

## New Frontiers in the Treatment of Multiple Sclerosis: An Evidence-Based Approach

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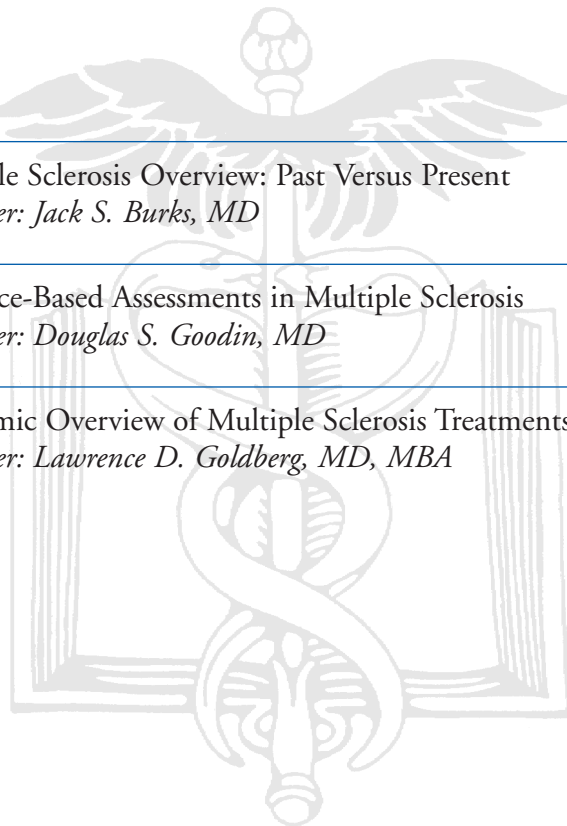
Multiple Sclerosis Overview: Past Versus Present  
*Presenter: Jack S. Burks, MD*

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Evidence-Based Assessments in Multiple Sclerosis  
*Presenter: Douglas S. Goodin, MD*

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Economic Overview of Multiple Sclerosis Treatments  
*Presenter: Lawrence D. Goldberg, MD, MBA*



# New Frontiers in the Treatment of Multiple Sclerosis: An Evidence-Based Approach

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Upon completion of this educational program, the participant should be able to:

- Review strategies to improve clinical and economic outcomes in the treatment of multiple sclerosis (MS)
- Analyze the most recent evidence for the use of disease-modifying drugs in the treatment of relapsing forms of MS
- Understand the use of evidence-based data in formulating effective care management strategies

Release Date: March 15, 2005; Expiration Date: March 15, 2006

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This program is intended for managed care professionals.

### Statement of Need

The goal of this educational program is to provide information to the healthcare and managed care communities on new clinical information available about multiple sclerosis treatment. New treatments may help lessen the economic burden on patients and the healthcare community, as well as offer improvement in quality of life and health.

### Grant Support

This educational activity has been supported by an unrestricted educational grant from Serono Inc.

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## New Frontiers in the Treatment of Multiple Sclerosis: An Evidence-Based Approach

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Innovative research on the pathogenesis of multiple sclerosis (MS) has revealed that this disease is more complex than previously understood. For example, instead of a single disease, research now identifies at least four different pathologies of the disease. In addition, magnetic resonance imaging (MRI) studies demonstrate that damage to the brain is accumulating even between clinical attacks. This progressive accrual of damage leads to irreversible disability. These findings, along with several other new discoveries about the pathogenesis of MS, are leading to a new rationale for treatment—treat early and aggressively.

Multiple sclerosis is a prevalent and costly disease, affecting between 350,000 and 400,000 people in the United States. The cost to individual patients in terms of morbidity and decreased quality of life is substantial, as are the costs of treatment and the long-term societal costs of caring for patients with MS. A 2003 fact sheet from The National Multiple Sclerosis Society estimated the annual cost of MS to be \$13 billion per year. Recent data suggests a more accurate estimate of \$18 to \$20 billion per year.

Disease-modifying drug therapies to treat MS, such as interferon beta and glatiramer acetate, may offer considerable clinical benefit in reducing the frequency of relapse and delaying disease progression and subsequent disability. A review of the available evidence on these drugs shows that they may be appropriate for patients with relapsing/remitting MS. Less convincing data are available on the available MS drugs' efficacy in reducing the severity of MS. These drugs are also costly, and the need to weigh the efficacy of these drugs against the high cost to the individual and society is an area that requires more examination on the part of both the patient and the healthcare provider.

In this issue of *Managed Care Consultant*<sup>™</sup>, experts in the field of MS discuss major concerns about treating patients with MS, including the new discoveries in the epidemiol-

ogy and pathogenesis of the disease, an analysis of the best trial data, and the need to evaluate the cost effectiveness of available therapies. The proceedings of this issue reflect the content of a recent CD-ROM and web cast program.

### MS Overview: Past Versus Present

Jack S. Burks, MD, provides a brief overview of the epidemiology and pathogenesis of the disease, followed by a more comprehensive discussion of the changing view of MS that has led to a new rationale for treatment. In addition, Dr. Burks summarizes the current therapies available for MS, including dosing and adverse effects.

### Evidence-Based Assessments in Multiple Sclerosis

Douglas S. Goodin, MD, describes an approach to clinical decision making that is currently emphasized in many clinical settings. Called evidence-based medicine, the approach is based on reviewing the medical literature for the best, most current published data to assist in clinical decision-making. Dr. Goodin applies this approach to the current evidence on disease-modifying drug therapies used in the treatment of MS. Recommendations on the use of these therapies are then provided based on the analysis of the current evidence regarding drug therapies used in treating MS.

### Economic Overview of Multiple Sclerosis Treatments

Lawrence D. Goldberg, MD, MBA, discusses the need for cost-effective analyses of MS treatment in lieu of the substantial financial burden of MS on patients and society. Dr. Goldberg presents the main data from several European trials, all of which demonstrate the need to extrapolate cost of care beyond the short-term trial data to more accurately estimate the true cost effectiveness of current MS therapies.

