such as trouble breathing, swelling in your ankles or legs, or a fast or uneven heartbeat. These problems generally occur if you receive a total lifetime dose of more than ten doses (usually more than 140 mg/m²) of Novantrone. Within the first several weeks after each infusion, Novantrone can increase your chance of getting an infection, so it is wise to report any signs of infection, such as fever, chills, cough, sore throat, and pain or burning with urination. However, isolation during this period is usually not recommended.

Novantrone can cause irregular or loss of menstrual periods and infertility. Women of childbearing age need to discuss this risk of infertility with their doctor and decide whether this medication is right for them. Women who do decide to take Novantrone must use birth control to avoid becoming pregnant. Your doctor should give you a pregnancy test before each dose of Novantrone. Novantrone should not be taken if you are trying to become pregnant, or breast-feeding. If you become pregnant while on Novantrone you need to tell your doctor right away because Novantrone can harm the fetus and cause birth defects. You should not plan on having children while taking Novantrone and for several months after the final treatment ends. Novantrone may also stop sperm production in men.

Before starting Novantrone, tell your doctor if you have any present or past history of: heart disease, cancer chemotherapy, liver disease, problems with your immune system, abnormal blood tests, blood-clotting problems, infections, unusual or unexpected bleeding, allergies or sensitivities, radiation treatment to the chest, or prior treatment with Novantrone. Novantrone affects blood tests and will cause your white blood cell count to go down, which increases your chance of getting an infection. This risk of infection is greatest within one month after each treatment.

The best thing you can do to prevent infection is to practice good hand-washing technique for several weeks after each Novantrone infusion. Novantrone can also cause your blood platelet count to go down, which increases the likelihood of bleeding and bruising. To ensure your safety, the doctor must monitor your blood tests before and after each treatment. Below are reviewed Novantrone concerns.

Checklist 2: Tips Review for Novantrone

In relation to your Novantrone treatments, are you remembering to do the following?

- I schedule my Novantrone appointment every three months.
- I cancel my Novantrone appointment if I'm sick, and I reschedule it when I'm feeling better.
- I tell my doctor or nurse about any problems that I'm having with the Novantrone.
- To prevent nausea: (a) I don't eat for a few hours before the infusion. (b) I drink cool, clear, and unsweetened juices. (c) I eat small meals throughout the day.
- To reduce the chances of my hair thinning after the Novantrone treatments: (a) I use a soft hairbrush and mild shampoo. (b) I don't color or perm my hair. (c) I use low heat when drying my hair.

- _____ To avoid infection within the first month after every Novantrone infusion: (a) I wash my hands frequently. _____ (b) I avoid people who are sick. _____ (c) I eat a well-balanced diet and drink plenty of fluids. _____ (d) I get adequate rest. _____
- _____ I will tell my doctor if I have an uneven or fast heartbeat, chest pain, trouble breathing, or swelling in my hands or feet.
- _____ I will not undergo surgery or dental work for several weeks before or after my Novantrone treatment.
- _____ I will tell all my doctors and healthcare providers that I am taking Novantrone.
- _____ I will not receive injections of live vaccinations while on Novantrone.

The benefits of Novantrone may not be felt until after the third or fourth treatment. This may mean you might not notice a change in your MS symptoms until nine months to a year after beginning treatment. Because Novantrone may cause heart damage during therapy or months to years after therapy ends, you must tell your doctor or nurse if you have any trouble breathing, chest pain or discomfort, or any other health problems.

TRAVELING WITH YOUR MEDICATION

There are a number of issues about traveling with MS disease-modifying medications that are important to remember. The checklist of travel tips below highlights these points and is helpful to review when you go on a trip. Many of you who are newly diagnosed may not be aware of some of these useful tips.

Checklist 3: Travel Tips

- _____ I always take my MS disease-modifying medication in my carry-on baggage when I'm traveling.
- _____ I always carry my MS disease-modifying medication in its original labeling and packaging.
- _____ I bring extra medication with me when I'm traveling because I may wish to stay longer or I may have an unscheduled delay.
- _____ I always carry my doctor's business card with his/her name and telephone number.
- _____ If I feel ill or have an MS exacerbation when traveling, I watch my symptoms for about twenty-four to forty-eight hours because I may start to feel better. If I think I'm having an exacerbation, I will find medical attention and I may need to go to an emergency room to be seen.
- _____ When traveling in the United States, I will carry a list of MS treatment centers located within the country. (This list can be provided by the National Multiple Sclerosis Society.)

Conclusion

Although there is no cure for MS at this time, there are many drugs that can slow down the progression of the disease and improve the quality of your life. The decision of which MS disease-modifying drug to select is ultimately yours. Your doctor, nurse, family, and close friends can help you in selecting the drug that best fits your needs. Hopefully, table 1.1 that compares the different medications will be helpful to you in making your personal choice. If you've forgotten where the table is located, you will find it under the heading Choosing What Is Best for You. It is recommended that you start a drug early to optimally reduce the number and severity of MS exacerbations, the progression of the disease, and the development of disability. Your health care team will work, in partnership with you, toward successful management of your health.

In this chapter, we have discussed only part of the complete medical treatment for MS, i.e., the commonly used medications that directly affect the disease process. There is often more that can be done in your particular case. Medications can be taken to improve various symptoms of the disease, such as fatigue, pain, spasticity, bladder problems, depression, etc. Consult your physician to determine whether any of these types of medication might be helpful to you.