

Economic Value for Early Treatment in Multiple Sclerosis

Ronald S. Murray, MD, FAAN

For a CME/CEU version of this article please go to <http://www.namcp.org/cmeonline.htm>, and then click the activity title.

Summary

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, and the most frequent cause of disability in young adults. The treatment of MS has been changing dramatically. With agents that are now available, relapse rates can be significantly reduced and disability can be minimized.

Key Points

- Controlling MS relapses slows the progression to disability.
- Minimizing disability improves quality of life for patients with MS.
- Minimizing disability decreases direct and indirect costs of MS care.
- For short-term reduction of relapses, there does not appear to be a significant difference among interferon beta-1b, interferon beta-1a, and glatiramer.
- Patients treated with glatiramer appear to have lower disability scores over the long term compared to patients treated with the two interferons.

MULTIPLE SCLEROSIS IS AN AUTOIMMUNE disease of the central nervous system characterized by chronic inflammation. The cause or trigger for the immune system to begin attacking the body in this disease is still unknown. There appears to be a complex interaction of genetics and environmental factors. There are geographic variations in incidence with low-, medium-, and high-incident areas. The incidence of MS increases with increasing distance from the equator north or south.

Some of the environmental factors that have been identified include cigarettes, vitamin D deficiency, viral infections, and bacterial infections. Male cigarette smokers develop MS at the same rate as female nonsmokers, which is double the risk of nonsmoking males. Smokers also can accelerate their progression by continuing to smoke. Young people who have vitamin D insufficiency have a higher risk for developing MS. Vitamin D appears to have a role in the immune system. Even in a sunny climate, two thirds of people in the developed parts of the world have insufficient or deficient vitamin D levels. Infections may trigger the disease or cause relapses in patients with MS.

The age of onset is between 15 to 45 years, with mostly women affected (70 percent). Exhibit 1

shows the range of symptoms that can occur with MS. Each patient will have a different complex of symptoms. MS is the most common disabling condition in young adults. Fifty percent of patients who are untreated will have a progressive course requiring walking aids within 15 years of diagnosis. The incidence is 8,500 to 10,000 new cases per year. The prevalence in the United States is approximately 400,000 cases and rising.^{1,2}

Treatment of MS has changed significantly in recent years. Previously, there were no really good treatments. As an example of MS treatment in 1990, a 40-year-old male previously diagnosed at age 25 with relapsing and remitting MS was bedridden, had neurogenic bowel and bladder, and partial spastic quadriplegia. He was admitted to the hospital for fever and was found to have a large infected sacral decubitus with underlying osteomyelitis. After eight weeks of intravenous antibiotics, three plastic surgery interventions, and an additional eight weeks of rehabilitation, he was discharged to a nursing home. The cost for this one episode was over \$800,000 in 1990.

As MS progresses, there is an increase in comorbidities. There is a loss of mobility and independence, spasticity, swallowing disorders, and neurogenic

Exhibit 1: MS Symptoms

Unpredictable Deficits Occurring Over Time	
Fatigue	Up to 90% of patients
Depression	50% to 70%; 7.5x higher suicide rate
Sensory	20%-55% initial presentation
Spasticity	40% initial, 60% as disease progresses
Pain	80%
Bladder	75%
Sexual dysfunction	40% (men)-50% (women)
Bowel	50%
Optic neuritis	14%-23% initial presentation
Cerebellar system	Ataxia, intention tremor, dysarthria

bowel and bladder. With higher levels of disability, the patient is prone to infections – pneumonia aspiration, urinary tract infection, sepsis, decubitus, and osteomyelitis. These problems rarely occur anymore with better disease control. MS is better controlled now with better treatments. Thus, patients can expect to have a good quality of life and remain ambulatory for many years.

Health care costs for patients with MS increase with worsening disease related disability. In one study, the total mean annual costs per patient (adjusted for gross domestic product purchasing power in Europe) were estimated at 18,000 Euro for mild disease (EDSS <4.0), 36,500 Euro for moderate disease (EDSS 4.0 to 6.5), and 62,000 Euro for severe disease (EDSS >7.0).³ In addition to increasing the cost of MS care, increasing MS disability decreases quality of life and increases probability of unemployment.