# Multiple Sclerosis Overview: Past Versus Present

Presenter

Jack S. Burks, MD  
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Past definitions identify multiple sclerosis (MS) as a relapsing/remitting disease of myelin that generally spares cognition. Current data, however, demonstrate a supplemental, more complex pathogenesis of this disease. First, recent data indicate that MS is a multifaceted disease, with four main courses, and that MS may be causing irreversible damage in the brain even when the disease is clinically silent. An additional challenge to the customary definition of MS is that it is not simply a disease of myelin. Current data exhibit that MS also damages axons and neurons, causing more axonal damage in the brain than previously thought. Recent research also indicates that more than 50% of MS patients have cognitive dysfunction, even in early stages of the disease. MS is additionally defined as an inflammatory disease, but newer data indicate that degeneration occurs, potentially attributed to early inflammations in the brain. The final challenge to the standing definition of MS is that it is not simply a disease, but rather has four pathologies, and may be more aptly classified as a syndrome. Interferon beta and glatiramer acetate have demonstrated efficacy as treatment options for MS. (*MCConsultant* 2005;4[1]:5–8)

Multiple sclerosis (MS) is a prevalent and highly expensive disease. It affects approximately 350,000 to 400,000 people in the United States and is the most common cause of neurologic disability in young adults aged 20 to 40. The age of onset of MS is usually between 15 and 50 years of age, although it can develop

in younger children as well as the elderly. The prevalence of MS is higher in Caucasians than other racial groups, and in women, who are three times more likely to develop MS than men.<sup>1</sup> Treating patients with MS is also costly. A 2003 fact sheet from The National Multiple Sclerosis Society estimated the annual cost to be between \$13 billion per year. Recent data suggests a more accurate estimate of \$18 to \$20 billion per year.<sup>1</sup>

Although the pathogenesis of MS is not fully understood, the higher prevalence in women suggests the possible role of hormonal influences, and the higher prevalence in Caucasians suggests a genetic role. Although MS is not a hereditary disease, there may be a genetic predisposition in families. Other data suggest that environmental factors, such as exposure to a virus, may be implicated in the pathogenesis of MS.<sup>2</sup>

In the past, MS has been defined as a relapsing/remitting disease of myelin secondary to inflammation that generally spares cognition. Recent emerging data has changed the fundamental understanding of MS. This research indicates a more multifaceted pathogenesis of MS, which challenges the way MS is defined and, ultimately, the way it is treated. This article describes a new, more complex understanding of MS, and the new rationale for treatment.

## Is MS Primarily a Relapsing/ Remitting Disease?

As stated previously, MS, in the past, has been identified as a relapsing/remitting disease. The

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first challenge to this definition is the recognition that MS is not just a relapsing/remitting disease. A 1996 study by Lubin and colleagues challenged this dated definition by describing four main disease courses of MS that more completely define all the presentations of MS seen in patients.<sup>3</sup> For approximately 85% of patients with MS, the first course of the disease begins with relapsing/remitting disease. Although the majority of patients begin with relapsing/remitting disease, most patients (approximately 90%) will convert to the second course of the disease—secondary-progressive MS—after 20 years. In the early phases of this second course, exacerbations and numerous lesions seen with magnetic resonance imaging (MRI) persist, but there are fewer attacks and fewer new gadolinium-enhanced lesions as the disease progresses. In later stages of this second course, MS is best characterized by a slow, increasing disability without attacks or new MRI gadolinium-enhanced lesions. The third course of the disease, called primary-progressive MS, is a late-onset course of the disease that usually involves the spinal cord. In primary-progressive MS, patients begin experiencing increasing lower extremity symptoms that slowly progress each year without definitive exacer-

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**Recent emerging data has changed the fundamental understanding of MS.**

**This research indicates a more multifaceted pathogenesis of MS, which challenges the way MS is defined and, ultimately, the way it is treated.**

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bations. Brain MRI may show a paucity of lesions with little evidence of inflammation. In the fourth course of the disease called progressive-relapsing MS—which is unusual—patients have predominantly progressive disease from the onset but they may also have interspersed exacerbations.

A further challenge to the older definition of MS as a relapsing/remitting disease comes from research on the natural history of the disease.<sup>4</sup> Previously, it was believed that the disease was only active during attacks, since patients were clinically stable between attacks. However, numerous MRI lesions can be detected in patients who are clinically stable. The old concept that there is an attack, the disease is dormant, and then there is another attack, is not supported by the MRI data. In fact, it is estimated that two new MRI lesions occur in the brain between every clinical attack. Although clinically silent, brain damage is accumulating and causing irreversible changes in the brain. Once the damage occurs, reversal is unlikely.

### **Is MS a Disease of Myelin?**

Another challenge to the standard definition of MS is the focus on MS as a disease of myelin. Current data show that, along with damage to the myelin, MS also does early, irreversible damage to axons and neurons.<sup>4</sup> As axonal damage increases, the severity of neurological disability increases. Although Doinikow described the effect of axonal damage on neurological disability more than 90 years ago,<sup>5</sup> it was a 1998 study by Trapp and colleagues that described the effect of axonal damage in more detail.<sup>6</sup> These study results showed that enormous numbers of transected axons are present in active MS plaques, even in patients with chronic active disease. These results also found that normal-appearing white matter also contains transected axons. These results demonstrate that there is more ongoing axonal damage in the brain, even in normal-appearing white matter, than previously believed.

### **Does MS Spare Cognition?**

With the recent recognition of the prevalence of axonal and neuronal damage in MS, a further challenge is made to the standard definition of MS—namely, that it spares cognition. For many years, cognitive problems were not perceived as part of the disease course of MS. However, research now indicates that more than 50% of patients with MS have cognitive dysfunction that can occur early in the course of the disease and is not linked to motor impairment.<sup>7</sup> Unlike the cognitive dysfunction of persons with Alzheimer's disease that is characterized as gray-matter dementia, cognitive dysfunction in MS patients is characterized as subcortical dementia and is linked to impairments in executive function and working memory. Impairment of executive function refers to the loss of ability to integrate higher cortical function, which leads to a number of difficulties in daily living, such as the ability to understand consequences, to get organized, to get things started, to know when to stop, and to follow through on a project. Impairment in working memory is the loss of ability to work on one project, switch to another project, and then return to the original project without losing one's place.

### **Is MS Caused by Inflammation Only?**

Defining MS as an inflammatory disease led to a focus on anti-inflammatory treatments. However, recent data show that degeneration (apoptosis or timed cell death) is also occurring in the brain, but may not be directly related to inflammation.<sup>8</sup> Rather, degeneration appears to be a separate process of damage. Although it is now suspected that degeneration is a major cause of disease progression, the cause of degeneration is not fully understood. One theory suggests that early inflammation may predispose cells to degeneration. This theory is based on the idea that when

inflammation occurs in early MS, cells in the area of inflammation frequently are damaged but not killed. Although these partially-damaged cells may fully recover and lead to improved functioning and reduced neurologic deficits in patients, these cells may be programmed to die earlier because of their previous damage and create an ongoing progressive disability when they die. Current anti-inflammatory MS medications have little or no effect on preventing the death of those cells once the initial damage from inflammation occurs. Therefore, early treatment is imperative to prevent or stop this cell damage. Early treatment may also reduce the number and severity of attacks, as well as decrease progression later in the disease.

