



NATIONAL
MULTIPLE SCLEROSIS
SOCIETY

Health Insurance Appeal Letters

A Toolkit for Clinicians



Professional Resource Center
National Multiple Sclerosis Society

733 Third Avenue
New York, NY 10017



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This guide is designed to aid in the dialogue between MS clinicians and health insurance plans when disputes over coverage arise. This book is accompanied by a CD that contains easy-to-edit and user-friendly model appeal letters.

This publication is dedicated to Dr. Labe Scheinberg, former Dean of the Albert Einstein College of Medicine in the Bronx, who is considered the "Father of Comprehensive MS Care." He would have been pleased by this effort to improve access to multiple sclerosis (MS) therapies for people with MS. We are pleased to continue his work and his philosophy of care for those with MS.

Professional **R_x** Resource Center



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Introduction: What Is This Toolkit For?

Due to the increasing pressures of health care cost containment, health plans (both public and private) are demanding greater clinical justification for professional services, drugs, rehabilitation therapies and more. Common strategies for containing costs within both private plans (employment-based and individually purchased) AND public plans (Medicare and Medicaid) now include:

- prior-authorization (a.k.a. pre-approval) requirements
- utilization review
- drug formularies
- 'fail first policies' (a.k.a. 'step therapy')
- tiered drug benefits
- denials of coverage for off-label use of FDA-approved drugs

It is important to acknowledge that cost containment is valuable to all users of the health care system when such measures promote quality and accountability, but may also delay or deny optimal care.

The National Multiple Sclerosis Society (NMSS) has developed this guide, which includes template appeal letters on MS clinical issues, as a resource for clinicians who treat people with MS and administrative staff in clinical practice settings. The purpose of this guide is to aid in the dialogue between MS clinicians and health plans when disputes over coverage arise. Comparable information about appeal rights, responsibilities and procedures is being developed for people with MS, and should always be described in writing in the Members' Handbook or Plan Manual.

The appeal process of virtually all health plans, including Medicare and Medicaid, are based on the procedures initially developed by the health insurance industry. Nearly two-thirds of all people with MS who are insured are covered by private health plans, and an increasing number of others are covered by private plans that contract with Medicare or Medicaid.

Clinicians and their office colleagues are encouraged to review the following overview and make best use of the template letters as they see fit. Each letter is written as a model only, and includes citations from published studies whenever possible. Note that the more tailored the letter is to the medical necessity of the prescribed

therapy, service or item for that particular patient, the greater the likelihood of gaining coverage for it. In addition, the model letters reference relevant National MS Society Expert Opinion papers and we strongly encourage their inclusion in all communications with insurers. This will help promote knowledge of MS among health plan personnel, as well as visibility of the National MS Society as a resource for information about medically necessary and appropriate therapies for people with MS.

Finally, it is hoped that users of this guide find ways of making use of these templates, journal citations, and Expert Opinion Papers for communications in other ways. These may include:

- telephone discussion/appeals with health plan Medical or Pharmacy Directors;
- dialogue with regional Medicare carriers and advisors;
- advocacy for coverage by self-insured employer and union health plans; and
- analysis of hospital (and other institutional) formularies.

We strongly encourage your feedback on this first group of model appeal letters and materials. Many thanks to the numerous individuals who contributed to this effort. We plan to develop additional letters and materials, and strongly encourage your feedback and good thinking. Most importantly, the people with MS whom we all serve will benefit greatly from our joint efforts on health coverage concerns, and we thank you on their behalf.

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Coverage Denials and Appeals: An Overview

THE RIGHT OF EVERY INSURED PERSON

Challenging a coverage denial by a health insurance plan is a legal right guaranteed to all insured individuals. Every plan—including private policies, employer-sponsored health plans, Medicare and Medicaid—must provide a process for re-consideration of any adverse determination by the plan. Among people with MS who are health plan members, anecdotal reports show that delays or denials are most common for non-formulary or off-label drugs; for services that are not covered, have been exhausted or were not properly authorized; and supplies or equipment that are not covered or deemed not medically necessary.

SUCCESSFUL APPEALS

The success rate of health coverage appeals provides the most compelling argument for pursuing them—*more than 50% of appeals of denials for coverage or reimbursement by health insurers are ultimately overturned* in favor of the covered individual. Success may not be achieved at the first level of appeal, and is more likely with consecutive and (politely) persistent appeal challenges. Private and employer-sponsored health plans typically provide at least two levels of appeal, and Medicare and Medicaid guarantee multiple levels of appeal that are roughly comparable to the first and second level appeals in private plans.

Appeals are most likely to be successful when presented in accordance with the plan's appeals process and timeframe. The most effective appeal letters are very clear statements about the purpose of the letter, factual and brief. Most importantly, *appeal letters must be tailored to the specific patient's need(s) as documented in the medical record, and provide a clinical justification in support of the recommended treatment, item or service.*

THE ROLE OF PATIENTS, AND HEALTH CARE PROFESSIONALS, IN THE APPEALS PROCESS

An appeal of a coverage denial may be initiated by the individual patient (or his/her caregiver) OR the prescribing health care professional (HCP), and are best viewed as a collaboration between patient and clinician. However, insured patients should

understand that the health plan is accountable to them as the covered individual and contract holder, not the patient's health professional. Additionally, both patient and HCP should be aware that health plans have no legal obligation to accept appeals received after the time-frame spelled out in the insurance contract. When requesting assistance from an HCP for an appeal (or negotiation over benefits of any type), a patient should be prepared to provide the HCP or his/her staff with the following if/when necessary.

- 1) accurate and up-to-date information about their health plan;
- 2) general information about their covered benefits; (in the form of written descriptions of benefits provided to all plan members), as well as appeal procedures and deadlines; and
- 3) copies of any/all relevant claims or correspondence to/from the plan.

The role of HCPs in the appeals process is an extension of their role as providers of high quality patient care. *Providing documentation* from the patient's medical record and *supporting evidence of medical necessity* in the form of a letter to the health plan may seem like a time-consuming duplication of effort, but is also a check on accountability, safeguard of quality and a means of elevating standards of MS patient care. If or when health plans delay or deny coverage, the prescribing clinician should demonstrate *a willingness to back-up his/her clinical recommendation* with such a letter including citations from relevant published studies, personal experience and available evidence. HCPs should also be aware that when dealing directly with health plan personnel regarding coverage issues, *a cooperative and professional attitude* is cited by industry insiders as key to a successful appeal.

WHEN IS IT APPROPRIATE TO FILE AN APPEAL?

When a denial of coverage has been made, patients and/or their clinicians should pursue an appeal *after considering the following*:

- 1) Is the denial based on a clerical error or missing information? If the denial has not already been provided in writing, request it immediately and examine it for errors, such as in the member's ID number, diagnostic or service code, or date of service.
- 2) Is the treatment, service or item a covered benefit under the patient's plan? If the desired treatment, service or item is clearly listed as an uncovered benefit, there is virtually no value in pursuing an appeal. However, if the plan materials are unclear or silent on the matter, an appeal is warranted.
- 3) Is the treatment, service or item medically necessary and indicated for this patient, at this point in time?

THE APPEALS PROCESS

Although details of the appeals procedure vary among plans, they are generally similar enough that a basic overview of the appeals process is useful to health care professionals and patients alike. There are typically two, but often three levels of appeal available to plan members

depending on the type of plan. Although the medical expertise of the individuals responsible for conducting the appeals generally increases with each successive level, denial of the first level is required before the second level of appeal may be pursued. Both first and second levels of appeal (together referred to as internal appeals because they are conducted by the health plan), *must be* exhausted before an external review may be requested.

If, in the judgment of the prescribing provider, delay in treatment would pose a danger to the patient's health, or result in the inability to regain maximum function, an expedited or accelerated review should be requested. (Expedited reviews typically cut the review time to 2 to 3 days at most.)

First Level Appeal. Also known as an informal review, this level of appeal is the most cursory. Although typically conducted by a Claims Reviewer, federal law (ERISA) requires that a licensed medical professional sign off on all appeals.

Second Level Appeal. Also known as a formal appeal, a small group of reviewers (including one licensed physician in the same or similar specialty of relevance) conducts this level appeal. Some plans allow the member or his/her representative to attend a meeting of the group to present the case and any *new* information.

External Appeal. Also known as independent or external review, an external appeal is conducted by neutral parties. If availability to an external appeal is a right established by state law (and therefore limited to plans subject to state law/regulation), the state's Commissioner of Insurance is responsible and should be contacted for information regarding process, timeframes and possibly fees for the applicant. *First and second level appeals must be exhausted first.*



Common Terms and Concepts in the Appeals Process

Adverse Determination. Notification from the health plan or plan administrator advising the covered person of a reduction or denial of benefits.

Authorized Services. Services which have been pre-certified when required under the terms of the contract.

Carveout. A portion of covered benefits which are set apart from the body of the health plan, such as mental health or substance abuse treatment, and subject to the advice of entities with specific expertise in the relevant specialized field or practice under contract with the health plan.

Claims Reviewer or Adjuster. An employee of the health plan whose primary responsibility is to review claims for benefits before, during or after services are provided.

Concurrent Review. A coverage determination or appeal made during a course of treatment.

Expedited (or Accelerated) Review. An appeal reviewed on a shortened timeframe provided when/if the provider believes a delay in treatment poses an imminent or serious threat to the patient's health or ability to regain maximum function.

Experimental or Investigational Treatment. Treatments traditionally excluded from coverage by health insurance on the basis that 1) it is a drug not approved for marketing by the US Food & Drug Administration, including off-label indications of FDA approved drugs; or 2) a procedure or therapy outside the scope of generally accepted medical practice.

External Review. A program available to many privately insured individuals as an additional third level of appeal after internal appeals have been exhausted, and providing for legally binding review of a claim for benefits by a panel of independent clinicians.

Grievance. A request for re-consideration of an adverse determination concerning an administrative decision, rather than medical necessity, such as a dispute over date of enrollment.

Health Plan. Commonly accepted term to describe the organizational schema of health insurance policies or contracts.

Internal Review. The formal process of appeal of an adverse determination at the first or second levels.

Medical Necessity. The determination of whether health services provided to a patient are required to maintain health according to accepted medical practice, current research and efficiency considerations.

Off Label (or Unlabeled) Use. Use of a drug approved for marketing by the US Food & Drug Administration but used for a different indication than that described on the label.

Pharmacy & Therapeutics (P&T) Committee. A group of physicians, pharmacists and other health care providers from different disciplines who advise a managed care plan regarding safe and effective use of medications. The P&T Committee manages the formulary and acts as the organizational line of communications between the medical and pharmacy components of the health plan.

Pharmacy Benefit Manager (PBM). Organizations that contract with health plans (including risk and non-risk arrangements) for the purposes of administering prescription drug benefits to plan members.

Retrospective Review. A coverage determination or appeal made after a service or item was provided.



Model Appeal Letters: Templates for Common MS Therapies

This section includes template, or sample, letters of appeal to health plans for submission by the prescribing physician. The selection of specific subjects for these letters was based on input from MS specialists around the country, as well as the experiences of National Multiple Sclerosis Society clients and staff. They relate to those drugs, therapies and items that are thought to be most often denied for coverage by health plans, although others may also be warranted. Physicians or others using these templates should be careful to:

1. tailor the wording of the letter to the status of the pre-authorization request, claim, coverage denial or other;
2. include details from the patient's chart to support the argument (while keeping the letter to one page if possible); and
3. coordinate efforts directly with the patient before writing the appeal letter to avoid confusion and possible duplication of effort.

Please note that all template letters are marked with bold, italicized type wherever the prescribing physician needs to insert appropriate text.

For your convenience, all template letters are available on the enclosed CD in an easy-to-edit and user-friendly format.

MODEL APPEAL LETTER—AVONEX

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is an appeal for re-consideration of your denial of coverage of Avonex, an interferon beta-1a, for my patient ____ (*name*) _____. I have reviewed your letter to my patient and continue to recommend Avonex as the treatment of choice in this case based on my experience treating people with relapsing MS.

My records indicate that *Mr./Ms.* _____ sought my assistance with symptoms including _____ (*provide details*) _____, and that I made a diagnosis of relapsing MS on (*date*). Avonex is the preferred therapy for *him/her* because (*suggestions include*)

- *S/he* needs once a week injection for on-going adherence to therapy; and/or
- Higher dosed interferon caused intolerable side effects; and/or
- Non-interferon therapy was not successful in controlling relapses; and/or
- Serious skin reactions have occurred with subcutaneous therapy.

Avonex received FDA approval for marketing in 1996 for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. The agency's approval was based on review of data from a double-blind, placebo-controlled clinical trial demonstrating superior results for the treatment group as seen in slowed progression of disability, as well as rate of relapse or exacerbation.¹ Additionally, the number of new or active lesions seen on MRI scans was also significantly smaller than that in the placebo group.

Since that time, Avonex has continued to demonstrate safety and efficacy in a variety of studies, including a 2000 NIH/Biogen study demonstrating cognitive improvement and an eight year follow-up evaluation by investigators of the Cleveland Clinic in 2001.²

Finally, I include for your information, the National Multiple Sclerosis Society's Disease Management Consensus Statement. The statement asserts "all of 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". I have reviewed my original recommendation for Avonex and continue to believe it offers the greatest likelihood of benefit in this case.

I may be reached at the number above should you require additional information on this patient. Otherwise, I look forward to your response directly to me as soon as possible.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹Rudick RA, Goodkin DW, Jacobs LS, et.al., Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. *Annals of Neurology* 1996; 49(3): 285–294.

²Fisher E, Rudick RA, Simon JH et. al., Eight-year follow-up study of brain atrophy in patients with MS. *Neurology* 2002; 59: 1412–1420.

MODEL APPEAL LETTER—AVONEX AFTER FIRST DEMYELINATING EVENT

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is a request for (*review of your denial of coverage, prior authorization*) for Avonex for my patient ____ (*name*) _____. I prescribed Avonex for this patient after (*he/she*) experienced an episode of (*optic neuritis, or numbness on one side, other*) as documented in (*his/her*) medical record (*describe with detail*).

An isolated neurological event of this type, known as clinically isolated syndrome (CIS), is indicative of a demyelinating process and is often a precursor to multiple sclerosis. The goal of treatment with Avonex is the delay of a second event indicating clinically definite multiple sclerosis, as well as potential disability.