The current goal in MS treatment is to prevent

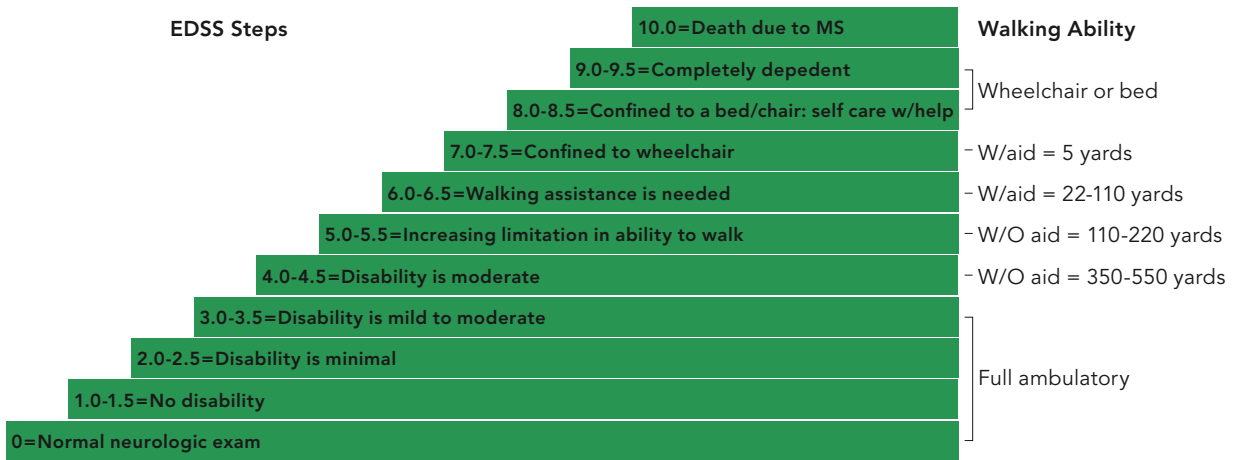
people from reaching an Expanded Disability Status Scale (EDSS) score of 6 (Exhibit 2).⁴ At a score of less than 4, a patient’s disabilities may not be obvious to most people. At 8, the patient is confined to a wheelchair.

Exhibit 3 shows data from a French natural history study of MS.⁵ Different groups of patients progress at different rates but once the person reaches a certain level of disability (EDSS score of 4), the slope of the curves become parallel. It is then just a matter of time before the patient will reach a significant level of disability. This is the transition point from a relapsing and remitting form of the disease to the slow progressive form of MS. The goal of avoiding having people reach a disability score of 4 has not yet been incorporated into clinical trials. Trials currently aim to prevent patients reaching a score of 6. Disease course can be modified if patients are treated before they reach an EDSS of 4.

The keys to treatment are disease modification and treatment of associated systems. Disease modification is preventing or delaying permanent neurologic deficits that lead to the progression of disability. It is important to note that function that is lost cannot be regained. Treatment of associated systems includes improving quality of life and preventing the development of confounding medical problems.

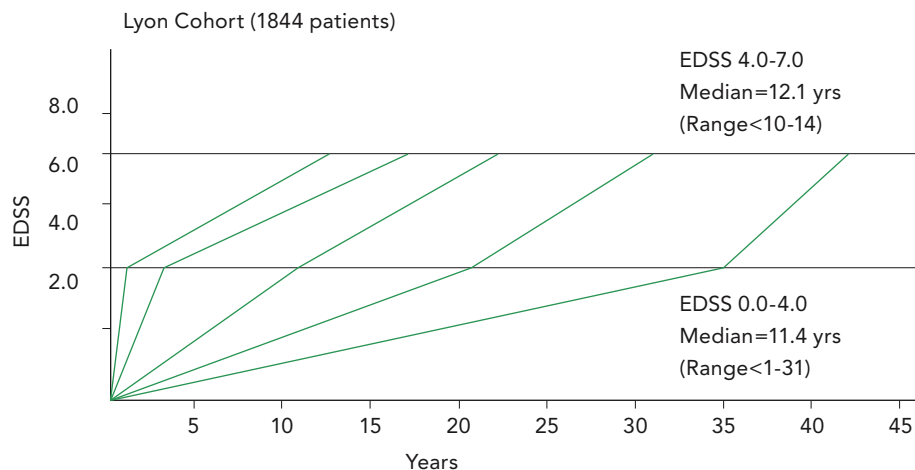
MS is characterized by periodic relapses or attacks. A clinical relapse is the appearance of a new neurological sign, symptom, or deficit that is present for at least 24 hours. This is usually accompanied by changes in the patient’s physical exam and may be associated with new lesions in the brain on MRI. Suppression of relapses early in the disease may modify the course of MS. This is the rationale for early

Exhibit 2: Clinical Event – Change in EDSS



Reference: 3

Exhibit 3: Natural History
Progression Rate of Neurological Disability in MS Patients



Reference: 4

treatment. High levels of attacks early in the disease process indicate a higher risk of high level of disability (Exhibit 4).⁶

The goal of disease modifying therapy is long-term efficacy that reduces relapse rate, delays disability progression, decreases disease activity on MRI, and reduces symptoms associated with disease. The primary agents for MS are glatiramer acetate (Copaxone[®]) and interferon (IFN) betas (IFN beta-1b [Betaseron[®]], IFN beta-1a [Avonex[®], Rebif[®]]). All are FDA approved for use in MS. Mitoxantrone, a chemotherapy agent, is approved for progressive forms of MS. Natalizumab is approved for relapsing and remitting MS in patients who are not stable on the other primary interventions. Exhibit 5 shows the acquisition costs for these agents.