**Is MS Really a Disease?**

The final challenge to the standard definition of MS is its emphasis on being a disease. Recent research on the neuropathology of MS shows that there are four separate pathologies of MS. Type I pathology is a T cell-mediated disease involving macrophages and cytokines, and is what is believed to be the typical MS pathology. Type II pathology is actually type I pathology plus antibodies. For years, the role of antibodies has been downplayed in the pathogenesis of multiple sclerosis. As it turns out, type II pathology is the most common pathology identified by researchers. This is a problem, since the current drugs are focused on T cells only and not on antibodies. The third type of pathology in MS differs dramatically from type I and II. In type III, the damage is very diffuse and appears to be viral or toxic or even diffuse ischemia. Type III does not present discreet lesions, just a general damage to the nervous system. Type IV pathology is even more challenging than the other pathologies because it does not appear to be inflammatory, and it is not even primarily a disease of myelin.<sup>9</sup> It appears to be a degenerative disease of oligodendroglial cells, the cells that make myelin. An intrinsic metabolic problem that leads to oligodendroglial cell degeneration is potentially present in this pathology. These four differing pathologies suggest that MS may be more accurately defined as a syndrome, and indicates that a singular treatment will not help all patients.

**Treatment of MS: Changing Rationale**

Based on the recent evidence regarding the pathogenesis and disease course of MS, the new rationale of treatment is to treat early and aggressively instead of delaying treatments until deficits in physical and cognitive function accumulate.

**Table 1—New Criteria for Diagnosis of MS Lesions in Time and Space<sup>11</sup>**

Clinical presentation	Space (MRI)	Time (Months)
2 attacks; 2 locations	No	No
2 attacks; 1 location on exam	MRI abnormal or 2 MRI lesions + CSF	No
1 attack; 2 locations	No	MRI ≥3 months or second attack
1 attack; 1 location (CIS)	MRI abnormal or 2 MRI lesions + CSF	MRI ≥3 months or second attack

MRI = magnetic resonance imaging; MS = multiple sclerosis; CSF = Cerebral spinal fluid. Reprinted with permission.

Data suggest, based on MRI evidence of ongoing damage after a first episode (or clinically-isolated syndrome), that patients may benefit by being treated before the second clinical episode. The predictive value of a clinically-isolated syndrome on the potential development of clinically-definite MS was described in a study by Filippi and colleagues, in which 90% of patients with a T2 lesion load of greater than 1.23 cc would develop clinically-definite MS in 5 years, but only 55% would develop clinically-definite MS in 5 years with a lesion load of less than 1.23 cc. Only 6% in patients with a normal MRI might develop clinically-definite MS in 5 years.<sup>10</sup>

In the past, the diagnosis of MS relied on two attacks in two locations. With new information about the ongoing brain damage that occurs between attacks, new diagnostic criteria are needed for earlier diagnosis and treatment. **Table 1** provides new criteria based on diagnosing lesions both in time and space.<sup>11</sup> In the past, the diagnosis of MS relied on two attacks in two locations. With the new information regarding the ongoing brain damage that occurs between attacks, new diagnostic criteria are needed for earlier diagnosis and treatment. Because of the “silent symptoms” that are associated with MS, diagnosis of MS can be challenging. It is clear that even when the patients are not experiencing the physiological symptoms of MS there is still ongoing dynamic MRI evidence of disease. Furthermore, it is known that not only is myelin being damaged, but also axons and neurons are being damaged, even in the lack of clinical evidence of a new attack. Lastly, the time between the first and second attack of MS may be a few years, while the underlying damage is ongoing. While the need to treat early is recognized, if healthcare providers cannot make the diagnosis of MS without a second attack,

treatment is not an option despite that the damage is accumulating. Therefore, a diagnosis needs to be assigned and the treatment regimen needs to begin earlier before the onset of a second attack.

In addition to the change in treatment rationale, we also have a better understanding of the efficacy of treatment. In the past it was thought that all available MS therapies were approximately 30% effective in reducing relapse rates in patients with relapsing/remitting MS, and that all drugs were equally effective in other areas. Current MRI data now suggest that some medications may be up to 90% effective when considering the overall reduction in gadolinium-enhanced lesions, and may decrease severe relapses by 50% or more. Also important is the widely recognized view that response to treatment is highly variable among patients, which may be attributed to genetics, the varying disease pathologies of MS, or treatment compliance.

Current immunomodulating therapies for relapsing/remitting disease include three categories of drugs: high-dose interferons delivered subcutaneously and frequently, including interferon beta-1a given three times a week and interferon beta-1b given every other day; low-dose interferon beta-1a, given intramuscularly once weekly; and non-interferon therapy, or glatiramer acetate, delivered subcutaneously daily. All these therapies are effective, yet differ in their side effect profile. The most common side effects associated with interferon are flu-like symptoms, injection-site reactions, and blood

chemistry changes, whereas the most common side effects associated with glatiramer acetate are mild injection-site reactions, immediate post-injection systemic reaction (flushing, shortness of breath, palpitations, pressures in the chest), and lipoatrophy (dimpling of the skin).

In the past, these side effects were a significant barrier to compliance. However, with new treatment recommendations and delivery devices, compliance rates approach 90%. Important advances in managing the side effects of interferon therapy include evening dosing, dose escalation for patients receiving high-dose interferon (eg, start at a quarter or half dose and slowly increase over several weeks), prophylactic treatment with acetaminophen and/or ibuprofen or steroids prior to delivering interferon, and good injection technique. Careful management of adverse effects is vital to having successful patient compliance.

## Conclusion

Multiple sclerosis may be more complex than previously thought. The damage resulting from MS is considerable, even when patients appear to be doing well. Early and aggressive treatment is needed to prevent irreversible damage, with current data now suggesting treatment after the first clinically-isolated attack. Treatment choice should be based on combining clinical experience with evidence-based data to identify the most appropriate agent for a given clinical situation. ■

## REFERENCES

- Whetten-Goldstein K, Sloan FA, Goldstein LB, Kulas ED. A comprehensive assessment of the cost of multiple sclerosis in the United States. *Mult Scler* 1998;4:419-425.
- Multiple Sclerosis: Diagnosis, Medical Management, and Rehabilitation*. Eds: Burks JS, et al. New York: Demos Medical, 2000.
- Lubin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996;46(4):907-911.
- Lyseng-Williamson KA, Plosker GL. Management of relapsing-remitting multiple sclerosis: Defining the role of subcutaneous recombinant interferon beta-1a (Rebif). *Disease Management & Health Outcomes* 2002;10(5):307-325.
- Doinikow B. Über De- und Regenerationserscheinungen an Achsenzylindern bei der multiplen Sklerose. *Z ges Neurol Psych* 1915;27:151-178.
- Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med* 1998;338:276-285.
- Rao SM. Neuropsychology of multiple sclerosis. *Curr Opin Neurol* 1995;8(3):216-220.
- Peterson JW, Bo L, Mork S, Chang A, Trapp BD. Transected neuritis, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol* 2001;50(3):389-400.
- Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Ann Neurol* 2000;47(6):707-717.
- Filippi M, Horsfield MA, Morrissey SP, et al. Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology* 1994;44(4):635-641.
- McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50(1):121-127.



