National Multiple Sclerosis Society
733 Third Avenue
New York, NY 10017-3288

# Expert Opinion Paper

*Medical Advisory Board of the National Multiple Sclerosis Society*

*Treatment Recommendations for Physicians*

## Disease Management Consensus Statement

### RECOMMENDATIONS

The Executive Committee of the Medical Advisory Board of the National Multiple Sclerosis Society, while recognizing that the factors that enter into a decision to treat are complex and best analyzed by the individual patient's neurologist, has adopted the following recommendations regarding use of the current MS disease-modifying agents (in alphabetical order):

*Immunomodulators:* beta interferon 1a-intramuscular (Avonex®)
beta interferon 1a-subcutaneous (Rebif®)
beta interferon 1b (Betaseron®)
glatiramer acetate (Copaxone®)

*Immunosuppressant:* mitoxantrone (Novantrone®)

- Initiation of therapy with an immunomodulator should be considered as soon as possible following a definite diagnosis of MS with active disease, and may also be considered for selected patients with a first attack who are at high risk of MS.
- Patients' access to medication should not be limited by frequency of relapses, age, or level of disability.
- Treatment is not to be stopped while insurers evaluate for continuing coverage of treatment.
- Therapy is to be continued indefinitely, except for the following circumstances: there is clear lack of benefit; there are intolerable side effects; better therapy becomes available.
- All of the these FDA-approved agents should be included in formularies and covered by third party payers so that physicians and patients can determine the most appropriate agent on an individual basis—failure to do so is unethical and discriminatory.
- Movement from one immunomodulatory drug to another should occur only for medically appropriate reasons.

- Immunosuppressant therapy with Novantrone® (mitoxantrone) may be considered for selected relapsing patients with worsening disease or patients with secondary-progressive multiple sclerosis.
- Most concurrent medical conditions do not contraindicate use of the immunomodulatory drugs.
- None of the therapies has been approved for use by women who are trying to become pregnant, are pregnant, or are nursing mothers.

## Introduction

The management of multiple sclerosis (MS) has been substantially advanced by the availability of the disease-modifying agents beta interferon 1a and 1b and glatiramer acetate, and the immunosuppressant agent, mitoxantrone. A number of positive outcomes have been demonstrated in people with relapsing disease: reduction in the frequency and severity of relapses[1] [Betaseron[2–5]; Avonex[6–9]; Copaxone[10–11]; Rebif[12–14]; Novantrone[15]]; reduction of brain lesion development, as evidenced by magnetic resonance imaging (MRI) [Betaseron[2,16–17]; Avonex[6–9]; Copaxone[18–20]; Rebif[12–14,21–22]; Novantrone[23]]; and the possibility of reduction of future disability[24] [Betaseron[2,16–17]; Avonex[6–9]; Copaxone[10–11], Rebif[12–14], Novantrone[15,23]].

Based on several years of experience with the beta interferons and glatiramer acetate, it is the consensus of researchers and clinicians with expertise in MS that these agents can reduce future disease activity and improve quality of life for many individuals with relapsing forms of MS, including those with secondary progressive disease who continue to have relapses. For those who are appropriate candidates for one of these drugs, treatment must be sustained for years. Cessation of treatment may result in a resumption of pre-treatment disease activity [(25)].

Clinical trials are designed to evaluate the smallest number of people, over the shortest period of time, at the lowest cost. In order to accomplish this, inclusion criteria are necessarily narrow. These restricted parameters of clinical trials are not intended to regulate subsequent clinical use of the agent. With demonstrated benefit to people with MS from continued use of Betaseron®, Avonex®, Rebif®, or Copaxone®, it is critical that these therapies be made available early in the disease process to appropriate candidates as indicated in the labeling of each of these medications, and that Novantrone® be available for judicious use in aggressive relapsing disease and for those not responding to immunomodulators.

## Background

In August, 1994, the Quality Standards Subcommittee of the American Academy of Neurology published an advisory statement on the selection of patients with multiple sclerosis for treatment with Betaseron® (beta interferon 1b). Since then, four additional agents that modify the underlying disease process have been approved by the Food and Drug Administration (FDA): Avonex® (beta interferon 1a), Copaxone® (glatiramer acetate), Novantrone® (mitoxantrone), and Rebif® (interferon beta 1a). The benefits of these agents include direct evidence of disease modification [(1–23)], with inferred advantage to function and quality of life. The National MS Society has

maintained the timeliness of its consensus statement as additional agents have been studied and approved, and new clinical trial data have become available. The current revision references all of the currently approved drugs.