The efficacy of treatment with interferon beta-1a following an initial demyelinating event was the focus of the CHAMPS Study (Controlled High-Risk Subjects Avonex MS Prevention Study).¹ During three years of follow-up, the cumulative probability of the development of clinically definite multiple sclerosis was significantly lower in the interferon beta-1a group than in the placebo group. CHAMPIONS, an open-label extension of the CHAMPS study, showed that over 70% of patients with minimal disease (less than eight T2 lesions) developed clinically definite multiple sclerosis or MRI evidence for ongoing demyelination within five years.²

Additionally, I have enclosed for your information the treatment recommendations of the National Multiple Sclerosis Society, 'Disease Management Consensus Statement'. This consensus statement by national experts in the diagnosis and management of multiple sclerosis supports the use of immunomodulating therapy for select patients with a first attack who are at high risk of MS.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹Jacobs LS, Beck, RW, Simon JH and the CHAMPS Study Group, *NEJM* 343(13): 898–904.

²Kinkel RP, Kollman C, Glassman A, et al. Interferon beta-1a (Avonex) delays the onset of clinically definite MS over 5 years of treatment: results from CHAMPIONS study. Program and abstracts of the 56th Annual Meeting of the American Academy of Neurology; April 24–May 1, 2004; San Francisco, California. Abstract S29.006.

MODEL APPEAL LETTER—BETASERON

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

It has come to my attention that you have denied coverage for Betaseron to my patient _____ (*name*)_____, who is under my care for the treatment of multiple sclerosis. I write as a practicing neurologist with considerable experience in making treatment choices among the few available drug therapies for MS, and strongly encourage you to authorize this treatment choice as discussed with my patient.

Betaseron was first approved in 1993 after review of data from a placebo-controlled, double-blind and multi-pronged clinical trial.¹ (*If patient has SPMS include: Not only was it the first approved treatment for MS, it received an expanded approval for labeling in 2003 to specifically include people with secondary-progressive MS who continue to have relapses.*)² Betaseron is the preferred therapy for him/her because: _____

Each of the FDA-approved therapies causes side effects in most people, and the range of clinical responses and side effects to them can vary significantly among the MS patient population. For these reasons, and the fact that no clinically superior agent has yet been identified, physicians and their patients must be allowed to determine the most appropriate agent on an individual basis. This assertion is firmly supported among experts in MS, as illustrated by the Society's Disease Management Consensus Statement.

I urge your re-consideration of this determination, and encourage you to draw on the expertise and resources of the National Multiple Sclerosis Society in your review of this information and relevant data. Feel free to contact me at _____.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹The IFNB Multiple Sclerosis Study Group, Interferon beta-1b is effective in relapsing-remitting multiple sclerosis I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 655–661.

²European Study Group, Placebo-controlled multicentre randomized trial of interferon beta-1a in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; 352(9139): 1491–97.

MODEL APPEAL LETTER—COPAXONE

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is to support an appeal of your denial of Copaxone (glatiramer acetate) for my patient _____ (*name*) _____. I have reviewed your letter and continue to recommend Copaxone as the treatment of choice in this case based on my experience treating people with relapsing-remitting multiple sclerosis.

My records indicate that Mr./Ms. _____ sought my assistance with symptoms including _____ (*provide details from chart*) _____, and has been definitively diagnosed with relapsing MS.

Copaxone is the preferred therapy for this patient because I believe it offers the greatest likelihood for benefit as first line therapy for this patient (*provide reason(s) here*) OR because he/she experienced intolerable side effects on interferon therapy (*describe*).

Copaxone received FDA approval for marketing in 1996 for the treatment of patients with relapsing-remitting forms of multiple sclerosis. Glatiramer acetate is not interferon therapy. The agency's approval was based on review of data from a phase III multicenter, double-blind placebo-controlled trial by the Copolymer 1 Multiple Sclerosis Study Group. A reduction in relapse rate and neurologic improvement were demonstrated again in a later study of Copaxone concluded in 1998.

Finally, I include for your information the National Multiple Sclerosis Society's Disease Management Consensus Statement. The Society's Medical Advisory Board asserts "all of 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". I have reviewed my original recommendation for Copaxone and continue to believe it offers the greatest likelihood of benefit in this case.

I look forward to your response as soon as possible.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹The Copolymer 1 Multiple Sclerosis Study Group, Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology* 1995; 45(7): 1268–1276

²Johnson KP, Brooks BR, Cohen JA et al., Extended use of glatiramer acetate is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. *Neurology* 1998; 50: 701–708.

MODEL APPEAL LETTER—REBIF

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

I am writing in response to your denial of Rebif, an interferon beta-1a approved by the FDA for relapsing forms of multiple sclerosis. This is a request for re-consideration of this decision based on the medical necessity and appropriateness of Rebif for this patient ____(*name*)____, and consistency with the Disease Management Consensus Statement of the National Multiple Sclerosis Society (enclosed).

The pivotal study demonstrating the efficacy of Rebif is the PRISMS trial, and is the largest placebo controlled clinical study of interferon beta in relapsing remitting multiple sclerosis to date. In this trial comparing treatment to placebo over two years, Rebif 44 mcg taken subcutaneously three times per week significantly reduced the number of exacerbations, increased the time to the first exacerbation during the study and increased the time between exacerbations. Rebif also demonstrated a significant delay in the time to confirmed progression of disability, and reduction of lesion activity and T2 lesions area as measured by MRI scans.^{1,2}

I believe Rebif is the best therapeutic option for Mr./Ms. ____(*name*)____ at this time because (*suggestions include*):

- *High dose, frequently administered interferon is necessary due to the frequency of relapses and/or severity of symptoms; AND/OR*
- *Non-interferon therapy was not successful*

I may be reached at the number above should you require additional information on this patient. Otherwise, I look forward to your response directly to me as soon as possible.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹PRISMS Study Group "Randomized double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; 352: 1498–1504.

²PRISMS Study Group and University of British Columbia MS MRI Analysis Group, "PRISMS-4: Long-term efficacy of interferon-beta 1a in relapsing MS." *Neurology* 2001; 56: 1628–1636.

**MODEL APPEAL LETTER—REBIF AFTER FIRST DEMYELINATING EVENT
(CLINICALLY ISOLATED SYNDROME)**

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is a request for (*review of your denial of coverage, prior authorization*) for Rebif for my patient ____ (*name*) _____. I prescribed Rebif for this patient after (*he/she*) experienced an episode of (*optic neuritis, or numbness on one side, other*) as documented in (*his/her*) medical record (*describe with detail*).

An isolated neurological event of this type, known as Clinically Isolated Syndrome (CIS), is indicative of a demyelinating process and is often a precursor to multiple sclerosis. The goal of treatment with Rebif is the delay of a second event and diagnosis of clinically definite multiple sclerosis, as well as permanent disability.

The efficacy of treatment with interferon beta-1a following an initial demyelinating event was the focus of the so-called CHAMPS Study (Controlled High-Risk Subjects Avonex MS Prevention Study).¹ During three years of follow-up, the cumulative probability of the development of clinically definite multiple sclerosis was significantly lower in the interferon beta-1a group than in the placebo group. Likewise, a separate trial by the Early Treatment of Multiple Sclerosis (ETOMS) Group showed that interferon beta-1a is effective in reducing conversion to clinically definite multiple sclerosis and in slowing progressive loss of brain tissue in patients with clinically isolated syndromes.²

Additionally, I have enclosed for your information the treatment recommendations of the National Multiple Sclerosis Society, 'Disease Management Consensus Statement'. This consensus statement by national leaders in the diagnosis and management of multiple sclerosis supports the use of immunomodulating therapy for select patients with a first attack who are at high risk of MS.

I urge your approval of this treatment as soon as possible.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

¹Jacobs LS, Beck, RW, Simon JH and the CHAMPS Study Group, *NEJM*; 343(13): 898–904; September 28, 2000

²Fillippi M, Rovaris M, Inglese M and the ETOMS Study Group, *Lancet* 2004; 364: 1489–96.

MODEL APPEAL LETTER—NOVANTRONE

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is a request for (*authorization, re-authorization, or reconsideration of your prior denial of coverage*) of Novantrone (mitoxantrone) for my patient ____ (*name*) _____. This patient suffers from (*select from below*):

- *secondary progressive multiple sclerosis, (disease that has changed from relapsing-remitting to progressive at a variable rate);*
- *progressive-relapsing multiple sclerosis (disease characterized by gradual increase in disability from onset with clear, acute relapses along the way;*
- *worsening relapsing-remitting multiple sclerosis (resulting in a step-wise worsening of disability)*

and has been under my care since ____ (*date*) ____.

As a clinician experienced in treating patients with various forms of multiple sclerosis, I believe it timely and medically necessary for Ms./Mr. _____ to begin treatment with Novantrone as soon as possible. A review of *his/her* chart clearly indicates a worsening of

(*include specifics, noting symptoms and consequences*). Knowing this patient's history as I do, I believe *him/her* to be an excellent candidate for this therapy. I will assure that an evaluation of cardiac output is done prior to the first infusion, and that blood counts and liver function tests are done prior to each dose.

The largest clinical trial of Novantrone in persons with multiple sclerosis was conducted by Hartung and associates at the Heinrich Heine University, Dusseldorf, Germany (*Lancet*, 360: 2018–25). Novantrone received FDA approval in October 2000 following review of this and a previous trial demonstrated its ability to slow progression of neurologic disability in secondary-progressive and relapsing-remitting forms of multiple sclerosis (Edan G., Miller D et. al., *J Neurol Nuerosurg Psychiatry*, 62(2) 112–118).

I include for your information the National Multiple Sclerosis Society's Disease Management Consensus Statement which states "all of 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".

I may be reached at the number above should you require additional information on this patient. Otherwise, I look forward to your positive response.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Disease Management Consensus Statement*

MODEL APPEAL LETTER—INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is an appeal for re-consideration of your denial of IntraVenous ImmunoGlobulin (IVIG) for my patient ____ (*name*)____, who suffers from relapsing-remitting multiple sclerosis.

Although IVIG is not presently considered a first-line therapy for MS, a review of this patient's medical record provides strong rationale for IVIg therapy for the following reasons. (*Provide detailed rationale based on the following*)

- detailed history and outcome of other therapy(ies) previously prescribed;
- patient's inability to tolerate standard, first-line therapies;
- history of earlier benefit from IVIG in this patient (if applicable);
- your professional opinion of deterioration you think may occur if patient is not treated with IVIG;

Describe positive outcomes of IVIG in other patients (without names or other identifying information) in your practice or clinic.)

Data supporting IVIG as an alternative treatment option for relapsing-remitting MS can be found in the following:

1. The Austrian Immunoglobulin in Multiple Sclerosis (AIMS) Study (Strasser-Fuchs S, Fazekas F, Deisenhammer F, Nahler G, Mamoli B., *Mult Scler* 2000; 6:Suppl 2:S9–13.
2. IntraVenous ImmunoGlobulin Reduces MRI Activity In Relapsing Multiple Sclerosis, Sorensen PS, Wanscher B, Jensen CV, Schreiber K, Blinkenberg M, Ravnborg M, Kirsmeier H, Larsen VA, Lee ML, *Neurology* 1998 May; 50(5):1273–81, Copenhagen University Hospital, Department of Neurology, Rigshospitalet, Denmark.

I am anxious to initiate this therapy as soon as possible to avoid further disability and risk of exacerbation. Please contact me as soon as possible to discuss this recommendation. I may be reached at ____ (*phone number*)____.

Sincerely,

John Smith, MD

MODEL APPEAL LETTER—NEURONTIN

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is a request for re-consideration of your (*denial of coverage or pre-authorization*) for Neurontin (gabapentin) for ____ (*name of patient*) _____. I prescribed Neurontin for the management of pain caused by lesions and spasticity, both of which are well-documented symptoms of *her/his* multiple sclerosis. Pain in MS occurs both as a consequence of the disease and as a consequence of the disability that it produces.

A review of my patient's chart illustrates complaints of (*trigeminal neuralgia, episodic facial pain, painful Lhermitte's, paroxysmal limb pain, tonic seizures, dysesthetic pain, other*). I have treated numerous MS patients with comparable pain syndromes with Neurontin successfully, and believe it will improve *her/his* (*examples: pain level, mobility, disability, quality of life, sleep, other—explain*).

For your information, Cutter and colleagues at the Denver VA Medical Center conducted a prospective, double-masked, placebo-controlled study of gabapentin in MS patients with spasticity. Their results were a statistically significant reduction in the impairment of spasticity found in the gabapentin-treated subjects compared with placebo as measured by the self-report scales of the Spasm Severity Scale, Interference With Function Scale, Painful Spasm Scale, and Global Assessment Scale and by the Physician-Administered Scales of the Modified Ashworth and plantar stimulation response (Cutter NC, Scott DD, Johnson JC, Whiteneck G., *Arch Phys Med Rehabil* 2000; 81(2): 164–169).

In an earlier study, gabapentin demonstrated efficacy in relieving MS-related pain in an open label study by Houtchens et. al. (Houtchens MK, Richert JR, Sami A, Rose JW. *Multiple Sclerosis* 1997; 3: 250–253).

Finally, I enclose for your further information a *Clinical Bulletin* from the National Multiple Sclerosis Society describing pain and pain management for the MS patient. We look forward to your positive response to this appeal.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Clinical Bulletin: Pain in Multiple Sclerosis*

MODEL APPEAL LETTER—REHABILITATION/PHYSICAL THERAPY

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is a request for (*prior authorization, continuation of benefits, appeal of your denial*) for physical rehabilitation for my patient ____ (*name*) ____, who lives with multiple sclerosis. I prescribed a medically necessary program of (*inpatient or outpatient*) physical rehabilitation to enable *her/him* to achieve and maintain optimal functioning.

A thorough physical therapy evaluation and development of a treatment plan by an appropriately skilled therapist is needed at this time (*fill in specific details of short and long-term treatment goals, e.g., to regain as much functioning as possible following an exacerbation, for symptom management, to develop risk reduction strategies in the home, other—site functional limitations, ADLs/IADLs, etc.*).

The National Multiple Sclerosis Society defines rehabilitation as “a process that helps a person achieve and maintain maximal physical, psychological, social and vocational potential, and quality of life consistent with physiological impairment, environment, and life goals”. Further, the Society’s clinical guidelines assert that rehabilitation is an essential part of the management of MS, including the reduction of risk (see enclosed). The goal is to establish corrective exercises and activity programs that are appropriate, realistic, and meaningful, with a strong focus on improving and maintaining function.