# Evidence-Based Assessments in Multiple Sclerosis

## Presenter

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Medical literature, in addition to practical clinical experience, plays an important role in treatment decisions regardless of the disease state. Evidence-based medicine (EBM) provides a structured, thorough methodology to evaluate medical literature. In EBM, a question is formulated; published studies are then classified based on the EBM classification system; and recommendations are then crafted based on the provided evidence. The EBM approach is particularly useful when applied to current data on treatment for multiple sclerosis (MS) with interferon beta and glatiramer acetate. A comprehensive review of class I evidence is vital to the development of treatment strategies for MS.

(*MCConsultant* 2005;4[1]:9–12)

Evidence-based medicine (EBM) involves critically evaluating medical literature to determine the best data on which to base clinical decision-making. Although physician judgment and other approaches remain critical guides to clinical care, EBM is a useful and beneficial tool for clinical decision-making, because of the organized and rigorous guide it provides to assess the quality of medical literature. A thorough review of the class I evidence is key in treatment decision making.

EBM begins with defining a problem or formulating a specific clinical question that can be answered by the data, such as “what is the effect of drug X on outcome Y?” Once the question is formulated, published studies addressing the question are reviewed and classified according

to their quality (inclusion/exclusion). Several classification systems have been developed to determine the quality of the data, with most systems assigning the highest quality to large, randomized clinical trials. After assessing all relevant articles and assigning quality, recommendations are then developed based on this best evidence.

This article discusses an EBM approach to evaluate current data on treatment for multiple sclerosis (MS). In particular, the article discusses the current use of interferon beta and glatiramer acetate as examples of disease-modifying therapies in MS.

## **Application of EBM to MS: Objective and Methods**

To assess the current use of interferon beta and glatiramer acetate in the treatment of MS, the literature was evaluated with these two questions in mind: Does treatment reduce the disease activity of MS; and, does treatment reduce the severity of MS? A review of the current literature was limited to the analysis of evidence from large (greater than 150 patients), controlled trials of relapsing/remitting MS. A total of nine trials were found that met this criteria: three interferon beta trials, four glatiramer acetate trials, and two head-to-head interferon beta trials.

Outcome measures for both disease activity and disease severity were based on clinical and magnetic resonance imaging (MRI) assessment. For disease activity, clinical assessment included a measure of disease activity such as the

**Table 1—A Classification of Study Evidence**

Study Characteristics	Class of Study			
	I	II	III	IV
Control group	○	○	○	●
Representative population	○	○	○	●
Assessment independent of	○	○	○	●
Rx blinded outcome	○	○	●	●
Assessment Prospective Design	○	○	●	●
Randomized*	○	●	●	●
	○ Yes	● No		

\* Also meets standards of:  
 • Primary outcomes defined;  
 • Exclusion/inclusion criteria defined;  
 • Dropout rate low and accounted for;  
 • Baseline characteristics detailed and substantially equivalent.

attack rate, time to first relapse, and attack-free status. The MRI measure of disease activity was the number of new T2 lesions, the number of gadolinium-enhancing lesions, or a combination of these two outcomes. For disease severity, the clinical measure was confirmed disability progression on the expanded disability status scale (EDSS), and the MRI measure was the total volume of disease seen on the T2-weighted MRI scans. (Please reference the sidebar on page 15 for further information on EDSS scores.)

Classification of the evidence was based on the system used by the American Academy of Neurology, which is a four-tiered system with the best data listed as class I and the worst data listed as class IV (Table 1). The recommendations demonstrate that all class IV evidence is effectively discarded by this process. For example, if there is no control group, the study would be classified as a class IV study. If a control group is present, the study may be deemed as class I, II, or III. If the population of patients being studied is not representative, the study would be deemed class IV. If the patient population is representative, the study would be classified as class I, II, or III. If the assessment of outcome is independent of treatment, the study could be considered class I, II, or III, but, if the outcome is not independent, the study would be class IV. This does not mean blinded outcome assessment, but simply means that the surgeon is not reporting their own success rate. If the outcome is blindly assessed, it would be a class I or II study. If the study is a prospective design, it would be considered either class I or II, but all retrospective designs would be either class III or IV.

If the study is randomized it can be a class I study provided that it meets the following design features; that is, that the primary outcomes are clearly defined, the inclusion and exclusion criteria for patients in the study are laid out, the

drop out rate is low, and the dropouts are accounted for. As a rule, the dropout rate should not exceed approximately 20%. Finally, to be deemed a class I study, the baseline characteristics for the groups are substantially equivalent or there is an a priori statistical plan to take care of baseline covariates.

The classified evidence was then given a level of recommendation, an A recommendation establishing that it may be effective, ineffective, or harmful (Table 2). Once the evidence is classified, it is then translated into recommendations. More than one convincing class I study could lead to an A recommendation, A being established as effective, ineffective, or harmful. If there were two or more class II studies, that could also lead to an A recommendation. If there was only a single class II study present, the evidence may get a B recommendation and more than three class III studies may also lead to a B recommendation. In contrast, lesser amounts of class III evidence would lead to a C, C being possibly effective, ineffective, or harmful. If the data is inadequate or conflicting, the level of recommendation would be a U.

### Multiple Sclerosis Trials

All the trials selected from the literature as representing the best evidence on current use of interferon beta and glatiramer acetate were trials examining the efficacy and safety of treatment in relapsing/remitting MS patients. The format of these trials are detailed below; their outcomes will be discussed later in this article.

**Interferon Beta Trials.** Three interferon beta trials were reviewed, all of which were prospective, blinded, controlled, randomized trials, thus these trials were identified as class I.<sup>1,2,3</sup> The Interferon Beta Multiple Sclerosis Study Group included 372 MS patients randomized to placebo, 1.6 million international units (MIU) of interferon beta-1b, or 8 MIU of interferon beta-1b.<sup>1</sup> Median time on the study was 46, 45, and 48 months for the placebo, 1.6 MIU, and 8 MIU groups, respectively.

The Multiple Sclerosis Collaborative Research Group study evaluated whether interferon beta-1a delivered intramuscularly once weekly would slow progressive, irreversible neurological disability in 301 relapsing MS patients.<sup>2</sup> Patients were randomized to placebo or interferon beta-1a (30 micrograms) delivered intramuscularly once weekly. The Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis Study Group evaluated the effects of subcutaneous interferon beta-1a on 560 patients with relapsing/remitting MS.<sup>3</sup> All patients had EDSS scores of 0 to 5 and were enrolled from 22 centers in nine countries. Patients were randomized to subcutaneous recombinant

interferon beta-1a (22 micrograms), interferon beta-1a (44 micrograms), or placebo three times a week for 2 years.