Significant obstacles to obtaining these agents exist for appropriate candidates with MS. One is the lack of adequate information reaching primary care providers and general neurologists, who may each have only a few patients with MS, but collectively care for a large percentage of the MS population. Another is misunderstanding by some policy makers and insurers of the benefits of disease management therapy, leading to inadequate coverage, both initially and long term. This NMSS Disease Management Consensus Statement addresses these barriers, while acknowledging that the field is in flux, and frequent review of recommendations is essential. Other obstacles, such as non-adherence to protocols and "drop out" by those already on drug are not addressed in this statement. The controversial area of neutralizing antibodies is mentioned only to state that sufficient data do not yet exist to base clinical decisions exclusively on the results of neutralizing antibody assays.

## Discussion

The NMSS Consensus Statement is an education and advocacy tool. It is a component of the Society's professional education programs, and is used to promote increased access to the approved disease-modifying agents through legislative, judicial, and regulatory determinations. This Consensus Statement serves as a communication device for interactions with insurers, both nationally and locally.

The following points highlight the issues:

- Among patients who report that they have relapsing-remitting MS, 38% are not on immunomodulatory therapy (National MS Society-funded Sonya Slivka Longitudinal MS Study, unpublished data).
- This is of particular concern in light of numerous studies[26–29] confirming that axonal damage can coincide with destruction of the myelin sheath in the MS disease process, suggesting that even early relapses that appear benign may have permanent neurological consequences. Serial MRI studies [30–31] of individuals who are clinically in remission have demonstrated ongoing brain lesion development and atrophy despite a seemingly benign clinical course. These findings strengthen the argument for early intervention with a disease-modifying agent.
- Government advocacy is critical to address regulations regarding areas such as Medicare reimbursement for these injectable agents. Legislative measures are being debated regarding this and other issues, and some judicial decisions have broad implications for access to treatment. In one dispute, a patient was denied coverage for an MS disease-modifying drug based on her non-ambulatory status. This Consensus Statement supports efforts to expand governmental coverage to appropriate levels for this and similar cases.
- Variable and sometimes detrimental policies by insurers exist regarding the use of the immunomodulators, most likely resulting from insufficient information about the short-

and long-term benefits of these drugs, or strict interpretation of the original trial criteria. Insurance barriers include the following:

- Selection and availability of only one or two of the agents for coverage, or a financial penalty to a patient for not being treated initially with the highest-tiered medication approved by his or her health plan
- Evaluation of the need for ongoing treatment by cessation of treatment for a period of time
- Interpretation of absence of attacks as an indication for discontinuation of drug
- Arbitrary restrictions, such as ambulatory status, full recovery from an attack, and age
- Requirement of two relapses within the preceding year in order to begin or continue on drug
- Placement of a ceiling on cost of treatment
- Non-coverage of injectable agents

The recommendations contained within this Consensus Statement address these issues.

## Process

The Executive Committee of the Society's Medical Advisory Board identified the need for the Society to develop and periodically update a formal position on the topic of disease management with the disease-modifying agents. A Medline search was conducted to document major studies in this area. A task force was activated to develop the statement, and the NMSS Medical Advisory Board's Executive Committee provided final review of the document.

## Role of the National Multiple Sclerosis Society

The mission of the NMSS is to end the devastating effects of MS. Various strategies are employed, including professional education and advocacy. As a representative body and advocate for both people with MS and the medical/health professionals who provide their care, the Society is positioned to provide structure and support for a consensus statement to facilitate access to therapies for disease management. The NMSS has a nationwide network of chapters, each with a Clinical Advisory Committee composed of community health professionals with expertise in MS. Over 330,000 Society members have self-identified as having MS, and are part of a mailing list of almost 600,000 people interested in multiple sclerosis-related issues. Regular communication is made with these various audiences through national and chapter publications. This extensive network and process for dissemination will ensure that the updated Consensus Statement is expeditiously communicated to care providers, insurers, and people with multiple sclerosis.

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## This statement was updated by the Executive Committee of the Medical Advisory Board of the National Multiple Sclerosis Society.

Aaron Miller, MD, *Chair*
*Mount Sinai School of Medicine*

Jeffrey Cohen, MD
*Cleveland Clinic Foundation*

Corey Ford, MD
*University of New Mexico Medical Center*

George Garmany, MD
*Boulder, Colorado*

Andrew Goodman, MD
*University of Rochester Medical Center*

Barbara Green, MD
*St. John's Mercy Medical Center*

Kenneth Johnson, MD
*University of Maryland*

Robert Lisak, MD
*Wayne State University*

Fred Lublin, MD
*Mount Sinai Medical Center*

Henry McFarland, MD
*National Institutes of Health*

John Noseworthy, MD
*Mayo Clinic and Foundation*

Kottil Rammohan, MD
*Ohio State University*

Richard Rudick, MD
*Cleveland Clinic Foundation*

Randall Schapiro, MD
*Minneapolis Clinic of Neurology*

Randolph Schiffer, MD
*Texas Tech Health Sciences Center*

Stanley van den Noort, MD
*University of California at Irvine*

Jerry Wolinsky, MD
*University of Texas Health Sciences Center*