The effectiveness of physical therapy in the MS population has been demonstrated. Di Fabio and colleagues reported “an extended outpatient rehabilitation program for persons with definite progressive MS appears to effectively reduce fatigue and the severity of other symptoms associated with MS” (*Arch Phys Med Rehabil* Feb 1989; 79). Another study concluded “assessment of different aspects of motor impairment and the accurate determination of factors contributing to falls are necessary for individual patient management and therapy and for the development of a prevention program for falls” (Cattaneo, DeNuzzo, et. al., Risk of Falls in Subjects with Multiple Sclerosis. *Arch Phys Med Rehabil* June 2002; 83).

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Expert Opinion Paper: Recommendations for Persons with Multiple Sclerosis*

MODEL APPEAL LETTER—PROVIGIL

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

This is an appeal for re-consideration of your denial of coverage of modafinil (Provigil) for my patient ____ (*name*) ____, who has a diagnosis of relapsing-remitting multiple sclerosis. I write as both *Mr./Ms. _____'s (neurologist/primary care physician/other)* and as a specialist in the management of multiple sclerosis.

Fatigue is recognized by the National Multiple Sclerosis Society (NMSS) as the most common symptom of the disease, and is known to affect over three-fourths of all those living with MS. The diagnosis and management of MS-related fatigue is described in the Society's Clinical Bulletin "Management of Fatigue in Multiple Sclerosis", which is enclosed for your information. In a 2002 study to assess the efficacy and safety of modafinil for the treatment of fatigue in MS, Rammohan and colleagues found that 200 mg/day of modafinil significantly reduced fatigue and was well tolerated.¹

A review of Ms. _____'s record illustrates reports of fatigue dating to ____ (*date*) _____. *His/Her* quality of life has declined as demonstrated by (*provide details such as impact on ADLs, performance scales, etc.*). I believe treatment with Provigil is medically necessary and appropriate, and urge you to provide coverage of it as an off-label indication for *his/her* MS-related fatigue.

(If request is for Provigil as first line therapy, explain why, OR provide details of prior attempt(s) to treat patient's fatigue, including non-pharmacological management. Lack of improvement in his/her fatigue may result in preventable disability, inability to live independently or maintain employment, depression, immobility, muscle weakness, etc.)

I hope this information is helpful to you and others, and encourage you to contact me at ____ (*phone or e-mail*) ____ if I may be of further assistance.

Sincerely,

John Smith, MD

Encl.

¹*Journal of Neurology, Neurosurgery, and Psychiatry* 2002; 72: 179–183.

MODEL APPEAL LETTER—STERILE INTERMITTENT CATHETERIZATION

Today's date

Plan Name

Plan Address

Plan Address

Re: Client's name, Insurance ID #, (and claim # if applicable)

To Whom It May Concern:

My patient ____ (*name*) ____ suffers from bladder dysfunction related to (*his/her*) multiple sclerosis, resulting in acute urinary retention. A medically necessary intervention of intermittent catheterization is required to avoid further complications, including antibiotic resistant urinary tract infection. This is a request for coverage (*or an appeal of your denial for coverage*) for supplies necessary for (*him/her*) to maintain a prescribed regimen of intermittent catheterization.

Specifically, the supplies requested are:

Example: #14 French, male or female, with coude tip urinary catheters and lubrication (*insert amount required per day or month*).

The National Multiple Sclerosis Society recommends intermittent catheterization in their Algorithm for Analysis and Management of Bladder Symptoms described in the enclosed.

If this individual does not follow *his/her* schedule of catheterizations, (*he/she*) will be at risk of chronic bladder and kidney infections requiring medical intervention. Without these scheduled catheterizations, this patient also risks far greater social isolation, worsening disability and deterioration in (*his/her*) quality of life.

Feel free to contact me at _____ for further information.

Sincerely,

John Smith, MD

Encl.: National Multiple Sclerosis Society *Clinical Bulletin: Bladder Dysfunction in Multiple Sclerosis*



Abstracts of Studies Cited in Letters

Subject: AVONEX (INTERFERON BETA-1A)

Citation: *Annals of Neurology* 1996; 49: 285–294

Title: Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis

Authors: RA Rudick, DW Goodkin, LS Jacobs, et al.

Background and Objective: A phase III double-blind, placebo-controlled clinical trial demonstrated that interferon beta-1a (IFN beta-1a) (Avonex, Biogen) significantly delayed progression of disability in relapsing MS patients. The primary clinical outcome was time from study entry until disability progression, defined as ≥ 1.0 point worsening from baseline Kurtzke Expanded Disability Status Scale (EDSS) score persisting for at least two consecutive scheduled visits separated by 6 months. The objective of this study was to examine the magnitude of benefit on EDSS and its clinical significance.

Methods: Post hoc analyses related to disability outcomes using data collected during the double-blind, placebo-controlled phase III clinical trial.

Results: (1) Clinical efficacy related to disability did not depend on the definition of disability progression. A significant benefit in favor of IFN beta-1a was observed when ≥ 2.0 point worsening from baseline EDSS was required or when worsening was required to persist ≥ 1.0 year. (2) Placebo recipients who reached the primary clinical outcome worsened by a larger amount from baseline EDSS than did IFN beta-1a recipients who reached the primary study outcome. (3) Significantly fewer IFN beta-1a recipients progressed to ED milestones of 4.0 (relatively severe impairment) or 6.0 (unilateral assistance needed to walk.) (4) Cox proportional hazards models demonstrated that the only baseline characteristic strongly correlated with longer time to disability progression was IFN beta-1a treatment.

Conclusions: The primary clinical outcome for the IFN beta-1a clinical trial underestimated clinical benefits of treatment. Results in this report demonstrate that IFN beta-1a treatment is associated with robust, clinically important beneficial effects on disability progression in relapsing MS patients.

Subject: AVONEX (INTERFERON BETA-1A)

Citation: *Neurology* 2002; 59: 1412–1420

Title: Eight-year follow-up study of brain atrophy in patients with MS

Authors: E Fisher, RA Rudick, JH Simon, G Cutter, M Baier, JC Lee, D Miller, B Weinstock-Guttman, MK Mass, DS Dougherty, NA Simonian

Objective: To characterize whole-brain atrophy in relapsing-remitting MS (RRMS) patients over an 8-year period. The specific goals of this study were to determine if brain atrophy is related to subsequent disability status and to identify MRI correlates of atrophy progression.

Methods: A follow-up study was conducted to reassess patients from a phase III trial of interferon β -1a (IFN β -1a) 8 years after randomization. Clinical and MRI data from 172 patients followed over 2 years in the original trial were used as baseline data. Follow-up data were obtained on 160 patients, including 134 patients with follow-up MRI examinations. Brain atrophy was estimated by automated calculation of brain parenchymal. The relation between atrophy during the original trial and disability status at follow-up was determined. Correlations were also determined between lesion measurements from the original trial and the brain parenchymal fraction at follow-up.

Results: Brain atrophy was correlated with subsequent disability status. Atrophy rate during the original trial was the most significant MRI predictor of disability status at follow-up. Brain atrophy at follow-up was related to lesion volumes measured during the original trial.

Conclusions: The relation between atrophy progression and subsequent neurologic disability status suggests that atrophy progression during RRMS is clinically relevant. Therefore, atrophy progression may be a useful marker for disease progression in clinical trials. The relation between lesions and subsequent atrophy indicates that brain atrophy may be related to focal tissue damage at earlier points in time, but important predisposing or other factors contributing to atrophy remain undefined.

Subject: INTERFERON THERAPY AFTER FIRST DEMYELINATING EVENT, (CLINICALLY ISOLATED SYNDROME)

Citation: *New England Journal of Medicine* 2000; 343(13): 898–490

Title: Intramuscular Interferon Beta-1a Therapy Initiated During a First Demyelinating Event in Multiple Sclerosis

Authors: LD Jacobs, RW Beck, JH Simon and The CHAMPS Study Group

Background: Treatment with interferon beta has been shown to help patients with established multiple sclerosis, but it is not known whether initiating treatment at the time of a first clinical demyelinating event is of value.

Methods: We conducted a randomized, double-blind trial of 383 patients who had a first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or a brain-stem or cerebellar syndrome) and evidence of prior subclinical demyelination of magnetic resonance imaging (MRI) of the brain. After initial treatment with corticosteroids, 193 patients were randomly assigned to receive weekly intramuscular injections of 30 micrograms of interferon beta-1a and 190 were assigned to receive weekly injections of placebo. The study end points were the development of clinically definite multiple sclerosis and changes in findings on MRI of the brain. The trial was stopped after a preplanned interim efficacy analysis.

Results: During three years of follow-up, the cumulative probability of the development of clinically definite multiple sclerosis was significantly lower in the interferon beta-1a group than in the placebo group (rate ratio, 0.56; 95 percent confidence interval, 0.38 to 0.81; $P=0.002$). As compared with the patients in the placebo group, patients in the interferon beta-1a group had a relative reduction in the volume of brain lesions ($P<0.001$), fewer new or enlarging lesions ($P<0.001$), fewer new or enlarging lesions ($P<0.001$), and fewer gadolinium-enhancing lesions ($P<0.001$) at 18 months.

Conclusions: Initiating treatment with interferon beta-1a at the time of a first demyelinating event is beneficial for patients with brain lesions on MRI that indicate a high risk of clinically definite multiple sclerosis.

**Subject: AVONEX FOLLOWING FIRST DEMYELINATING EVENT
(CLINICALLY ISOLATED SYNDROME)**

Citation: Program and abstracts of the 56th Annual Meeting of the American Academy of Neurology; April 24–May 1, 2004; San Francisco, California. Abstract S29.006.

Title: Interferon B-1a (Avonex) Delays the Onset of Clinically Definite MS over 5 Years of Treatment: Results from CHAMPIONS Study

Authors: RP Kinkel, C Kollman, A Glassman, J Simon, P O'Connor, TJ Murray and the CHAMPIONS Study Group

Objective: To determine if the benefits of IM interferon beta-1a (IFN β -1a) therapy administered after a first clinical demyelinating event are sustained for up to 5 years.

Background: CHAMPS was a randomized, double-blind, placebo-controlled trial of IFN β -1a 30 micrograms IM once weekly in patients who experienced a first clinical demyelinating event. Results showed that IFN β -1a significantly lowered the rate of development of clinically definite MS (CDMS) and new MRI abnormalities over 2 years compared with placebo. The study was continued as an open-label extension study (CHAMPIONS).

Design/Methods: CHAMPS patients at participating CHAMPIONS sites were enrolled in the study. All patients were offered, but not required to take, IM IFN β -1a for up to 5 years (timed from randomization into CHAMPS). Patients in CHAMPS were considered the Delayed Treatment (DT) group and patients who originally received IFN β -1a in CHAMPS were considered the Immediate Treatment (IT) group. Outcomes included rate of development of CDMS, relapses, measures of disability, and MRI measure.

Results: Seventy percent (203/290) of patients from 32 participating sites were enrolled in CHAMPIONS (n=100, IT group; n=103, DT group). Baseline demographic, clinical, and MRI characteristics were well matched in the two CHAMPIONS treatment groups. In the DT group, the median time to initiation of IM IFN β -1a treatment was 29.9 months. The rate ratio for the development of CDMS over 5 years was reduced 35% in the IT group compared with the DT group (unadjusted rate ratio=0.65; 95% CI, 0.43 to 0.97; p=0.03). These results remain significant after adjusting for baseline variables independently associated with outcome (adjusted rate ratio=0.57; 95% CI, 0.38–0.86; p=0.008). Overall, 36% of the IT group and 48% of the DT group developed CDMS by 5 years. Mean number of relapses over 5 years (\pm SD) was 0.9 (\pm 1.3) in the IT group compared with 1.7 (\pm 2.7) in the DT group (p=0.008), representing a 47% reduction in the IT group. In both groups combined 13% of patients had an EDSS of \geq 3.0 at their 5-year visit (IT group 11%), DT group 14%). The median number of new enlarging T2 lesions at 5 years was significantly lower in the IT group than in the DT group (3.5 vs. 6.0, p=.05).

Conclusions: Initiation therapy initiated a median of 2.5 years later. These results support the recommendation to initiate disease-modifying therapy in high-risk patients at the time of a first demyelinating event significantly slowed the rate of conversion to CDMS over 5 years compared with patients at the time of a first demyelinating event for long term benefits.

Subject: BETASERON (INTERFERON BETA-1B)**Citation:** *Neurology* 1993; 43: 655–661**Title:** Interferon beta-1b is effective in relapsing-remitting multiple sclerosis**Author:** The IFNB Multiple Sclerosis Group

Abstract: We report a multicenter, randomized, double-blind, placebo-controlled trial of interferon beta-1b (IFNB) in 372 ambulatory patients with relapsing-remitting multiple sclerosis (MS). Entry criteria included an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and at least two exacerbations in the previous 2 years. One-third of the patients received placebo, one-third 1.6 million international units (MIU) of IFNB, and one-third 8 MIU of IFNB, self-administered by subcutaneous injections every other day. The primary endpoints were differences in exacerbation rates and proportion of patients remaining exacerbation-free. The annual exacerbation rate for patients receiving placebo was 1.27; for 1.6 MIU IFNB, 1.17; and for 8 MIU IFNB, 0.84 after 2 years. Exacerbation rates were significantly lower in both treatment groups compared with the placebo group (8 MIU versus placebo, $p=0.0001$; 1.6 MIU versus placebo, $p=0.0101$; and 8 MIU versus 1.6, $p=0.0086$), suggesting a dosage effect. The reduction in exacerbation severity in the 8 MIU group was attributable to a twofold reduction in the frequency of moderate and severe attacks. More patients in the 8 MIU group ($n=36$) were exacerbation-free at 2 years compared with the placebo group ($n=18$; $p=0.07$). EDSS scores changed little from baseline in both the placebo and treatment arms. Accordingly, a significant change in disability could not be discerned in this trial. Finally, in serial MRIs, MS activity was significantly less in the high-dose IFNB group. IFNB treatment was well tolerated: the significant reductions in exacerbation rates, severity of exacerbations; and accumulation of MRI abnormalities occurred in the absence of serious side effects. IFNB is the only treatment that has substantially altered the natural history of MS in a properly controlled clinical trial.

Subject: BETASERON

Citation: *Lancet* 1998 352(9139): 1491–1497

Title: Placebo-controlled multicentre randomized trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis

Authors: The European Study Group on interferon beta-1b in secondary progressive MS

Background: The beneficial effects of interferon beta have only been shown for patients in the relapsing-remitting phase of multiple sclerosis (MS). The role of interferon beta in the treatment of patients who are in the secondary progressive phase of the disease (SP-MS), and for whom no effective drug treatment is available, has not been assessed.

