



Complete Summary

GUIDELINE TITLE

Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines.

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Frohman EM, Garmany GP Jr, Halper J, Likosky WH, Lublin FD, Silberberg DH, Stuart WH, van den Noort S. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002 Jan 22;58(2):169-78. [55 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, this guideline has been reviewed and is still considered to be current as of October 2003. This review involved new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [July 29, 2008, Mitoxantrone Hydrochloride \(Novantrone, Mitroxone, Neotalem, Onkotrone, and Pralifan\)](#): The U.S. Food and Drug Administration (FDA) reminded health care professionals who treat patients with mitoxantrone about recommendations that left ventricular ejection fraction (LVEF) be evaluated before initiating treatment and prior to administering each dose of mitoxantrone. FDA offered additional recommendations for cardiac monitoring to detect late-occurring cardiac toxicity, and provided information for patients with multiple sclerosis who receive the drug.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

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SCOPE

DISEASE/CONDITION(S)

Multiple sclerosis

GUIDELINE CATEGORY

Technology Assessment
Treatment

CLINICAL SPECIALTY

Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To consider the clinical utility of disease-modifying agents for multiple sclerosis, including anti-inflammatory, immunomodulatory, and immunosuppressive treatments

TARGET POPULATION

Patients who have multiple sclerosis (MS), including relapsing/remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive/relapsing MS (PRMS)

INTERVENTIONS AND PRACTICES CONSIDERED

Disease-Modifying Treatment of Multiple Sclerosis:

1. Glucocorticoids
2. Interferon-beta-1a and interferon-beta-1-b (Avonex, Betaferon, Betaseron, Rebif)
3. Glatiramer acetate (Copaxone)
4. Cyclophosphamide

5. Methotrexate
6. Azathioprine
7. Cladribine
8. Cyclosporine
9. Mitoxantrone
10. Intravenous immune globulin
11. Plasma exchange
12. Sulfasalazine

Note: Symptomatic and reparative therapies are not considered.

MAJOR OUTCOMES CONSIDERED

- Effects of disease modifying therapies on clinical outcomes (e.g., clinical attack rate, relapse rate, disability progression)
- Clinical magnetic resonance imaging (MRI) outcomes:
 - Attack rate
 - Disease severity/progression
 - Relapse rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Guideline developers searched MEDLINE, EMBASE, and other pertinent databases.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Rating of Therapeutic Article

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- a. Primary outcome(s) is/are clearly defined.
- b. Exclusion/inclusion criteria are clearly defined.
- c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias

- d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above *or* a randomized controlled trial (RCT) in a representative population that lacks one criteria a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The author panel critically assessed the topic through analysis of the medical literature. Panel members reviewed the identified articles based upon a priori inclusion and exclusion criteria and pertinence to the topics. Selected articles were rated based on quality of study design, and clinical practice recommendations were developed and stratified to reflect the quality and the content of the evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Translation of Evidence to Recommendations

Level A rating requires at least one convincing Class I study or at least two consistent, convincing Class II studies.

Level B rating requires at least one convincing Class II study or at least three consistent Class III studies.

Level C rating requires at least two convincing and consistent Class III studies.

Rating of Recommendation

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting. Given current knowledge, treatment is unproven.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology (AAN) members, topic experts, and pertinent physician organizations.

The Therapeutics and Technology Assessment (TTA) Subcommittee approved the guideline recommendations on August 3, 2001. The Practice Committee approved the guideline recommendations on August 4, 2001, and the American Academy of Neurology (AAN) Board of Directors approved them on October 20, 2001.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of levels of evidence (Class I-IV) and the ratings of recommendations (A, B, C, U) are provided at the end of the Major Recommendations field.

Summary of Recommendations

Glucocorticoids:

1. On the basis of several, generally consistent Class I and Class II studies, glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in patients with acute attacks of multiple sclerosis (MS). It is appropriate, therefore, to consider for treatment with glucocorticoids any patient with an acute attack of MS (**Level A recommendation**).
2. There does not appear, however, to be any long-term functional benefit after the brief use of glucocorticoids in this clinical setting (**Level B recommendation**).

3. Currently, there is not compelling evidence to indicate that these clinical benefits are influenced by the route of glucocorticoid administration, the particular glucocorticoid prescribed, or the dosage of glucocorticoid, at least at the doses that have been studied to date (**Level C recommendation**).
4. On the basis of a single Class II study, it is considered possible that regular pulse glucocorticoids may be useful in the long-term management of patients with relapsing/remitting MS (RRMS) (**Level C recommendation**).

Interferon beta (IFN-beta):

1. On the basis of several consistent Class I studies, IFN-beta has been demonstrated to reduce the attack rate (whether measured clinically or by magnetic resonance imaging [MRI]) in patients with MS or with clinically isolated syndromes who are at high risk for developing MS (**Level A recommendation**). Treatment of MS with IFN-beta produces a beneficial effect on MRI measures of disease severity, such as T2 disease burden, and probably also slows sustained disability progression (**Level B recommendation**).
2. As a result, it is appropriate to consider IFN-beta for treatment in any patient who is at high risk for developing clinically definite MS (CDMS), or who already has either RRMS or secondary progressive MS (SPMS) and is still experiencing relapses (**Level A recommendation**). The effectiveness of IFN-beta in patients with secondary progressive MS but without relapses is uncertain (**Level U recommendation**).
3. It is possible that certain populations of MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy than others, although, at the moment, there is insufficient evidence regarding these issues (**Level U Recommendation**).
4. On the basis of Class I and II studies and several pieces of consistent Class III evidence, it is considered probable that there is a dose-response curve associated with the use of IFN-beta for the treatment of MS (**Level B recommendation**). It is possible, however, that a portion of this apparent dose-effect instead may be due to differences in the frequency of IFN-beta administration (rather than dose) between studies.
5. On the basis of several Class II studies, the route of administration of IFN-beta is probably not of clinical importance, at least with regard to efficacy (**Level B recommendation**). The side-effect profile, however, does differ between routes of administration. There is no known clinical difference between the different types of IFN-beta, although this has not been thoroughly studied (**Level U recommendation**).
6. On the basis of several Class I studies, treatment of patients with MS with IFN-beta is associated with the production of neutralizing antibodies (NAbs) (**Level A recommendation**). The rate of NAb production, however, is probably less with IFN-beta-1a treatment than with IFN-beta-1b treatment (**Level B recommendation**). The biological effect of NAbs is uncertain, although their presence may be associated with a reduction in clinical effectiveness of IFN-beta treatment (**Level C recommendation**). Whether there is a difference in immunogenicity between subcutaneous and intramuscular routes of administration is unknown (**Level U recommendation**). The clinical utility of measuring NAbs in an individual on IFN-beta therapy is uncertain (**Level U recommendation**).