**Glatiramer Acetate Trials.** Of the four glatiramer acetate trials included, two were identified as class I<sup>4,5</sup> (ie, they were prospective, blinded, controlled, randomized trials) and two were identified as class III<sup>6,7</sup> (ie, they were prospective, controlled trials, but not blinded or randomized). The two class I trials included a 1995 study by the Copolymer 1 Multiple Sclerosis Study Group on the efficacy of glatiramer acetate in 251 MS patients, which formed the basis of the US Food and Drug Administration's approval of glatiramer acetate in the treatment of relapsing/remitting MS patients.<sup>4</sup> Patients were randomized to receive subcutaneous glatiramer acetate (20 mg daily) or placebo for 2 years. Conducted by the European/Canadian Glatiramer Acetate Study Group, the second class I trial was fielded because the previous trial did not include MRI outcomes.<sup>5</sup> Subcutaneous glatiramer acetate (20 mg) or placebo were administered daily on a randomized basis to 239 patients. These patients underwent monthly MRI scans and clinical assessments over 9 months to evaluate the effect, onset, and durability of effect of glatiramer acetate on disease activity.

The first of the two class III trials included an extended open-label study by the Copolymer 1 Multiple Sclerosis Study Group. This study evaluated the effect of glatiramer acetate on the relapse rate and its ability in slowing the accumulation of disability in MS patients.<sup>6</sup> Of the 251 patients originally randomized to placebo or glatiramer acetate, 208 patients participated in this open-label extension study and were evaluated at 6-month intervals and during suspected relapse. The second class III trial compared the efficacy of interferon beta-1a, interferon beta-1b, and glatiramer acetate on relapse rate in 156 MS patients.<sup>7</sup> In this prospective, nonrandomized, open-label treatment trial, patients with clinically-definite relapsing/remitting disease and an EDSS score of 4 or less received no treatment, interferon beta-1b, or glatiramer acetate. Patients were monitored for 12 months. All of these trials were substantially smaller than the interferon trials, with the largest of the glatiramer acetate studies having less patients than the smallest interferon trial.

**Interferon Beta Head-to-Head Trials.** Of the two interferon beta comparative trials included, one was identified as class I and the other as class I/III.<sup>8,9</sup> The class I study, the Evidence for Interferon Dose-Effect: European-North American Comparative Efficacy Study (EVIDENCE), compared the efficacy and safety of high-dose, high-frequency (44 mg, three times weekly) interferon beta-1a sub-

**Table 2—Translating Evidence into Recommendations**

Level of Evidence	Level of Recommendation		
	A	B	C
≥1 Convincing Class I Study	●		
≥2 Convincing Class II Study	●		
≥1 Convincing Class II Study		●	
≥3 Convincing Class III Study		●	
≥2 Convincing Class III Study			●

A = Established as effective, ineffective, or harmful;  
 B = Probably effective, ineffective, or harmful;  
 C = Possibly effective, ineffective, or harmful;  
 U = Data inadequate or conflicting.

cutaneously versus lower dose, less frequent (30 mg, once weekly) interferon beta-1a intramuscularly in 677 patients.<sup>8</sup> This randomized, controlled, multicenter trial led to the approval of subcutaneous interferon beta-1a in the US. The Independent Comparison of Interferon (INCOMIN) study compared the efficacy of on-alternate-day interferon beta-1b (250 micrograms) with once-weekly interferon beta-1a (30 micrograms) in 188 MS patients.<sup>9</sup> This class I/III study met all the class I criteria except that the clinical outcomes were not blinded (although outcome assessment was), therefore INCOMIN provides a mixture of class I and class III data.

### Analysis of the Evidence

**Interferon Beta Trials.** In all three of the interferon beta trials, therapy significantly reduced the number of clinical attacks. Similarly, all three trials found a significant reduction in the amount of MRI activity measured, providing convincing evidence that interferon favorably impacts the clinical and MRI aspects of disease activity. The evidence on confirmed progression was not as convincing as the evidence on disease activity, within this study. Two of the three trials found a clinical benefit,<sup>2,3</sup> with the third<sup>1</sup> showing a trend toward a clinical benefit. Similarly, two of the three trials found a significant effect in terms of MRI severity,<sup>1,3</sup> whereas a third trial did not show a significant benefit on this outcome.<sup>2</sup>

**Glatiramer Acetate Trials.** All four trials of glatiramer acetate showed a reduction in clinical attacks,<sup>4,5,6,7</sup> although significance could not be evaluated in one of the studies because there was no concurrent control group.<sup>6</sup> In the only study that examined MRI activity,<sup>5</sup> a significant benefit to glatiramer acetate therapy was found.

Glatiramer acetate therapy was not found to benefit con-

firmed progression in either of the two class I trials.<sup>4,5</sup> In the other two class III trials, significance of this outcome could not be evaluated because of no concurrent control group<sup>6</sup> or because the study did not report this outcome.<sup>7</sup> Glatiramer acetate therapy was found to significantly benefit MRI severity in the one study that evaluated this outcome.<sup>5</sup>

**Interferon Beta Head-to-Head Trials.** Both of the head-to-head trials showed a benefit to high-dose, more frequently administered interferon beta on clinical attacks and MRI severity.<sup>8,9</sup> This provides convincing evidence that high-dose or more frequently administered interferon was superior at least over 1 to 2 years, in comparison to low-dose, once-weekly interferon. No significant difference in confirmed progression was found in the EVIDENCE trial which could be attributed to the short duration of the trial (12 months).<sup>8</sup> A significant benefit in confirmed progression with high-dose, more frequently administered interferon was found in the INCOMIN trial, which could be due to the extended length of the trial (24 months).<sup>9</sup> The INCOMIN trial also demonstrated that MRI severity lessened with high-dose, more frequently administered interferon; no data on this outcome were reported in the EVIDENCE trial.

### Answers to Clinical Questions: What the Evidence Indicates

In answering the first question on whether treatment reduces disease activity of MS, the evidence from these trials indicates that both interferon and glatiramer acetate may reduce

disease activity. Based on the high quality of the evidence, these therapies are granted a type A recommendation.

In response to the second question as to whether interferon treatment reduces the severity of MS, the evidence from these trials was less convincing than it was for disease activity. Therefore, interferon is given a type B recommendation. The evidence was even less convincing for the effect of glatiramer acetate on disease severity; for that reason, glatiramer acetate is given a type C recommendation.

For patients who have relapsing/remitting MS and who continue to experience relapses, it is appropriate to consider interferon beta for treatment. A dose-response curve associated with the use of interferon beta for the treatment of MS is probable—that is, higher doses or more frequent administration of interferon was more effective than low-dose, once-weekly interferon. For any MS patient with relapsing/remitting MS, glatiramer acetate is also an appropriate treatment.