In older trials of MS agents, patients had MS for a long time before being put on a study medication. In these studies, relapse rates were decreased 30 to 50 percent. Currently, most MS patients are being treated much earlier. In newer trials in early forms of multiple sclerosis, the primary agents appear to be approximately equal for time to next attack. In one study comparing IFN beta 1-a and glatiramer, the

Exhibit 4: Predictive Value of Relapses on Time to Disability Progression (EDSS)

# Attacks in First 2 Yrs	Time (yrs) to EDSS 6	Time (yrs) to EDSS 8
1	20	36
2	17	28
3	18	28
4	13	24
5	7	14

relapse rate was decreased by approximately 70 percent at two years.⁷ In another study comparing beta 1-b and glatiramer, the rate was decreased by 78 to 79 percent.⁸ Treating earlier appears to give a much better preventative rate.

In long-term outcome achievement with these agents, there may be some differences. Without treatment, 50 percent of patients will reach an EDSS of 4 by 15 years of disease. As seen in Exhibit 6, the percentage was significantly decreased with glatiramer and IFN 1-a subcutaneous but not reported for other

Exhibit 5: MS Immunomodulator Summary

Product Name	Product Type	Average Wholesale Price	FDA Approval Date
IFN beta-1a IM	Recombinant protein	\$20,775.67	1996
IFN beta-1b SC	Recombinant protein	\$22,644.48	1993
IFN beta-1a SC	Recombinant protein	\$23,947.65	2002
Glatiramer acetate SC	Polypeptide mixture	\$20,857.32	1996
Natalizumab IV	Monoclonal antibody	\$35,597.67	2004

Exhibit 6: Summary of Long-term Data: Patients Reaching EDSS Milestones

	Disease Duration (yrs)	% Reaching EDSS 4	% Reaching EDSS 6	% Reaching EDSS 8
Glatiramer acetate 10-year LTFU	18.5	24	8	1
IFN beta-1a SC PRISMS 8	~13	26.8	20	Not reported
IFN beta-1b SC 16 year (>80)	~20	Not reported	~45	29.4 (n=48)
IFN beta-1a IM 8-year atrophy	14.5	Not reported	35	Not reported
Natalizumab 2 year	5.3	Not reported	Not reported	Not reported

References: 6, 9-11

agents.^{6,9-11} The number of patients reaching an EDSS of 6 appears to be significantly lower with glatiramer. More long-term data in patients treated early in the disease process is needed to verify this finding.

Conclusion

A concerted effort to control MS relapses slows the progression to disability. Minimizing disability improves quality of life and decreases direct and indirect costs of MS care. The early treatment of MS is cost effective over the life of an individual with MS. *JMCM*

Ronald S. Murray, MD, FAAN, is director of the MS Clinic of Colorado in Lone Tree.

References

1. Anderson DW, Ellenberg JH, Leventhal CM, et al. Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol.* 1992;31:333-6.
2. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol.* 1997;84:223-43.

3. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry.* 2006;77:918-26.
4. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Exp Neurol.* 1983;33:1444-52.
5. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med.* 2000;343:1430-1438.
6. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain.* 1989;112:1419-28.
7. Mikol DD, et al. 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Prague, Czech Republic: ECTRIMS; 2007.
8. European Charcot Foundation satellite symposium. November 29, 2007. Fiuggi, Italy.
9. Ford CC, Johnson KP, Lisak RP, et al. A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients. *Mult Scler.* 2006;12:309-20.
10. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology.* 2006;67:944-53.
11. Ebers G, et al. For the Betaseron/Betaferon Study Group. Presented at AAN 58th Annual Meeting; April 8, 2006. San Diego, CA. PO 1.079.

**DON'T BE LEFT BEHIND!
SIGN UP FOR YOUR FREE SUBSCRIPTION**

Managed Care eNews

Genomics-Biotech eNews

- › Receive the most up-to-date news in managed care, genomics, and biotechnology.
- › Plus breaking news from CMS, FDA, and other regulatory bodies.

To view the eNews or subscribe, go to www.namcp.org, or contact Jeremy Williams, jwilliams@namcp.org, 804-527-1905.

Already a subscriber and not finding it in your Inbox?
Contact Jeremy to set the eNews as a safe sender!