Methods: In this multicentre, double-masked, randomised, placebo-controlled trial, outpatients with SP-MS having scores of 3.0–6.5 on the Expanded Disability Status Scale (EDSS) received either 8 million IU interferon beta-1b every other day subcutaneously, or placebo, for up to 3 years. The primary outcome was the time to confirmed progression in disability as measured by a 1.0 point increase on the EDSS, sustained for at least 3 months, or a 0.5 point increase if the baseline EDSS was 6.0 or 6.5. A prospectively planned interim analysis of safety and efficacy of the intention-to-treat population was done after all patients had been in the study for at least 2 years.

Findings: 358 patients with SP-MS were allocated placebo and 360 were allocated interferon beta-1b; 57 patients (31 placebo, 26 interferon beta-1b) were lost to follow-up. There was a highly significant difference in time to confirmed progression of disability in favour of interferon beta-1b ($p=0.0008$). Interferon beta-1b delayed progression for 9–12 months in a study period of 2–3 years. The odds ratio for confirmed progression was 0.65 (95% CI 0.52–0.83). This beneficial effect was seen in patients with superimposed relapses and in patients who had only progressive deterioration without relapses. Positive results were also obtained regarding time to becoming wheelchair-bound, relapse rate and severity, number of steroid treatments and hospital admissions, as well as on magnetic resonance imaging variables. The drug was safe and side effects were in line with previous experience with interferon beta-1b. The study was stopped after the interim results gave clear evidence of efficacy.

Interpretation: Treatment with interferon beta-1b delays sustained neurological deterioration in patients with SP-MS. Interferon beta-1b is the first treatment to show a therapeutic effect in patients with SP-MS.

Subject: COPAXONE (COPOLYMER 1)

Citation: *Neurology* 1995 Jul; 45(7): 1268–1276

Title: Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind placebo-controlled trial

Authors: The Copolymer 1 Multiple Sclerosis Study Group: KP Johnson, BR Brooks, JA Cohen, CC Ford, J Goldstein, RP Lisak, LW Myers, HS Panitch, JW Rose, RB Schiffer

Abstract: We studied copolymer 1 (Copaxone) in a multicenter (11-university) phase III trial of patients with relapsing-remitting multiple sclerosis (MS). Two hundred fifty-one patients were randomized to receive copolymer 1 (n=125) or placebo (n=126) at a dosage of 20 mg by daily subcutaneous injection for 2 years. The primary end point was a difference in the MS relapse rate. The final 2-year relapse rate was 1.19 ± 0.13 for patients receiving copolymer 1 and 1.68 ± 0.13 for those receiving placebo, a 29% reduction in favor of copolymer 1 ($p=0.007$) (annualized rates = 0.59 for copolymer 1 and 0.84 for placebo). Trends in the proportion of relapse-free patients and median time to first relapse favored copolymer 1. Disability was measured by the Expanded Disability Status Scale (EDSS), using a two-neurologist (examining and treating) protocol. When the proportion of patients who improved, were unchanged, or worsened by ≥ 1 EDSS step from baseline to conclusion (2 years) was evaluated, significantly more patients receiving copolymer 1 were found to have improved and more receiving placebo worsened ($p=0.037$). Patient withdrawals were 19 (15.2%) from the copolymer 1 group and 17 (13.5%) from the placebo group at approximately the same intervals. The treatment was well tolerated. The most common adverse experience was an injection-site reaction. Rarely, a transient self-limited systemic reaction followed the injection in 15.2% of those receiving copolymer 1 and 3.2% of those receiving placebo. (ABSTRACT TRUNCATED AT 250 WORDS, PubMed)

Subject: GLATIRAMER ACETATE (COPAXONE)**Citation:** *Neurology* 1998; 50: 701–708**Title:** Extended use of glatiramer acetate is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability**Authors:** KP Johnson, BR Brooks, JA Cohen, et al.**Abstract:** When 21 relapsing-remitting patients with multiple sclerosis were randomized to receive daily subcutaneous injections of glatiramer acetate, previously called copolymer 1 (Copaxone; n=125) or placebo (n=126) for 24 months, there were no laboratory abnormalities associated with glatiramer acetate treatment and it was well tolerated with few side effects. Patients receiving glatiramer acetate had significantly fewer relapses and were more likely to be neurologically improved, whereas those receiving placebo were more likely to worsen. This study was extended for 1 to 11 months (mean of 5.2 months for the glatiramer acetate group and 5.9 months for the placebo group). The blinding and study conditions used during the core 24-month study were unchanged throughout the extension. The results of this extension study confirm the excellent tolerance and safety profile of glatiramer acetate for injection. The clinical benefit of glatiramer acetate for both the relapse rate and for neurologic disability was sustained at the end of the extension trial.

Subject: REBIF (INTERFERON BETA-1A)

Citation: *Lancet* 1998; 352: 1498–1504

Title: Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis

Authors: PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group

Background: Previous trials of interferon beta in multiple sclerosis (MS) have shown efficacy, but the degree of clinical benefit remains uncertain, and the optimum dose is not known. We undertook a double-blind, placebo-controlled study in relapsing/remitting MS to investigate the effects of subcutaneous interferon beta-1a.

Methods: 560 patients with Kurtzke expanded disability status scale (EDSS) scores of 0–5.0, from 22 centres in nine countries, were randomly assigned subcutaneous recombinant interferon beta-1a 22 micrograms (n=189) or 44 micrograms (n=184), or placebo (n=187) three times a week for 2 years. Neurological examinations were done every 3 months. All patients had MRI twice yearly and 205 had monthly scans in the first 9 months of treatment. Analysis was by intention to treat.

Findings: Clinical data on 533 (95%) patients were available at 2 years. The relapse rate was significantly lower at 1 and 2 years with both doses of interferon beta-1a than with placebo (mean number per patient 1–82 for 22 micrograms group, 1–73 for 44 micrograms group vs. 2–56 for placebo group: risk reductions 27% (95% CI 14–39) and 33 (21–44)). Time to first relapse was prolonged by 3 and 5 months in the 22 micrograms and 44 micrograms groups respectively, and the proportion of relapse-free patients was significantly increased ($p < 0.05$). Interferon beta-1a delayed progression in disability, and decreased accumulated disability during the study. The accumulation of burden of disease and number of active lesions on MRI was lower in both treatment groups than in the placebo group.

Interpretation: Subcutaneous interferon beta-1a is an effective treatment for relapsing/remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures in a dose-related manner, and it is well tolerated. Longer-term benefits may become clearer with further follow-up and investigation.

Subject: INTERFERON BETA-1A (REBIF)

Citation: *Neurology* 2001; 56: 1628–1636

Title: PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS

Authors: The PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group and the University of British Columbia MS/MRI Analysis Group

Background: The PRISMS study demonstrated significant clinical and MRI benefit at 2 years for interferon-beta-1a, 22 and 44 mcg thrice weekly (tiw), compared with placebo in relapsing-remitting MS. Years 3 and 4 extension study results are reported.

Methods: Patients initially receiving placebo were randomized to blinded interferon beta-1a, 22 or 44 mcg tiw (n=172; crossover group); others continued blinded treatment with their originally assigned dose, 22 mcg (Rx22 group) or 44 mcg (Rx44 group) tiw (n=167 per group). Patients had 3 to 6 month clinical and annual MRI assessments.

Results: Relapse rates for 4 years were 1.02 (crossover), 0.80 (Rx22, p<0.001), and 0.72 (Rx44, p<0.001); the dose effect approached significant (p=0.069; risk ratio, 0.88; 95% CI, 0.76–1.01). Crossover groups showed reductions in relapse count, MRI activity, and lesion-burden accumulation with interferon beta-1a compared with their placebo period (p<0.001 both doses). Time to sustained disability progression was prolonged by 18 months in the Rx44 group compared with the crossover group (p=0.047). Rx22 and Rx44 reduced new T2 lesion number and lesion burden compared with crossover (p<0.001); Rx44 was superior to Rx22 on several clinical and MRI outcomes. Persistent neutralizing antibodies developed in 14.3% (Rx44) and 23.7% (Rx22) of patients and were associated with reduced efficacy.

Conclusions: Clinical and MRI benefit continued for both doses up to 4 years, with evidence of dose response. Outcomes were consistently better for patients treated for 4 years than for patients in crossover groups. Efficacy decreased with neutralizing antibody formation.

**Subject: REBIF AFTER FIRST DEMYELINATING EVENT,
(CLINICALLY ISOLATED SYNDROME)**

Citation: *Lancet* 2004; 364: 1489–1496

Title: Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial

Authors: M Filippi, M Rovaris, M Inglese et. al., and The ETOMS Study Group

Background: In patients who present with clinically isolated syndromes suggestive of multiple sclerosis, interferon beta -1a is effective in delaying evolution to clinically definite disease and in reducing MRI-measured disease activity. We aimed to assess whether this drug can also reduce the rate of brain volume decrease in such patients enrolled in the ETOMS (early treatment of multiple sclerosis) trial.

Methods: MRI data for brain volume measurements at baseline, month 12, and month 24 were available from 131, 111 and 112 patients assigned treatment (22 micrograms interferon beta-1a), and 132, 98, and 99 patients assigned placebo respectively. Normalised brain parenchymal volume (NBV) at baseline and percentage brain volume changes (PBVC) were measured with a fully-automated segmentation technique. The primary endpoint was conversion to clinically definite multiple sclerosis due to clinical relapse. Analysis was by intention to treat.

Findings: 141 (31%) of 131 patients on interferon beta-1a and 62 (47%) of 132 on placebo converted to clinically definite multiple sclerosis (odds ratio 0.52 (95% CI 0.31–0.86), $p=0.0115$). Mean PBVC for patients on placebo was -0.83% during the first year, -0.67% during the second year, and -1.18%. The changes in brain volume were significant in both groups at all timepoints. A significant treatment effect was detected for month 24 versus baseline values ($p=0.031$). The number of new T2 lesions formed during the first year correlated weakly with PBVC during the second year.

Interpretation: Early treatment with interferon beta-1a is effective in reducing conversion to clinically definite multiple sclerosis and in slowing progressive loss of brain tissue in patients with clinically isolated syndromes. The modest correlation between new lesion formation and brain volume decrease suggests that inflammatory and neurodegenerative processes are, at least partly, dissociated from the earliest clinical stage of multiple sclerosis onwards.

Subject: MITOXANTRONE (NOVANTRONE)

Citation: *Lancet* 2002; 360(9350): 2018–2025

Title: Mitoxantrone in progressive multiple sclerosis: A placebo-controlled, double-blind, randomized, multicentre trial

Authors: HP Hartung, R Gonsette, N Konig, et al.

Background: Treatment options for patients with secondary progressive multiple sclerosis are few. Encouraging results in open-label studies prompted this randomized trial of mitoxantrone in such patients.

Methods: 194 patients with worsening relapsing-remitting or secondary progressive multiple sclerosis were assigned placebo or mitoxantrone (5 mg/m squared) (exploratory group) or placebo (12 mg/m squared intravenously) every 3 months for 24 months. Clinical assessments were made every 3 months for 24 months. The primary endpoint was a multivariate analysis of five clinical measures. Analyses of mitoxantrone 12 mg/m squared versus placebo were based on patients who received at least one dose and returned for at least one assessment of efficacy.

Findings: Of 194 patients enrolled, 188 were able to be assessed at 24 months. There were no drug-related serious adverse events or evidence of clinically significant cardiac dysfunction. At 24 months, the mitoxantrone group experienced benefits compared with the placebo group for the primary outcome (difference 0–30 (95% CI 0.17–0.44); $p < 0.0001$) and the preplanned univariate analyses of those measures: change in expanded disability status scale (0–24 (0.04–0.44); $p = 0.0194$), change in ambulation index (0.21 (0.02–0.40); $p = 0.0306$), adjusted total number of treated relapses (0.38 (0.18–0.59); $p = 0.0002$), time to first treated relapse (0.38 (0.18–0.59); $p = 0.004$), and change in standardized neurological status (0.23 (0.03–0.43); $p = 0.0268$).

Subject: MITOXANTRONE (NOVANTRONE)

Citation: *Journal of Neurology, Neurosurgery, and Psychiatry* 1997; 62: 112–118

Title: A randomized multicentre study of active disease using MRI and clinical criteria

Authors: G Edan, D Miller, M Clanet, et al.

Objective: To evaluate the efficiency of mitoxantrone in multiple sclerosis.

Methods: Forty two patients with confirmed multiple sclerosis, selected as having a very active disease on clinical and MRI criteria were randomized to receive either mitoxantrone (20 mg intravenously (IV) monthly) and methylprednisolone (1 g IV monthly) or methylprednisolone alone over six months. In the steroid alone group five patients dropped out due to severe exacerbation.

Results: Blinded analysis of MRI data showed significantly more patients with no new enhancing lesions in the mitoxantrone group compared with the steroid alone group (90% vs. 31%; $p < 0.001$). In the mitoxantrone group there was a month by month decrease almost to zero in the number of new enhancing lesions, and in the total number of enhancing lesions, whereas both remained high in the steroid alone group. The differences were significant for both indices at all months from 1–6. Unblinded clinical assessments showed a significant improvement in change in EDSS at months 2–6 in the mitoxantrone group, with a final mean improvement of more than one point (-1.1 vs. $+0.3$; $p < 0.001$). There was a significant reduction in the number of relapses (7 vs. 31; $p < 0.01$), and an increase in the number of patients free of exacerbation (14 vs. 7; $p < 0.05$).

Conclusion: In this selected group of patients with multiple sclerosis with very active disease, mitoxantrone combined with methylprednisolone was effective in improving both clinical and MRI indices of disease activity over a period of six months whereas methylprednisolone alone was not. Further double blinded long term studies are needed to properly evaluate the effect of mitoxantrone on progression in disability.