### Conclusion

EBM provides an important and rigorous guide for accessing the quality of the medical literature. A thorough review of class I data is critical to the development of decisions about the efficacy of the various disease-modifying therapies used to treat MS. An important caveat to the use of EBM is that some clinical questions pertinent to the care of individual patients may never have answers based on high-quality evidence, and treatment decisions will continue to rely on the clinical experience and judgement of the practicing clinician. ■

### REFERENCES

1. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology* 1995;45(7):1277-1285.
2. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996;39(3):285-294.
3. Randomized double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet* 1998;352(9139):1498-1504.
4. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 1995;45(7):1268-1276.
5. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging—measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Ann Neurol* 2001;49(3):290-297.
6. 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;6(4):255-266.
7. Khan OA, Tselis AC, Kamholz JA, Garbern JY, Lewis RA, Lisak RP. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFN beta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol* 2001;8(2):141-148.
8. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE trial. *Neurology* 2002;59(10):1496-1506.
9. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: Results of a 2-year prospective randomized multicenter study (INCOMIN). *Lancet* 2002;359(9316):1453-1460.

# Economic Overview of Multiple Sclerosis Treatments

## Presenter

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Multiple sclerosis (MS) is a prevalent disease, with a high clinical and economic burden. The relapsing/remitting nature of MS is associated with rapidly decreasing quality of life and increasing costs, especially as the disease progresses to later stages. Data from several European cost-effectiveness trials suggest that disease-modifying drugs for MS offer substantial economic advantages to patients and society. These data also suggest economical quality-adjusted life year costs with the application of such drugs in a treatment regimen. Lastly, an unmet need exists for detailed studies and economic models calculating US-based costs for MS treatment. From these US studies, a better understanding of the cost-effectiveness of MS treatments in the US healthcare delivery system may be gained.

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Relapsing forms of multiple sclerosis (MS) are associated with exacerbations that vary in number and severity, greatly affecting the use of healthcare resources. Most patients with relapsing forms of MS will eventually develop secondary-progressive MS, which is associated with increasingly severe episodes of disability and significant costs for the patient. As the MS patient's level of disability increases, the costs quickly increase.<sup>1</sup>

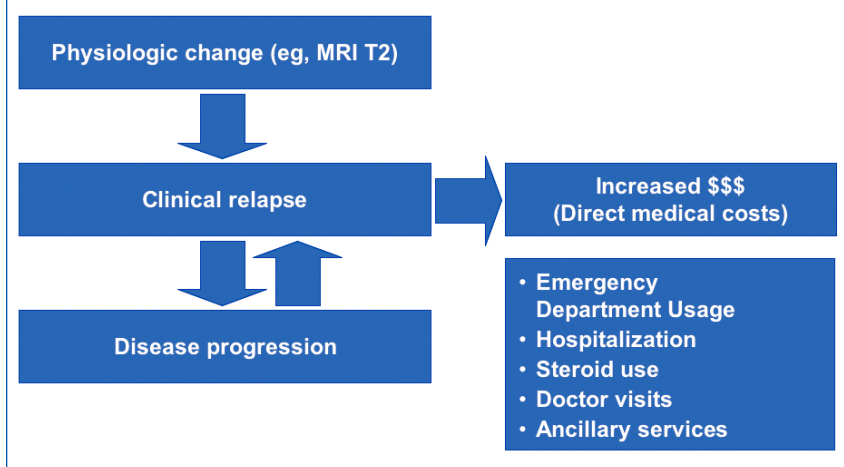
In translating direct and indirect cost data to the perspective of managed care, it is important to examine what drives cost. Simply, MS patients' encounters with the healthcare system drive expenses; the more severe and frequent

these encounters, the greater the costs. An accurate understanding of these direct costs is needed when weighing the benefits and costs of the currently available immunomodulatory therapies. **Figure 1** illustrates how relapses drive the direct medical costs of MS by highlighting the progression from diagnosis of demyelination as evidenced by T2 changes on the MRI, to clinical relapses and the incremental accumulation of direct medical costs. Direct medical costs include emergency department visits, hospitalizations, intravenous steroid use, physician visits, and use of expensive ancillary services. Parallel to relapses is further progression of disease and disability, which also affects direct medical costs.

Along with the direct costs of MS, the indirect costs of the disease have a major impact on the quality-of-life of the patient and his or her family. Somatic symptoms may affect family life, economic status, and social interactions.<sup>2</sup> Cognitive dysfunction, which affects 50% or more of patients, may result in decreased professional activity, increased dependence, and increased sexual dysfunction.<sup>3</sup> The cost to society of caring for MS patients is substantial and is critical to include in cost-effective analyses of treatment.

This article discusses the overall cost of MS to society and to individual patients. Although few published studies describe economic models used to evaluate this cost, the considerable cost of MS makes it imperative that healthcare providers, particularly managed care, evaluate the effectiveness of disease-modifying therapies in chang-

**Figure 1—Relapses Drive the Direct Medical Costs of MS**



ing the course of long-term outcomes of patients with MS and in lowering the costs associated with the disease.

### Evaluating the Cost Effectiveness of Therapy for MS

Most of the current economic models applied to the cost of MS come from cost-effectiveness studies conducted in Europe. These studies include a study from the United Kingdom published in 2000,<sup>4</sup> a study from Sweden published in 2000 with follow-up studies published in 2001 and 2002,<sup>5,6,7</sup> and a French study published in 2003.<sup>8</sup>

Overall, these data show that treating MS with disease-modifying drug therapies is economical, with data showing a clear benefit of treatment on reducing the frequency of relapses as well as the benefit on disability-related medical costs. These trials include little analysis of direct and indirect medical costs; however, reflecting the emphasis European healthcare providers place on indirect costs (ie, burden of cost incurred by caring for a patient with MS), the economic models used in the studies describe cost in terms of quality-adjusted life-year (QALY) gained. A cost of \$50,000 USD is normally the mean threshold amount that is considered a “good value” in terms of treatment costs.

In the study from the United Kingdom, Kendrick and colleagues used a cost-effective model to evaluate the effect on healthcare services and cost to society of delaying disease progression by treating MS.<sup>4</sup> Although previous studies have shown the high cost of treatment associated with its clinical benefit to reducing relapses and delaying disease progression, few data are available on the long-term cost to society of caring for a patient with MS. This study was conducted based on the hypothesis that delaying disease progression through treatment would confer both short-term clinical benefits and

significant improvement over the long term in quality of life. This long-term improvement, in turn, would potentially postpone increased disability and demonstrate the cost effectiveness of therapy.

In this study, the authors compared the estimated mean disease progression in patients with MS treated with subcutaneous interferon beta-1a with patients who received only placebo.<sup>4</sup> The economic model used suggested that significant cost savings would be realized after approximately 12 years of treatment with subcutaneous interferon beta-1a. The authors then applied QALY scores to facilitate estimates of cost effectiveness and found that the cost attributed to QALY

ranged from \$40,000 USD after 2 years of treatment to about \$55,000 USD after 20 years of treatment.