Glatiramer acetate:

1. On the basis of Class I evidence, glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS (**Level A recommendation**). Treatment with glatiramer acetate produces a beneficial effect on MRI measures of disease severity, such as T2 disease burden, and possibly also slows sustained disability progression in patients with RRMS (**Level C recommendation**).
2. As a result, it is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS (**Level A recommendation**). Although it may be that glatiramer acetate also is helpful in patients with progressive disease, there is no convincing evidence to support this hypothesis (**Level U recommendation**).

Cyclophosphamide:

1. Based on consistent Class I evidence, pulse cyclophosphamide treatment does not seem to alter the course of progressive MS (**Level B recommendation**).
2. Based on a single Class III study, it is possible that younger patients with progressive MS might derive some benefit from pulse plus booster cyclophosphamide treatment (**Level U recommendation**).

Methotrexate:

1. Based on limited and somewhat ambiguous Class I evidence from a single trial, it is considered possible that methotrexate favorably alters the disease course in patients with progressive MS (**Level C recommendation**).

Azathioprine:

1. On the basis of several, but somewhat conflicting, Class I and II studies, it is considered possible that azathioprine reduces the relapse rate in patients with MS (**Level C recommendation**).
2. Its effect on disability progression has not been demonstrated (**Level U recommendation**).

Cladribine:

1. On the basis of consistent Class I evidence, it is concluded that cladribine reduces gadolinium (Gd)-enhancement in patients with both relapsing and progressive forms of MS (**Level A recommendation**).
2. Cladribine treatment does not, however, appear to alter favorably the course of the disease, either in terms of attack rate or disease progression (**Level C recommendation**).

Cyclosporine:

1. Based on this Class I study, it is considered possible that cyclosporine provides some therapeutic benefit in progressive MS (**Level C recommendation**).

2. However, the frequent occurrence of adverse reactions to treatment, especially nephrotoxicity, together with the small magnitude of the potential benefit, makes the risk/benefit of this therapeutic approach unacceptable (**Level B recommendation**).

Mitoxantrone:

1. On the basis of generally consistent Class II and III studies, it is concluded that mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS (**Level B recommendation**). The potential toxicity of mitoxantrone, however, may outweigh the clinical benefits early in the course of disease.
2. On the basis of several Class II and III observations, it is considered possible that mitoxantrone has a beneficial effect on disease progression in MS, although, at the moment, this clinical benefit has not been established (**Level C recommendation**).

Intravenous immunoglobulin:

1. The studies of intravenous immunoglobulin (IVIg), to date, have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS (**Level C recommendation**).
2. The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (**Level C recommendation**).

Plasma exchange:

1. On the basis of consistent Class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS (**Level A recommendation**).
2. On the basis of a single small Class I study, it is considered possible that plasma exchange may be helpful in the treatment of severe acute episodes of demyelination in previously nondisabled individuals (**Level C recommendation**).

Sulfasalazine:

1. Based on a single Class I study, it is concluded that treatment of MS with sulfasalazine provides no therapeutic benefit in MS (**Level B recommendation**).

Definitions:

Rating of Therapeutic Article

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- b. Exclusion/inclusion criteria are clearly defined.
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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

These guidelines may assist physicians in making appropriate clinical decisions regarding the use of disease-modifying agents for patients with multiple sclerosis.

POTENTIAL HARMS

Potential harms include adverse effects and toxicities of disease modifying therapies:

- The frequent occurrence of adverse reactions to cyclosporine treatment, especially nephrotoxicity, together with the small magnitude of the potential benefit, makes the risk/benefit of this therapeutic approach unacceptable.
- The potential toxicity of mitoxantrone may outweigh the clinical benefits early in the course of disease.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Jan 22 (reviewed 2003 Oct)

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society
Multiple Sclerosis Council - Disease Specific Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee of the American
Academy of Neurology
Multiple Sclerosis Council for Clinical Practice Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: D.S. Goodin, MD; E.M. Frohman, MD; G.P. Garmany, Jr., MD; J. Halper, MSN, ANP, FAAN; W.H. Likosky, MD; F.D. Lublin, MD; D.H. Silberberg, MD; W.H. Stuart, MD; and S. van den Noort, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

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GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#).

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology.

Electronic copies: Available from the [American Academy of Neurology Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on February 3, 2004. This summary was updated by ECRI on March 22, 2005 following release of a public health advisory from the U.S. Food and Drug Administration regarding the use of Avonex. This summary was updated by ECRI on May 27, 2005, following the U.S. Food and Drug Administration (FDA) advisory on Novantrone (mitoxantrone for injection concentrate). This summary was updated by ECRI Institute on August 11, 2008 following the U.S. Food and Drug Administration advisory on mitoxantrone hydrochloride.

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