Subject: IMMUNOGLOBULIN (IVIG)

Citation: *Multiple Sclerosis* 2000; 6(Suppl 2): S9–S13

Title: The Austrian Immunoglobulin in MS (AIMS) study: Final analysis

Authors: S Strasser-Fuchs, F Fazekas, F Deisenhammer, G Nahler, B Mamoli

Abstract: From observational studies and positive experience in other autoimmune disorders it has been speculated that intravenous immunoglobulin (IVIG) may be effective for the interval treatment of MS. The Austrian Immunoglobulin in Multiple Sclerosis (AIMS) study was the first to test this assumption in a randomized, double-blind, placebo controlled trial of 148 patients with relapsing remitting MS. IVIG given monthly at a dosage of 0.15–0.2 g/kg bodyweight over 2 years was associated with a significantly more favourable course of disability as measured by the EDSS (–0.23 vs. 0.12; $p=0.008$) and caused a significant reduction of the frequency of relapses (0.52 vs. 1.26; $p=0.011$). Beneficial effects on these outcome measures were already seen within 6 months of treatment and did not appear to depend on the severity of baseline disability. IVIG treatment also had a positive effect on daily and social living according to patient self rating on the Incapacity Status and Environmental Status Scales and was associated with a lower, though not significantly different number of hospital admissions and days spent in hospital. These data support IVIG as an alternative treatment option for relapsing-remitting MS and encourage further studies to clarify the optimal usage of this substance for this indication.

Subject: INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Citation: *Neurology* 1998; 50: 1273–1281

Title: Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis

Authors: PS Sorensen, MD, DMSc; B Wanscher, MD, PhD; CV Jensen, MD; et al.

Abstract: We wanted to assess whether intravenous immunoglobulin G (IVIG) decreases disease activity on MRI in relapsing MS. Previous trials of IVIG in relapsing-remitting MS demonstrated a reduction of acute relapses, but these studies did not include MRI. We treated 26 patients in a randomized, double-blind, crossover study of IVIG 1 g/kg daily or placebo on 2 consecutive days every month during two 6-month treatment periods. The primary endpoint was the number of gadolinium-enhancing lesions on monthly serial MRI. Secondary efficacy variables were the occurrence of exacerbations, clinical neurologic ratings, total MS lesion load on T2-weighted MRI, and multimodal evoked potentials. Eighteen patients completed the entire trial; eight patients did not. Twenty-one patients completed the first treatment period and at least two MRI examinations in the second treatment period and were included in the intention-to-treat analysis. On serial MRI, we observed fewer enhancing lesions per patient per scan during IVIG treatment (median, 0.4; range, 0 to 9.3) than during placebo treatment (median, 1.3; range, 0.2 to 25.27; $p=0.03$). During IVIG treatment, 15 patients were exacerbation free compared with only 7 ($p=0.02$). The total number of exacerbations in the IVIG period was 11 and in the placebo period, 19 (not significant). None of the remaining secondary efficacy measures were significantly different between the two treatment periods. The number of adverse events, in particular eczema, was significantly higher during IVIG therapy than during placebo treatment. These results suggest that IVIG treatment is beneficial to patients with relapsing MS.

Subject: NEURONTIN (GABAPENTIN)

Citation: *Arch Phys Med Rehabil* 2000 Feb; 81(2): 164–169

Title: Gabapentin effect on spasticity in multiple sclerosis: A placebo-controlled, randomized trial

Author(s): NC Cutter, DD Scott, JC Johnson, G Whiteneck

Objective: To investigate the effect of gabapentin on subject self-report and physician-administered spasticity scales in individuals with multiple sclerosis.

Design: Prospective, double-masked, placebo-controlled, crossover design.

Intervention: Subjects were titrated to either 900 mg gabapentin orally three times a day or placebo over a 6-day period. Subjects underwent a 14-day washout and then were crossed over. No other changes were made to their medication regimen.

Main Outcome Measures: The outcome measures were divided into two categories: subject self-report scales and physician-administered scales. Subject self-report scales included the spasm frequency scale, spasm severity scale, interference with function scale, painful spasm scale, and global assessment scale. Physician-administered scales included the Modified Ashworth Scale, clonus scale, deep tendon reflexes, plantar stimulation response, and the Kurtzke Expanded Disability Status (EDSS) Scale. Digit Span and Digit Symbol subtests of the WAIS-R Intelligence Scale were administered to assess for possible impaired concentration. The Fatigue Impact scale was administered to assess for changes in fatigue. The adjective generation technique was administered to assess for alterations in mood.

Results: A statistically significant reduction in the impairment of spasticity was found in the gabapentin-treated subjects compared with placebo as measured by the self-report scales of the spasm severity scale, interference with function scale, painful spasm scale, and global assessment scale and by the physician-administered scales of the Modified Ashworth and plantar stimulation response. No significant difference was noted in the Digit Span, Digit Symbol, adjective generation technique, and EDSS.

Conclusion: Gabapentin reduces the impairment of spasticity, compared with placebo, without the side effects of worsening concentration and fatigue.

Subject: NEURONTIN (GABAPENTIN)**Citation:** *Multiple Sclerosis* 1997; 3: 250–253**Title:** Open label gabapentin treatment for pain in multiple sclerosis**Authors:** MK Houtchens, JR Richert, A Sami, JW Rose

Abstract: Pain is a frequent and distressing complaint in patients with multiple sclerosis (MS) and may present a difficult therapeutic problem. Conventional therapy is moderately effective and includes, among others, a variety of anticonvulsant medications. Gabapentin (Neurontin) is a new generation antiepileptic drug which appears to be advantageous in treatment of intractable pain of reflex sympathetic dystrophy. This study investigates the benefits of open-label treatment with gabapentin for pain control in 25 patients with MS. Excellent to moderate pain relief was obtained in a substantial number of patients. Throbbing pains, pins and needles, and cramping pains responded best, and dull aching pains responded least to the medication. There was no significant change in distribution and type of pain as a result of this treatment. Mild to moderate side effects were observed. Cautious escalation of the dose of gabapentin is advisable in MS patients. Further clinical trials with larger patient groups are recommended.

Subject: PHYSICAL THERAPY

Citation: *Arch Phys Med Rehabilitation* 2002; 83: 854–857

Title: Risks of falls in subjects with multiple sclerosis

Authors: D Cattaneo, PT; C De Nuzzo, PT; T Fascia, PT; M Macalli; I Pisoni, PhD

Objectives: To quantify fall risk among patients with multiple sclerosis (MS) and report the importance of variables associated with falls.

Design: Retrospective case-control study design with a 2-group sample of convenience.

Setting: A hospital and home settings in Italy.

Participants: A convenience sample of 50 people with MS divided into 2 groups according to their reports of falls.

Main Outcome Measure: Subjects were assessed with questionnaires for cognitive ability and were measured on their ability to maintain balance, to walk, and to perform daily life activities. Data regarding patients' strength, spasticity, and transfer skills impairment were also collected.

Results: No statistical differences were found between groups of fallers and nonfallers using variables pertaining to years after onset, age, gender, and Mini-Mental State Examination. Near statistically significant differences were found in activities of daily living and transfer skills ($p < .05$). Three variables were associated with fall status: balance, ability to walk, and use of a cane ($p < .01$). Those variables were analyzed using a logistic regression. The model was able to predict fallers with a sensitivity of 90.9% and a specificity of 58.8%.

Conclusions: Variables pertaining to balance skills, gait impairment, and use of a cane differed between fallers and nonfallers groups and the incidence of those variables can be used as a predictive model to quantify fall risk in patients suffering from MS. These findings emphasize the multifactorial nature of falls in this patient population. Assessment of different aspects of motor impairment and the accurate determination of factors contributing to falls are necessary for individual patient management and therapy and for the development of a prevention program for falls.

Subject: PHYSICAL THERAPY

Citation: *Archives of Physical Medicine and Rehabilitation* 1998 Feb; 79: 141–146

Title: Extended Outpatient Rehabilitation: Its Influence on Symptom Frequency, Fatigue, and Functional Status for Persons With Progressive Multiple Sclerosis

Authors: RP Di Fabio, PhD, PT; J Soderberg, MSW; Thomas Choi, PhD; CR Hansen, PT; RT Schapiro, MD

Objectives: To determine the influence of an extended outpatient rehabilitation program on symptom frequency, fatigue, and functional status for persons with multiple sclerosis (MS).

Design: Nonequivalent pretest/posttest control-group design, with posttest 1 year after initial assessment. Multiple regression analysis of covariance were used to control for symptom severity at the initial assessment and co-morbid factors including depression, cognitive function, and social interaction. Effect sizes (ES) provided a descriptive measure of the change in outcomes.

Setting: Outpatient multidisciplinary rehabilitation clinic.

Participants: Forty-six patients with definite chronic progressive MS; 20 received treatment and 26 were in a non-treatment comparison group ("waiting list").

Intervention: Rehabilitation services for 5 hours, 1 day per week, over 1 year.

Main Outcome Measure: The MS-Related Symptom Checklist composite score, fatigue frequency, and selected items from the Rehabilitation Institute of Chicago Functional Assessment Scale.

Results: Receiving treatment was a significant predictor of reduced symptom frequency (partial r squared = .26) at the 1-year follow-up. The ES adjusted for baseline values indicated substantial reductions in symptom frequency for the treatment (ES treatment = .27 vs. ES waitlist = -.32). Fatigue was significantly reduced at the time of follow-up for the treatment group compared with the waiting list group (ES treatment = .07 vs. ES waitlist = -.70).

Conclusions: An extended outpatient rehabilitation program for persons with definite progressive MS appears to effectively reduce fatigue and the severity of other symptoms associated with MS.

Subject: PROVIGIL (MODAFINIL)**Citation:** *J Neurol Neurosurg Psychiatry* 2002; 72: 179–183**Title:** Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: A two centre phase 2 study**Authors:** KW Rammohan, JH Rosenberg, DJ Lynn, AM Blumenfeld, CP Pollak, HN Nagaraja**Objective:** To assess the efficacy and safety of modafinil for the treatment of fatigue in multiple sclerosis (MS).**Methods:** Patients aged 18–65 years with a diagnosis of MS, a stable disability level ≤ 6 on the Kurtzke extended disability status scale (EDSS), and a mean score >4 on the fatigue severity scale (FSS) were eligible for the 9 week, single blind, phase 2, two centre study. Exclusion criteria included a diagnosis of narcolepsy, sleep apnoea, or clinically significant major systemic disease and recent use of medications affecting fatigue. All patients, who remained blinded for the treatment regimen, received placebo during weeks 1–2, 200 mg/day modafinil during weeks 3–4, 400 mg/day modafinil during weeks 5–6, and placebo during weeks 7–9. Safety was evaluated by unblinded investigators. Efficacy was evaluated by self rating scales, using the FSS, the modified fatigue impact scale (MFIS), a visual analogue scale for fatigue (VAS-F), and the Epworth sleepiness scale (ESS). Adverse events were recorded.**Results:** Seventy two patients (MS type: 74% relapsing-remitting; 7% primary progressive; 19% secondary progressive) received treatment. After treatment with 200 mg/day modafinil for 2 weeks, a significant improvement in fatigue versus placebo run in was demonstrated. Mean scores after treatment with 200 mg/day modafinil were: FSS, 4.7 versus 5.5 for placebo ($p < 0.001$); MFIS, 37.7 versus 44.7 ($p < 0.001$); and VAS-F, 5.4 versus 4.5 ($p = 0.003$). Fatigue scores for 400 mg/day modafinil were not significantly improved versus placebo run in. Mean ESS scores were significantly improved ($p < 0.001$) with 200 mg/day modafinil (7.2) and 400 mg/day (7.0) versus the score at baseline (9.5). Serious adverse events were not found at either dose. The most common adverse events were headache, nausea, and aesthenia. Sixty five patients (90%) completed the study.**Conclusions:** These data suggest that 200 mg/day modafinil significantly improves fatigue and is well tolerated in patients with MS.



National MS Society *Expert Opinion Papers* and *Clinical Bulletins* Cited in Letters

This section includes copies of the National MS Society's *Expert Opinion Papers* and *Clinical Bulletins* that are specifically cited in the template appeal letters. Please refer to the Additional Resources section for other National MS Society publications, or to www.nationalmssociety.org.

Including a copy of the relevant National MS Society *Expert Opinion Paper* or *Clinical Bulletin* in an appeal letter to a health plan is recommended to strengthen your clinical recommendation and appeal.

Expert Opinion Papers are treatment recommendations from our Medical Advisory Board.

- Disease Management Consensus Statement
- Rehabilitation: Recommendations for Persons with Multiple Sclerosis
- Management of MS-Related Fatigue
- Changing Therapy in Relapsing Multiple Sclerosis: Considerations and Recommendations

Clinical Bulletins are discussions of topics of importance in the clinical assessment and management of MS and its symptoms.

- Pain in Multiple Sclerosis
- Spasticity
- Physical Therapy in Multiple Sclerosis Rehabilitation
- Bladder Dysfunction in Multiple Sclerosis

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 relapses¹ [Betaseron²⁻⁵; Avonex⁶⁻⁹; Copaxone¹⁰⁻¹¹; Rebif¹²⁻¹⁴; Novantrone¹⁵]; reduction of brain lesion development, as evidenced by magnetic resonance imaging (MRI) [Betaseron^{2,16-17}; Avonex⁶⁻⁹; Copaxone¹⁸⁻²⁰; Rebif^{12-14,21-22}; Novantrone²³]; and the possibility of reduction of future disability²⁴ [Betaseron^{2,16-17}; Avonex⁶⁻⁹; Copaxone¹⁰⁻¹¹, Rebif¹²⁻¹⁴, 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
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Expert Opinion Paper

Medical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Physicians

Rehabilitation: Recommendations for Persons with Multiple Sclerosis

RECOMMENDATIONS

The Medical Advisory Board (MAB) of the National Multiple Sclerosis Society has adopted the following recommendations to provide guidance to physicians, nurses, therapists, insurers, and policy makers, regarding the appropriate use of rehabilitative therapies in MS. This document addresses physical rehabilitation. Cognitive and vocational rehabilitation will be addressed in future documents.

Definition: Rehabilitation in MS is a process that helps a person *achieve and maintain* maximal physical, psychological, social and vocational potential, and quality of life consistent with physiologic impairment, environment, and life goals. *Achievement and maintenance* of optimal function are essential in a progressive disease such as MS.

While the disease course cannot be altered by rehabilitation, a growing body of evidence indicates that improvement in mobility, activities of daily living (ADL), quality of life, prevention of complications, reduction in health care utilization, and gains in safety and independence, may be realized by a carefully planned program of exercise, functional training, and activities that address the specific needs of the individual. Thus, rehabilitation is considered a necessary component of comprehensive, quality health care for people with MS, at all stages of the disease.

- ◆ The physician* should consider referral of individuals with MS for assessment by rehabilitation professionals** when there is an *abrupt or gradual* worsening of function or increase in impairment that has a significant impact on the individual's mobility, safety, independence, and/or quality of life.