In the Swedish studies, a Markov model was used to examine the cost effectiveness of interferon beta-1b in patients with remitting/relapsing or secondary-progressive MS.<sup>5,6,7</sup> The model is designed to estimate the effect of early treatment on long-term outcome by using data from clinical trials to measure effectiveness. Effectiveness is calculated as the number of QALYs gained from reducing disease progression. To calculate the effect of treatment beyond the clinical trial period, the model extrapolated the long-term cost-effectiveness of treatment from complementary, epidemiological data. In specific, the model uses states based on disability expressed by expanded disability status scale (EDSS) scores, and transition probabilities were calculated from 3-year clinical trial data and then extrapolated to 10 years. (See the EDSS sidebar on next page for further information on EDSS scores.) Using a population-based, cross-section study from Sweden, mean costs and utilities for each Markov state were then calculated.

The first Swedish study, published in 2000, estimated the cost-effectiveness of interferon beta-1b to treat patients with secondary-progressive MS.<sup>5</sup> Based on 3-year clinical data and 10-year extrapolated data, the study investigators found the cost of interferon beta-1b per QALY gained to be approximately \$40,000 USD. When adding indirect costs, the costs per QALY gained rose to about \$60,000 USD. These estimated costs fall around the mean threshold value of \$50,000 USD, and therefore, are considered cost-effective.

In the 2001 follow-up study, a Markov model was used to estimate the cost-effectiveness of interferon beta-1b as treatment for patients with relapsing/remitting MS and secondary-progressive MS.<sup>6</sup> Similar to the 2000 study, the goal was to assess the impact of both direct and indirect costs of treat-

ing MS from a societal perspective. This study included new data that allowed for updating the original Markov model, in order to be able to estimate the effect of early treatment on the long-term outcome. In the study, data from two large clinical trials were combined—one that included patients with relapsing/remitting MS and another that included patients with secondary-progressive MS. The rationale for combining data from these two clinical trials arose from the fact that no difference was found between the number of relapses at given levels of disability between patients in these two different disease courses. Further support of combining these patient groups came from observational studies that show no difference in costs and quality of life at given EDSS levels between patients experiencing these two different disease courses. Similar to the 2000 study, transition probabilities between the Markov states were estimated from clinical trial data and extrapolated from a large epidemiological database on the natural history of MS. The results of this updated analysis showed that the cost of interferon beta-1b was from approximately \$45,000 USD to \$70,000 USD per QALY gained. In 80% of patients who initiated treatment when their disability EDSS scores measured between 4 and 5.5 (or in states 3 and 4), treatment was considered cost effective.

In the 2002 study, the authors again used the Markov model to estimate the cost effectiveness of interferon beta-1b in patients with secondary-progressive MS. However, unlike the 2000 study, this analysis estimated the cost effectiveness of therapy based on the continuation of disease progression, rather than on the cessation of disease progression.<sup>7</sup> The authors hypothesized that patients with secondary-progressive MS treated with interferon beta-1b would improve even after 3 years. The study found that the clinical trial data appeared to underestimate the progression of long-term disability and thus, the potential benefit of treatment. In addition the incremental cost per QALY gained—including direct and indirect costs—was approximately \$25,000 USD. Compared to the \$40,000 USD estimated in the 2000 study, this lower cost-effective ratio was found to be largely due to greater QALY gained with treatment. This study highlights the need to evaluate the long-term cost-effectiveness of treatment beyond clinical trial results.

In the French study published in 2003, LePen and colleagues evaluated the cost effectiveness of treating patients with relapsing/remitting MS with subcutaneous interferon beta-1a (44 micrograms) three times weekly. Four-year data from the Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis trial, which randomized patients to receive interferon beta-1a (22 or 44

## WHAT IS THE EDSS SCALE?

The expanded disability status scale (EDSS) is a disability status scale in which eight functional systems (FS) are evaluated in patients with multiple sclerosis (MS). These systems include visual, cerebellar, brain stem, pyramidal, sensory, visual, cerebral, and bowel and bladder symptoms. Scores of 1 to 4.5 represent FS problems without disturbances in ambulation.

### EDSS SCORE IMPAIRMENT

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest for about 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest for about 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair for about 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms; retains some self care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

The Kurtzke Expanded Disability Status Scale. <http://www.mult-sclerosis.org/expandeddisabilitystatusscale.html>. Accessed: May 11, 2004. Reprinted with permission.

micrograms) subcutaneously three times a week or placebo, was used to assess the efficacy of interferon beta-1a in delaying progression of relapsing/remitting MS. Using the MS-specific EDSS score, progression of disability was clinically measured every 3 to 6 months and by MRI annually. Increases in the EDSS score indicated increased disability. To evaluate the cost effectiveness of treatment based on the EDSS score, an econometric model was used that measured disability as an area under the EDSS score-time curve and effectiveness of therapy expressed as EDSS-months of disability prevented.<sup>8</sup> Cost-effectiveness of therapy was estimated comparing patients who received interferon beta-1a treatment to those who received placebo for up to 4 years. Using a time regression model, results were projected to 10 and 20 years.

Based on this long-term model, the costs associated with delaying disease progression by interferon beta-1a decreased over time. Treatment prevented 121 disability months over 10 years at a cost of 732 euros (\$950 USD) per year. Over 20 years, this treatment prevented 321 months at a cost of 359 euros (\$466 USD) per year. This study shows that interferon beta-1a is cost-effective in patients with relapsing/remitting MS and is increasingly cost effective over time.

### Limitations of Economic Models

Although the European trials show a clinical benefit of disease-modifying drug therapy on reducing the frequency of relapses and slowing disease progression, as well as the economic value of managing disability-related medical costs, the data from these trials are limited and caution is warranted with regard to interpretation. These limitations largely

rely on the fact that data from clinical trials (ie, in a research setting) may not accurately reflect the cost of treating MS in individual patients. In the clinical setting, patients with MS have variable courses, and therefore the evolution of costs in practice is variable, not fixed as estimated in clinical trials. In addition, as no US studies on total direct costs have been performed, US-based data are needed to further evaluate the economic value of MS treatment with disease-modifying drugs. Furthermore, the disability scale to assess the level of disease burden associated with a patient may depend on an observer. In particular, the use of the EDSS scale to establish disability levels may have large inter-rater variability outside the research setting. Lastly, improvements in clinical status may occur over time in the clinical setting, whereas in the research setting the patient is assumed to be stable or have progressively worsening disease.