* or nurse practitioner or physician's assistant

** includes rehabilitation physician, occupational, physical, speech and language therapists and others

- ◆ Patients who present with any functional limitation should have an initial evaluation and appropriate management.
- ◆ Assessment for rehabilitation services should be considered early in the disease when behavioral and lifestyle changes may be easier to implement.
- ◆ The complex interaction of motor, sensory, cognitive, functional, and affective impairments in an unpredictable, progressive, and fluctuating disease such as MS, requires periodic reassessment, monitoring, and rehabilitative interventions.
- ◆ The frequency, intensity and setting of the rehabilitative intervention must be based on individual needs. Some complex needs are best met in an interdisciplinary, inpatient setting, while other needs are best met at home or in outpatient settings. The health care team should determine the most appropriate setting. Whenever possible, patients should be seen by rehabilitation therapists who are familiar with neurological degenerative disorders.
- ◆ Research and professional experience support the use of rehabilitative interventions*** in concert with other medical interventions, for the following impairments in MS:
 - ◆ Mobility impairments (i.e. impaired strength, gait, balance, range of motion, coordination, tone and endurance)
 - ◆ Fatigue
 - ◆ Pain
 - ◆ Dysphagia
 - ◆ Bladder/bowel dysfunction
 - ◆ Decreased independence in activities of daily living
 - ◆ Impaired communication
 - ◆ Diminished quality of life (often caused by inability to work, engage in leisure activities and/or to pursue usual life roles)
 - ◆ Depression and other affective disorders
 - ◆ Cognitive dysfunction
- ◆ Appropriate assessments and outcome measures must be applied periodically to establish and revise goals, identify the need for treatment modification, and measure the results of the intervention.
- ◆ Known complications of MS, such as contractures, disuse atrophy, decubiti, risk of falls, and increased dependence may be reduced or prevented by specific rehabilitative interventions.

*** Includes: exercise, functional training, equipment prescription, provision of assistive technology, orthotics prescription, teaching of compensatory strategies, caregiver/family support and education, counseling, and referral to community resources.

- ◆ In a fluctuating and progressive disease, maintenance of function, optimal participation, and quality of life are essential outcomes.
- ◆ Maintenance therapy includes rehabilitation interventions designed to preserve current status of ADLs, safety, mobility, and quality of life, and to reduce the rate of deterioration and development of complications.
- ◆ A thorough assessment for wheelchairs, positioning devices, other durable medical equipment (DME) and environmental modification by rehabilitation professionals is recommended and will result in the use of the most appropriate equipment.
- ◆ Regular and systematic communication between the referring health care provider and rehabilitation professionals will facilitate comprehensive, quality care.
- ◆ Third party payers should cover appropriate and individualized restorative and maintenance rehabilitation services for people with MS.

Background

While multiple sclerosis is highly variable, most patients experience functional losses and increasing impairment over time. Many people with MS face obstacles accessing rehabilitative services because of inadequate referrals and/or inadequate third party coverage. The National MS Society determined that a statement by its expert medical advisors was therefore necessary to support the use of rehabilitative interventions and thus promote physician referral to these services and third party coverage of them.

A number of studies have demonstrated positive outcomes of rehabilitation on people with MS, and data support the use of rehabilitative interventions for a number of specific MS impairments. Patients with MS who received multidisciplinary rehabilitation in addition to IV steroids demonstrated increased improvement in functional status, mobility, quality of life, and disability over those who received steroids alone (Craig et al., 2003). A study of the effect of inpatient rehabilitation on individuals with relapsing/remitting (RR) MS suggested that inpatient rehabilitation is useful for patients with incomplete recovery from relapses who have accumulated moderate to severe disability (Liu et al., 2003). Another study showed a significant decrease in length of stay in a rehabilitation inpatient unit for patients who were given more intensive rehabilitation therapies (Slade et al., 2002). Patients with progressive MS who received out-patient rehabilitation, experienced reductions in fatigue and MS related symptoms (DiFabio et al., 1997; 2003). Furthermore, a physiotherapy program conducted at home or in a hospital outpatient clinic resulted in significant improvements in mobility, subjective well-being, and mood in patients with chronic MS (Wiles et al., 2001). This study suggests that ongoing physiotherapy might be necessary for sustaining improvement in mobility or prevention of deterioration. Other studies demonstrated positive impact of multidisciplinary rehabilitative care on the daily life of patients with multiple sclerosis (Freeman et al., 1999; Solari et al., 1999).

In studies regarding access to rehabilitation services by people with disabilities, respondents report difficulty in accessing services, largely due to insurance coverage limitations (Beatty et al., 2003). Many insurance policies and state/federal regulations require that rehabilitation services be 'restorative' rather than oriented to maintenance of function and prevention of avoidable disability and complications. However, for individuals with chronic, progressive or disabling conditions such as MS, maintenance therapy is critical for preserving overall health and functioning, maintaining independence, avoiding institutionalization, and preventing secondary medical conditions and the associated need for costly hospitalizations that may include surgeries.

While additional research is needed, recent findings along with expert opinion and clinical experience demonstrate the value of rehabilitation in MS. Physicians should prescribe appropriate rehabilitation therapies for their patients with MS and insurers should cover these therapies.

Process

The clinical care committee of the National MS Society's Medical Advisory Board (MAB) identified the need to develop and periodically update a formal position about rehabilitation as a necessary component of quality health care for people with MS, at all stages of the disease. The MAB convened a multidisciplinary task force of MS experts to develop recommendations. The task force conducted a comprehensive review of the literature and compiled professional opinion based on the literature and clinical practice. The Medical Advisory Board's Executive Committee provided final review and approval of the document.

Use of the Recommendations

The National MS Society rehabilitation and MS statement is an educational and advocacy tool. It will be a component of the Society's professional education programs and will be used to promote increased access to rehabilitative therapies through legislative and regulatory determinations. It will serve as a communication device for interactions with insurers both nationally and locally. It supports self-advocacy for persons with MS and will encourage them to talk with their health care providers and insurers about whether rehabilitation is indicated.

Role of the National Multiple Sclerosis Society

The mission of the National MS Society is to end the devastating effects of multiple sclerosis. Various strategies are employed to do so, including professional education and advocacy. As a representative body and advocate for people with MS and medical/health professionals who provide their care, the Society is positioned to provide structure and support for the development of an expert opinion document to facilitate access to rehabilitative therapies for disease management. The National MS Society has a nationwide network of chapters and regular contact with persons with MS and their families as well as with health care professionals. This extensive network and process for dissemination of information will ensure that the recommendations regarding rehabilitation and MS will be communicated to providers, insurers, and people with MS.

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Expert Opinion Paper

Medical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Physicians

Management of MS-Related Fatigue

BACKGROUND

Fatigue is the most common MS symptom—experienced by 75 to 95% of people with the disease. Approximately 50 to 60% of people with MS describe fatigue as one of their most troubling symptoms, regardless of their disease course or level of disability. The Social Security Administration recognizes fatigue as a significant cause of unemployment among people with MS.

Fatigue was recently defined by the Fatigue Management Panel of the Multiple Sclerosis Council on Clinical Practice Guidelines as:

A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.

RECOMMENDATIONS

Based on clinical experience and careful review of the medical literature and research findings pertaining to MS-related fatigue, the Medical Advisory Board of the National MS Society makes the following recommendations:

- ◆ Because of the complexity of MS-related fatigue, the first step in effective treatment is to identify the cause(s) of the fatigue (e.g., any combination of factors, including co-existing medical illnesses, side effects of medications, depression, disrupted sleep, and fatigue caused by the MS itself).
- ◆ Once the source(s) of the fatigue have been identified, the treatment of MS-related fatigue is approached in a step-wise fashion in order to address all contributing factors. The treatment of fatigue should include **TWO** major steps:

1. Management and elimination of any secondary causes of fatigue:

- a. Treatment of any co-existing medical conditions (including depression) that are causing fatigue.
- b. Adjustment of any medications that may be producing excessive fatigue and/or sleepiness. Many common medications, including anticonvulsants, antihistamines, antihypertensives, sedatives, and certain antidepressants, have fatigue and/or sleepiness as a side effect.
- c. Management of any conditions or symptoms that interfere with sleep (e.g., sleep apnea, leg spasms, depression, MS symptoms such as bladder dysfunction, spasticity, or pain). Research indicates that 25 to 35% of people with MS experience disturbed sleep, which may contribute significantly to daytime fatigue.
- d. Management of any MS symptoms that may be producing additional fatigue. Symptoms such as weakness, spasticity, and ataxia may significantly increase the amount of exertion needed to carry out daily activities.
- e. Education about energy effectiveness strategies—defined as “the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home, and leisure activities. . . .” These strategies are frequently taught by a nurse or rehabilitation specialist (e.g., occupational and/or physical therapist)
 - i. Appropriate rest to activity ratio
 - ii. Use of assistive devices to conserve energy
 - iii. Environmental modifications to make activities more energy-efficient
 - iv. Cooling strategies to avoid the fatigue caused by elevations in core body temperature due to heat, exercise-related exertion, and fever
 - v. Regular aerobic exercise, geared to the person’s ability, to promote cardiovascular health, strength, improved mood, and reduce fatigue
 - vi. Stress management techniques

2. Treatment of primary MS fatigue:

- a. Pharmacologic management of chronic fatigue that remains after other factors have been addressed. Although no drugs have been approved by the U.S. Food and Drug Administration specifically for MS, recommended medications include:
 - i. **Amantadine (Symmetrel®):** An antiviral agent that has been used to treat MS-related fatigue since the early 1980s. Approximately 20 to 40% of mild to moderately disabled people with MS experience significant reductions in fatigue while using amantadine. Side effects are generally mild. The recommended dose of amantadine is 100 mg morning and early afternoon.

- ii. **Modafinil (Provigil®):** A wakefulness-promoting agent currently approved by the FDA for the treatment of narcolepsy, which has been shown to reduce self-reported fatigue in people with MS. The recommended dose of modafinil is 200 mg per day.
- iii. **Pemoline (Cylert®):** A central nervous system stimulant that has been used for many years to treat MS-related fatigue. While study results have been contradictory, pemoline may be an effective therapy for people with MS who do not respond to amantadine or modafinil. The usual effective dose is 75–140 mg per day (titrated slowly from a starting dose of 18.75 mg), divided into 2–3 equal doses prior to mid-afternoon. As directed by the Food and Drug Administration, Abbott Laboratories, the manufacturer of Cylert®, has recommended evaluation of liver function prior to starting this medication, followed by bi-weekly liver function evaluations while the drug is being used. [*Note:* Although hepatotoxicity has been reported primarily in children taking Cylert® for other conditions, no toxicity has been reported in patients with MS. Nevertheless, extra care should be taken when prescribing this medication to any patient who is using Cylert® in combination with other drugs that may be hepatotoxic.]
- iv. **Methylphenidate (Ritalin®):** A central nervous system stimulant that has been used to treat MS-related fatigue. The usual effective dose is 10–20 mg early in the morning and again at noon. Those individuals who experience little or no fatigue in the morning can take a single dose in the early afternoon.

Note: Prokarin, a drug containing histamine, caffeine, and other undisclosed ingredients, has been marketed to pharmacists for compounding (creating a preparation using the ingredients) for individual patients. It was reported in a recent controlled trial to reduce fatigue in a small sample of patients with either relapsing-remitting or progressive MS. **It is the opinion of this board that while Prokarin does not appear to be harmful, its level of benefit does not justify its very high cost.**

- b. Maintenance of energy effectiveness strategies as previously described

SUMMARY

Fatigue is a complex, potentially debilitating symptom experienced by the majority of people with MS. Anyone experiencing ongoing fatigue, or the sudden onset of severe, disabling fatigue should consult his or her physician so that the factor(s) contributing to the fatigue can be identified and effectively managed. Successful treatment of fatigue may require a variety of interventions, including behavioral adaptations, environmental modifications, and medication.



Expert Opinion Paper

Medical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Physicians

Changing Therapy in Relapsing Multiple Sclerosis: Considerations and Recommendations of a Task Force of the National Multiple Sclerosis Society

INTRODUCTION

The last decade has witnessed the introduction of a series of disease-modifying agents as rational therapies to alter the near term course of multiple sclerosis (MS). Their general acceptance in relapsing forms of MS is based on adequate Class I evidence from controlled clinical trials used to gain approval from the Food and Drug Administration (FDA). These include several different formulations of interferon beta (interferon beta-1a; Avonex® and Rebif®, and interferon beta-1b; Betaseron®), glatiramer acetate (Copaxone®) and mitoxantrone (Novantrone®). The evidence supporting the use of the immunomodulatory drugs interferon beta and glatiramer acetate has been reviewed in a practice guideline issued by the American Academy of Neurology.¹ The data supporting approval of the chemotherapeutic immunosuppressant mitoxantrone were published in 2002.²

Unfortunately, while all of these drugs represent advances for MS management, none is fully effective. The pivotal trials of all of these agents show that only limited numbers of patients were free of disease activity over each study's duration, that this proportion was only modestly larger than that found in the trial's placebo arm, and that for most subjects, treatment was only partially effective in controlling the clinical and magnetic resonance imaging (MRI)-monitored expressions of their disease. Whatever the relative merits of these drugs, all can only be considered partially effective agents. This reality raises the difficult problem of the identification of a suboptimal response or treatment failure in an individual case and, once identified, leads to consideration of the appropriate avenues for alternative treatments. Regrettably, primary data for evidence-based recommendations on these important concerns do not exist. Given the pressing nature of these issues, the Medical Advisory Board believed that some expert advice would be useful to help guide decision-making for the general physician confronted with this problem.

BACKGROUND

Treatment failure is readily recognized when the expected effect is the rapid reversal of an obvious abnormality. Failure to reduce symptoms of bladder infection and sterilize the urine within several days of initiating antibiotic therapy is one example. Prevention of the development of a late and variable complication of a disease can be more difficult, such as when stroke occurs as a complication of hypertension. However, anticipation of future drug failure might be recognized by such treatment's inability to reduce hypertension. The goal of current disease-modifying treatments in MS is to prevent further disability, not to reverse existing deficits. When the clinical state that the drug is expected to prevent is delayed and not precisely defined, substitute targets for treatment efficacy are often used. In relapsing MS, these include clinical attacks, which in and of themselves are of concern and importance for patients, and acute subclinical activity as monitored by MRI. While both likely contribute to disability over time, neither is highly correlated with either disability or even accumulated, persisting neurological deficits within most clinical trials of only a few years' duration. Nevertheless, the effects of current therapies on attack rates and MRI measures of newly accumulated lesion burdens are the outcome measures that are best described by modern treatment trials, and are the events that are most readily available to the clinician when considering treatment failure or suboptimal response in an individual patient. In relapsing MS, clinical events occur relatively infrequently, making it unlikely that treatment failure can be declared with any assurance within six months of compliant drug exposure.

The concept of "rescue therapy" is deceptive as applied to MS. It implies that treatment failure or suboptimal response can be defined and consistently identified in the individual patient, even though these concepts derive from the results of grouped data reported in relevant clinical trials.³ It also assumes that the rescue treatment is either too toxic to be considered for all patients with relapsing MS, or is itself only partially effective for the majority of patients so treated. Were rescue treatment safe, universally effective, and its protection sustained, that treatment should be the definitive first line therapy. Even if toxic, risk-benefit considerations might also favor the "rescue" treatment as a primary therapy were it highly effective in preventing disability for the vast majority of patients in a sustained manner. Rescue therapy also implies a sense of urgency, a step that if not taken expeditiously will result in irreparable harm. For MS, this suggests that the level of recent disease activity observed despite therapy predicts a high likelihood of impending disability if not aggressively managed. Such strong outcome predictors remain to be defined for MS.

Currently, it is unclear to what extent the effectiveness of approved MS treatments reflects a partial responsiveness of all treated patients, or a complex mix of complete, partial, and unresponsive patients within the study cohorts.⁴ Nor is it fully appreciated whether unresponsiveness or partial responsiveness to a treatment may develop over time.⁵ Thus, in failing to show a response to an initially-selected immunomodulatory therapy, the perceived need to switch within interferon beta formulations, or to change therapy from an interferon to glatiramer acetate or vice versa, is appropriately considered selection of an alternative therapy rather than rescue therapy. Similarly, the patient's inability to cope with local or systemic drug side effects

or be adequately compliant with treatment, while a treatment failure in the strict sense, is not a failure of drug efficacy. In some cases, it may reflect a failure of the patient's physician to adequately prepare the patient for the commitment to chronic treatment with injectable drugs, or to provide adequate management of side effects.

POSSIBLE MARKERS OF TREATMENT FAILURE

Attacks (Relapses). Although not always the primary outcome measure in pivotal trials of relapsing MS, acute attacks with concomitant neurologic disability are measured and reported in all modern, controlled MS studies. Across all studies immunomodulators reduce relapses by about 30% compared to placebo treatment. While in all studies, the decrease in relapses found during the study compared to the number reported in the 2–3 years prior to enrollment is proportionately greater on active treatment, it is also substantial in controls. There are a number of possible explanations; undoubtedly one is that relapses counted on trial are defined more rigorously and objectively than those recalled or recorded before trial. Certainly, continued attacks at a rate similar to that found before starting a patient on an immunomodulator is therefore a concern. In practice, however, this is likely to be more difficult to discern than in trials. Often there is pressure to determine if a single attack reflects treatment failure, regardless of the duration of treatment or number of attacks prior to initiating therapy. Moreover, pressures to initiate treatment early in the disease course will mean that increased numbers of treated patients may have a single or very few attacks before initiation of treatment. Nevertheless, declaring treatment failure based on a single attack on therapy is not justified by the known efficacy of these agents. Nor is it reasonable to declare treatment failure within a few months of initiating treatment.

Acquired Neurologic Deficits (Disability). All modern MS trials have reluctantly embraced the Expanded Disability Status Scale (EDSS)⁶ as the best available measure of neurologic disability. Despite its complexity and shortcomings, the EDSS is easier to apply in everyday practice than more quantitatively-derived composite measures of disability,⁷ and its general use might help practitioners better understand possible treatment failures based on evidence from clinical trials. Change in the EDSS linked to an acute attack only measures the severity of the relapse, may spontaneously recover over 3–6 months with or without corticosteroid therapy, and should not be used in isolation to determine a suboptimal response or treatment failure. However, an annual increase in the EDSS of 1 point from a previous score of 3.0 to 5.5, or a 0.5 point increase from a previous score of 6.0 or greater in the absence of clinical attacks, should raise concern. This may indicate that the previously relapsing-remitting patient has transitioned to secondary-progressive disease, or that the secondary-progressive patient has only a partial response to therapy. Measurement of change in the very low EDSS ranges (<3.0) is too variable to be used in isolation to define treatment failure.

MRI Activity. Findings on random MRI, or on MRI performed at arbitrary, predefined intervals in the absence of clinical activity, are difficult to interpret. MRI activity at the time of an acute clinical attack provides little additional data for the assessment of treatment failure. However, patients on treatment that exhibit high enhancing activity or substantial new lesion

formation after an attack has subsided, particularly in the presence of attack-independent EDSS worsening, are likely to be treatment failures. Precise benchmarks for excessive MRI activity are difficult to define, but might include three or more enhancements or two or more new T2 lesions on each repeated scan separated by at least quarterly intervals. While quantitative measures of lesion activity on periodic MRI may eventually prove useful indicators of the risk of future clinical treatment failure, providing timely indicators for the need for alternative therapy, the use of MRI as a sole surrogate indicator of treatment failure for any of the available approved treatments is not adequately developed at this time. If and when available, it will require a standardized MS imaging protocol that currently does not exist in general practice.

SUMMARY

- ◆ There are no direct comparative data to allow a fully informed choice of the best immunomodulatory drug class (interferon beta or glatiramer acetate) with which to initiate therapy in relapsing forms of MS.
- ◆ Higher-dosed, more frequently administered formulations of interferon beta may provide better short-term clinical efficacy than lower, less frequently dosed formulations of interferon beta in relapsing MS.^{8,9}
- ◆ The presence of neutralizing antibodies to interferon beta may be associated with incomplete response to therapy in patients taking one of the interferon products. The presence of neutralizing antibodies to interferon in the face of continued frequent relapses or excessive MRI activity may justify the use of non-interferon disease-modifying drugs. Presently, in the absence of clinical or MRI activity, finding high titer interferon beta neutralizing antibodies in the serum does not warrant a change in therapy. This conclusion may need to be revised as additional evidence accrues.
- ◆ Mitoxantrone (or other chemotherapeutic agents not specifically approved for use in MS) is not advised as a first choice for most relapsing MS patients due to its relative toxicity profile.
- ◆ Continued, frequent relapses, or non-relapse associated excessive MRI activity, may justify selection of an alternative immunomodulating strategy—increased dose frequency of an interferon beta or switch to glatiramer acetate, switch from glatiramer acetate to an interferon beta, or consideration of mitoxantrone. While this is a widely accepted practice, it is re-emphasized that there are unfortunately no Class I data to support the underlying assumption that switching therapy improves clinical outcome. Ideally, this could be evaluated in the setting of well-conceived trials that could lead to data substantiating the use of these drugs in such a manner.
- ◆ Continued frequent relapses, or non-relapse associated excessive MRI activity, may justify combination therapy using different classes of FDA-approved drugs, or an FDA-approved drug with a currently available drug without an FDA approved indication for MS. The Task Force recognizes that clinicians familiar with treating MS and the toxicities of these

drugs may use combination therapy for suboptimal responders and treatment failures as an alternative to changing immunomodulator therapy under these circumstances. While this may be a widely accepted practice, it is re-emphasized that there are unfortunately no Class I data to support the underlying assumption that adding therapy improves clinical outcome. This is preferably done in the setting of well-conceived trials that could lead to data substantiating the use of these drugs in such a manner.

- ◆ Treatment failure due to continued, frequent, severe relapses, particularly those with incomplete recovery, justifies consideration of mitoxantrone or an alternative chemotherapeutic agent.
- ◆ Patients failing approved therapies as defined above should be considered for well-designed, institutional review board (IRB)-approved therapeutic trials of drugs deemed promising for treatment of MS.

In the development of these guidelines, the Task Force recognized a number of areas where additional clinical research would translate into better-informed use of these drugs. **First**, we encourage the re-analysis of data from existent trials to determine early clinical and MRI measures that best predict a favorable and unfavorable course on active treatment. **Second**, we encourage a national registry of treated patients to better understand the importance of early therapy and early recognition of treatment failure and their longer-term consequences. **Third**, we encourage the development of regional networks between centers highly experienced in the use of these drugs and primary treating physicians in more isolated settings.

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Pain in Multiple Sclerosis

by Heidi Maloni, RN, BSN

Adapted by Debra Entin, MS, RN, with permission from Maloni H, Schapiro RT: Pain. In van den Noort S, Holland N (eds): *Multiple Sclerosis in Clinical Practice*. New York: Demos Medical Publishing, 1999.

INTRODUCTION

Until the 1980s multiple sclerosis (MS) was often considered to be a painless disease. It is now known that two-thirds of all people with MS experience pain at some time during the course of the disease, that the pain associated with MS may be severe, and that it may have multiple causes. Pain in MS occurs both as a consequence of the disease and as a consequence of the disability that it produces.

Pain in MS is not a poor prognostic sign. In comparing people with MS who experience pain with those who are pain-free, no distinction is found with regard to age of onset, disease duration, degree of disability, gender, depressive symptoms, or MS subgroups (relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing).

The following is a review of the types of pain seen in MS and the management of paroxysmal and chronic pain.

PAROXYSMAL PAIN

Patients with MS often experience brief and paroxysmal pain (sharp intermittent spasms of sudden and spontaneous onset). These paroxysms are described as lancinating, intense, sharp, shooting, electric shock-like, ticlike, and burning. The most common types of episodic pain experienced in MS include trigeminal neuralgia, paroxysmal limb pain, and headache.

Trigeminal Neuralgia

Neuralgia, the paroxysmal pain that occurs along the distribution of a peripheral nerve, is often lightning-like in quality and extremely severe. Trigeminal neuralgia (tic douloureux) involves

the second and third divisions of the trigeminal nerve that innervates the face, cheek, and jaw. It affects 2% of all people with MS and is 400 times more common in people with MS than in the general population.

Touching, chewing, smiling, or any facial movement may precipitate or exacerbate the pain of trigeminal neuralgia, which may be accompanied by numbness of the face. Periods of remission follow periods in which sharp shocklike attacks of 2 to 3 seconds in duration—or occasionally several minutes—occur at varying frequency. In rare instances, the patient experiences continuous pain. Trigeminal neuralgia in MS is often cyclical, and treatment with medication is preferred over invasive surgical procedures. Management strategies include the use of anticonvulsant medications. Carbamazepine (Tegretol®) is the most effective, but phenytoin (Dilantin®) and gabapentin (Neurontin®) are often helpful. These and other drugs are listed in Table 1. Misoprostol (Cytotec®) can also be helpful in some patients.

When pain relief is not obtained by medical interventions, surgical radio frequency or nerve block procedures that interrupt the pain pathway may become an option. The gamma knife is a noninvasive means of relieving pain with focused radiation.

Paroxysmal Limb Pain

Paroxysmal pain is a burning, aching, or itching that lasts several seconds to several minutes. While it can affect any part of the body, this type of pain most often involves the extremities. Paroxysmal limb pain responds best to carbamazepine, amitriptyline, clonazepam, diazepam, gabapentin, or applications of heat and cold.

Headache

The association between headache and MS is unclear. The incidence of headache in MS is greater than in the general population and is usually described as a migraine or tension-contraction headache. Treatment is ordained by the nature of the headache pain.

CHRONIC PAIN

Chronic pain is defined as any pain that persists for longer than one month. Two kinds of chronic pain in MS are detailed below: dysesthetic extremity pain and back pain.

Dysesthetic Extremity Pain

Dysesthetic extremity pain is the most common chronic pain syndrome seen in MS. It occurs more often in people with minimal disability and is characterized as a “burning” type of pain. This persistent type of pain often affects the legs and feet but may also involve the arms and trunk, and is described as prickling, tingling, tight, dull, warm, or burning. It is sometimes difficult to distinguish dysesthetic extremity pain due to MS, from pain due to disk herniation.

TABLE 1 Pharmacological Treatment of Pain in Multiple Sclerosis

Agent	Dosage	Adverse events	Indications
carbamazepine (Tegretol®)	100–200 mg tid pain usually resolved in 4–24 hours if effect is expected	nystagmus, rash, fatigue, dizziness, hepatotoxicity, diplopia, ataxia, bone marrow toxicity, drowsiness	drug of choice for trigeminal neuralgia, tonic seizures, painful Lhermitte's paroxysmal limb pain, episodic facial pain, dysesthetic pain
baclofen (Lioresal®)	30–80 mg qd	weakness, drowsiness, dizziness, nausea, fatigue, seizures	trigeminal neuralgia, episodic facial pain, flexor/extensor spasm
diphenylhydantoin (Dilantin®)	200–400 mg qd	drowsiness, dizziness	trigeminal neuralgia, episodic facial pain, dysesthetic pain
gabapentin (Neurontin®)	slow titration of 300–900 mg qd minimum dose maximum dose 2400 mg over 3 weeks to increase tolerability	dizziness, somnolence, tremor, diplopia, ataxia, fatigue, nystagmus few drug interactions (does not generate blood dyscrasia)	trigeminal neuralgia, episodic facial pain, painful Lhermitte's, paroxysmal limb pain, tonic seizures, dysesthetic pain
tricyclic antidepressants amitriptyline (Elavil®) imipramine (Tofranil®)	10–25 mg hs increase to 150–200 mg hs	dry mouth, drowsiness, blurred vision, constipation, urinary retention	episodic facial pain, paroxysmal limb pain, headache, dysesthetic pain
capsaicin (Axsain®, Zostrix®)	a thin film of 0.075% cream tid (over the counter) apply with gloves	initial burning, redness, mild tingling	dysesthetic pain
non-steroidal antiinflammatories ibuprofen (Motrin®, Advil®) naproxen (Naprosyn®)	 200–800 mg tid 250–500 mg bid	headache, drowsiness, dizziness, peripheral edema, ringing in ears, GI upset, nausea	back pain
tizanidine (Zanaflex®)	2–4 mg, slow titration to 20 mg qd	sedation, drowsiness, hypotension	flexor/extensor spasm
diazepam (Valium®)	2–5 mg prn or hs	sedation, drowsiness, memory disturbances, drug tolerance, back pain	flexor/extensor spasm

Dysesthetic extremity pain is often worse at night and after exercise, and may be aggravated by temperature elevations or changes in weather. Low doses of amitriptyline (Elavil®), imipramine (Tofranil®), or desipramine (Norpramin®) are considered first-line treatment. Capsaicin cream reduces the burning and tingling pain by interfering with pain transmission in the periphery. This type of pain is frustrating for both the person with MS and the clinician because treatment options do not always bring long-term pain relief.