### Conclusion

MS is a devastating disease that can occur early in life, progresses to rapid disability, and decreases quality of life. Although the costs of treatment are high, the costs to society of caring for a patient disabled by MS are greater. According to European data, disease-modifying drugs offer significant economic benefits by reducing the frequency of relapses and slowing disease progression. European economic data also suggest reasonable costs per QALY of approximately \$40,000 USD to \$60,000 USD. As more robust and detailed economic models are developed based on US direct costs, a better understanding will emerge on the cost effectiveness of MS treatment in the context of the US health-care delivery system. ■

### REFERENCES


1. Catanzaro M, Weinert C. Economic status of families living with multiple sclerosis. *Int J Rehabil Res* 1992;15(3):209-218.
2. Rudick RA, Miller D, Clough JD, Gragg LA, Farmer RG. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. *Arch Neurol* 1992;49(12):1237-1242.
3. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* 1991;41(5):692-696.
4. Kendrick M, Johnson KL. Long-term treatment of multiple sclerosis with interferon-beta may be cost effective. *Pharmacoeconomics* 2000;18(1):45-53.
5. Kobelt G, Jonsson L, Henriksson F, Fredrikson S, Jonsson B. *Cost-utility of interferon beta-1b in secondary progressive multiple sclerosis*. *Int J Technol Assess Health Care* 2000;16(3):768-780.
6. Kobelt G, Jonsson L, Fredrikson S, Jonsson B. *Cost-utility analysis of interferon B-1B in the treatment of different types of multiple sclerosis*. SSE/EFI Working Paper No. 459; August 2001.
7. Kobelt G, Jonsson L, Miltenburger Jonsson B. Cost-utility analysis of interferon beta-1B in secondary progressive multiple sclerosis using natural history disease data. *Int J Technol Assess Health Care* 2002;18(1):127-138.
8. LePen C, Coyle P, Vollmer T, Blumhardt L, Lilliu H, Beresniak A. Long-term cost effectiveness of interferon-beta-1a in the treatment of relapsing-remitting multiple sclerosis: An econometric model. *Clin Drug Invest* 2003;23(9):571-581.



# New Frontiers in the Treatment of Multiple Sclerosis: An Evidence-Based Approach

## March 2005

The University of Minnesota designates this educational activity for a maximum of 2 category 1 credits toward the AMA's Physician Recognition Award. Each physician should claim only those hours of credit that he/she actually spent on the educational activity. Participants must have a passing grade of 70% to receive CME credit for this activity.

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Expiration date: March xx, 2006. Estimated time to complete: 2 hours

1. The past definition of multiple sclerosis is:
  - a) A relapsing/remitting disease of myelin secondary to inflammation that generally spares cognition
  - b) A progressive-relapsing disease of myelin secondary to inflammation that generally spares cognition
  - c) A cognitive disease of myelin secondary to inflammation that generally spares disability
  - d) A relapsing/remitting disease of myelin secondary to inflammation that generally depletes cognition
2. What percent of multiple sclerosis patients develop secondary-progressive multiple sclerosis after 20 years?
  - a) 25%
  - b) 80%
  - c) 60%
  - d) 90%
3. Which of the following is NOT true regarding axonal and neuronal damage in multiple sclerosis?
  - a) As axonal damage increases, the severity of neurological disability also increases
  - b) As axonal damage decreases, the severity of neurological disability increases
  - c) Early damage to axons and neurons contributes greatly to the increase in disability
  - d) None of the above
4. Which of the following is an adverse event of interferon beta?
  - a) Flu-like symptoms
  - b) Injection-site reactions
  - c) Blood chemistry changes
  - d) All of the above
5. The purpose of evidence-based medicine is to:
  - a) Critically evaluate the medical literature in order to better understand the true value of different therapeutic interventions
  - b) To aid in medical decision making
  - c) To be the sole guide to physician behavior
  - d) Both a and b
6. Which of the following is an aspect of the structure of evidence-based medicine?
  - a) Classifying and interpreting the evidence
  - b) Assembling the evidence
  - c) Defining the problem
  - d) All of the above
7. An "A" recommendation refers to what level of study data?
  - a) Probably effective, ineffective, or harmful
  - b) Established as effective, ineffective, or harmful
  - c) Possibly effective, ineffective, or harmful
  - d) Data inadequate or conflicting
8. Based on the data presented, which of the following statements may be accurate regarding the use of interferon beta and glatiramer acetate?
  - a) It is considered probable that there is a dose-response curve associated with the use of interferon beta for the treatment of multiple sclerosis.
  - b) It is appropriate to consider interferon beta for treatment in any patient who already has relapsing/remitting multiple sclerosis and is still experiencing relapses.
  - c) It is appropriate to consider glatiramer acetate for treatment in any patient who has relapsing/remitting multiple sclerosis.
  - d) All of the above
9. In the first Swedish study published in 2000 secondary-progressive multiple sclerosis study, excluding indirect costs, the cost per quality-adjusted life-year was approximately:
  - a) \$40,000 US
  - b) \$60,000 US
  - c) \$65,000 US
  - d) \$70,000 US
10. Which of the following is NOT a limitation of current economic models for multiple sclerosis?
  - a) There are no published cost-effectiveness models reflecting total direct costs for multiple sclerosis in the United States.
  - b) Data from clinical trials may not accurately reflect the evolution of costs in the general population.
  - c) Future models based on US direct medical costs will provide a better understanding of the cost effectiveness of multiple sclerosis treatment in the context of the US healthcare system.
  - d) The data demonstrate the economic value of treatment in the avoidance of relapses and disability-related medical costs.

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## PROGRAM EVALUATION

The University of Minnesota and the University of Tennessee College of Pharmacy would appreciate your comments on the quality of this educational activity. Please answer the following 6 questions—1 through 4 using a 5-point grading system, with 1 being the lowest rating (strongly disagree/poor) and 5 being the highest (strongly agree/excellent).

1. After reading this educational activity, the participant was able to:

### Review strategies to improve clinical and economic outcomes in the treatment of multiple sclerosis (MS)

1      2      3      4      5

### Analyze the most recent evidence for the use of disease-modifying drugs in the treatment of relapsing forms of MS

1      2      3      4      5

### Understand the use of evidence-based medicine data in formulating effective care management strategies

1      2      3      4      5

2. Please indicate your overall evaluation of the activity.

1      2      3      4      5

3. I intend to make changes to my practice as a result of this educational activity.

1      2      3      4      5

4. This educational activity was objective, balanced, and free of commercial bias.

\_\_\_\_\_ Yes                      \_\_\_\_\_ No

5. What aspects of this educational activity were of most interest to you?

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

6. Do you have any comments or suggestions for this or future educational activities?

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Please indicate your answers to the continuing education post-test by circling one answer to each question.

- |                  |                   |
|------------------|-------------------|
| 1. A   B   C   D | 6. A   B   C   D  |
| 2. A   B   C   D | 7. A   B   C   D  |
| 3. A   B   C   D | 8. A   B   C   D  |
| 4. A   B   C   D | 9. A   B   C   D  |
| 5. A   B   C   D | 10. A   B   C   D |

## New Frontiers in the Treatment of Multiple Sclerosis:

### *An Evidence-Based Approach*

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