Many patients also complain of painful bands around the limbs or torso. Gabapentin (Neurontin®) in doses up to 900 mg every eight hours may be helpful.

Chronic Back Pain

Chronic back pain in patients with MS often results from disability-related mechanical stress on the muscles, bones, and joints. Back pain is often the result of postural abnormalities, a weakened torso, the ache of sitting or standing too long, or the compensatory use of muscles to lift and move weakened limbs. Nonsteroidal anti-inflammatory agents such as ibuprofen and naproxen are the pharmacologic agents of choice for back pain. Heat, cold, position change, and firm support when sitting or sleeping may ameliorate pain of structural cause. Aggressive physical therapy becomes critical because issues of gait aids, the use of ankle-foot orthoses, exercise for maintaining strength and posture, and safety considerations all impact back pain.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Some alternative methods for pain relief include acupuncture, massage, moist heat, dorsal column stimulation, and transcutaneous electric nerve stimulation (TENS). These agents may stimulate endorphin release, thereby promoting pain relief. Exercise programs such as Tai Chi, meditation, centering, hypnotherapy, imagery, and biofeedback are techniques that may serve to improve quality of life.

SUMMARY

Pain is a symptom that demands serious attention, as it has such a pervasive impact on role, mood, capacity to work and rest, and interpersonal relationships. Untreated pain causes isolation, anger, and depression. Optimum therapeutic treatment involves a commitment to the goal of controlling pain and improving quality of life.

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Spasticity

by Sue Kushner, MS, PT and Kathi Brandfass, MS, PT

Spasticity is one of the most common symptoms of multiple sclerosis (MS). It can be defined as a velocity-dependent increase in muscle tone, which is usually associated with hyperactive deep tendon reflexes. It is seen in upper motor neuron disorders and occurs most frequently in muscles of the upper and lower extremities. MS-related spasticity is usually the result of increased co-contraction of muscles during movement. Increased stiffness, or tone, can lead to decreased range of motion of major joints and result in shortening of connective tissue around the joints. This, in turn, can result in contractures. Fortunately, this common symptom responds to a variety of therapeutic approaches.

CLINICAL SIGNS AND SYMPTOMS

Clinical indications of spasticity are highly variable and may include:

- ◆ An increase in deep tendon reflexes
- ◆ Clonus, a repetitive rhythmic beating movement of a foot or wrist
- ◆ Difficulty initiating movements
- ◆ Impaired voluntary control of muscles
- ◆ Difficulty relaxing muscles once a movement has ceased
- ◆ Sensation of muscle tightness or pain
- ◆ Flexion or extension synergy patterns
- ◆ Decreased range of motion

These clinical signs and symptoms may be aggravated by fatigue, stress, urinary tract infections, infections of other origins, and pain. Additionally, spasticity may lead to increased fatigue due to the extra energy expended to overcome tone during voluntary movements involved in activities of daily living.

ASSESSMENT

Screening for spasticity involves assessing range of motion of upper and lower extremities, and the ability to carry out activities of daily living. This includes examination of mobility, transfers, self-care, assistive devices/braces, strength, and balance. Recent changes in spasticity should signal a need for additional assessment. Aggravating factors such as local or systemic infections or noxious stimuli need to be identified. Noxious stimuli that can contribute to the severity of spasticity may include pain, decubitus ulcers, ingrown toenails, and bladder or bowel distention. Removal of the noxious stimuli will often lead to significant reductions in tone. The Modified Ashworth Scale (Table 1) is used to grade spasticity. This scale measures the presence of velocity-dependent resistance on a 0 to 4 scale, with zero representing normal muscle tone, and four representing a limb that is fixed in flexion or extension.

Significant changes in spasticity may signal the need to review the patient's medications. Adjustment in dosages or addition of other anti-spasticity medications may successfully reduce tone. For those individuals managed with intrathecal baclofen, the healthcare team needs to be familiar with the management of baclofen pumps. These systems can have mechanical failures, or the medicine-distributing catheters can become dislodged or plugged, resulting in loss of delivery of baclofen to the patient.

A thorough assessment includes consideration of function in addition to increased tone, since some spasticity can be beneficial. Totally eliminating spasticity is not always a goal; some individuals with muscle weakness use their tone to stand and transfer. Consideration of how much spasticity is actually beneficial is important when determining pharmacologic treatment, and medications should be titrated accordingly.

MANAGEMENT

Long-term rehabilitation for MS-related spasticity is essential and should be initiated as early as possible. It is critical to identify the underlying causes and components of the spasticity so that appropriate treatment can be provided to maximize the patient's physical abilities and comfort. The most effective management approach involves the use of a multidisciplinary team including the physician, nurse, and occupational and physical therapists.

Spasticity usually requires both pharmacological and non-pharmacologic interventions (Figure 1). Oral medications are often effective, especially in the early stages of the disease. Baclofen administered intrathecally (Intrathecal Baclofen™) through an implanted pump, can be an excellent option when large doses of oral medications are required to manage tone or when side effects of oral medication outweigh these benefits. Botulinum toxin (Botox®) and phenol injections into specific target areas can be effective adjuncts to oral medications. In exceptionally difficult cases, surgical intervention may be necessary, including tenotomy, neurectomy and rhizotomy.

TABLE 1 Modified Ashworth Scale for Physical Therapy—Spasticity Evaluation

Date/Time														
	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Shoulder Flexors														
Shoulder Extensors														
Elbow Flexors														
Elbow Extensors														
Wrist Flexors														
Wrist Extensors														
Hip Flexors														
Hip Extensors														
Hip Abductors														
Hip Adductors														
Knee Flexors														
Knee Extensors														
Ankle Dorsiflexors														
Ankle Plantarflexors														
Average for UE														
Average for LE														

Date/Comments

Modified Ashworth Scale for Grading Spasticity

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension.
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM.
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

FIGURE 1 Treatment of Spasticity

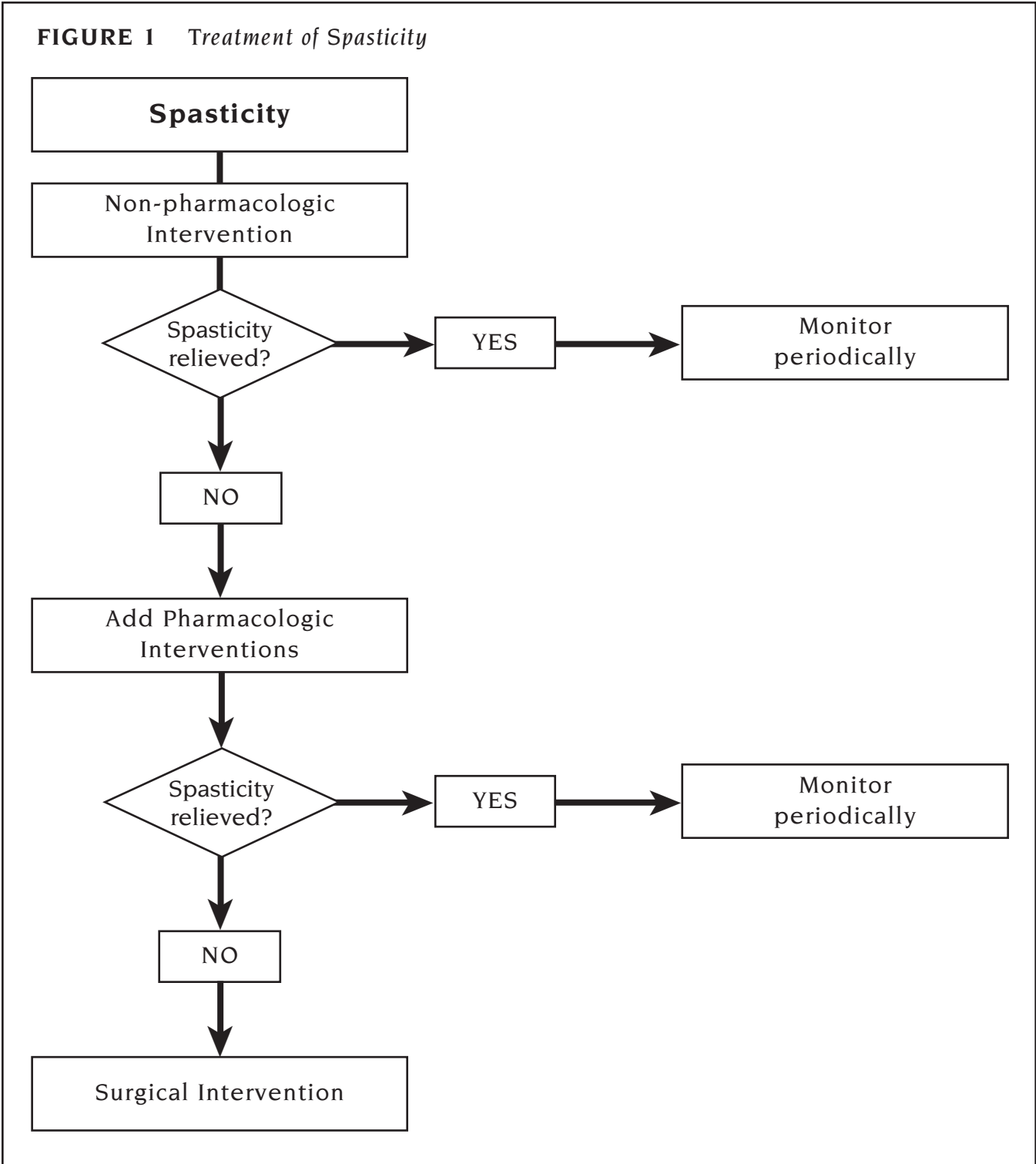
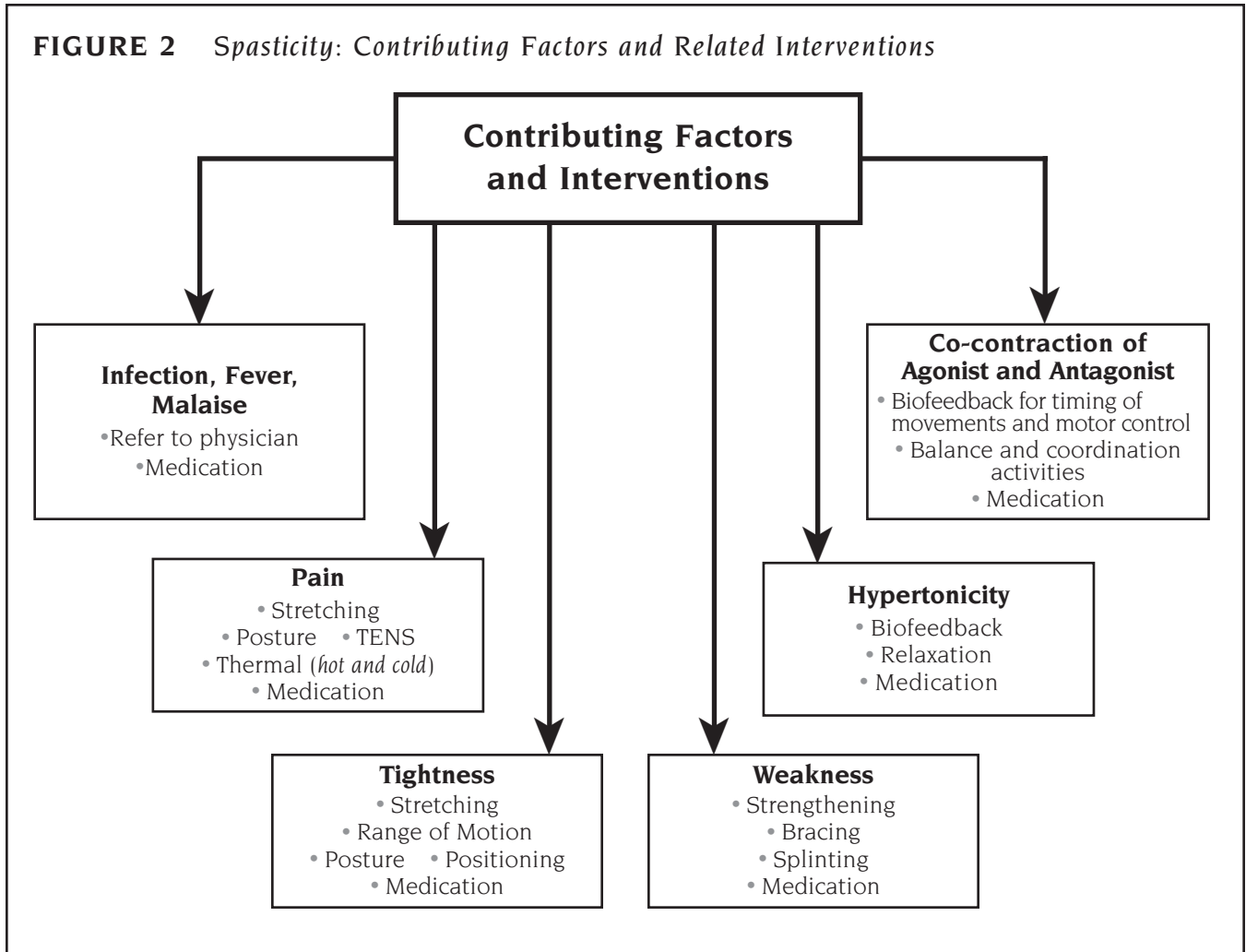


FIGURE 2 *Spasticity: Contributing Factors and Related Interventions*



INTERVENTIONS

Treatment of spasticity will vary from patient to patient, based on the wide spectrum of factors presented. Specific interventions are determined after performance abilities and limitations are clearly identified (Figure 2).

Non-pharmacologic Interventions

Possible non-pharmacologic interventions are as follows:

- ◆ **Stretching and range of motion exercises**, following a thorough musculoskeletal exam, can treat connective tissue tightness. *Posture* may be a focus for improved body alignment and decreased musculoskeletal problems. This may include evaluation and adjustment of a wheelchair seating system. *Gait and assistive devices* may need to be further evaluated. A manual muscle test may assist in determining whether or not upper extremity strength can compensate for spasticity. This test is not always valid, since spasticity can interfere with the results.

- ◆ **Problems with co-contractions** can be treated with *timing exercises* and by focusing on *motor control*. One goal is to minimize fatigue through energy conservation techniques and adequate fluid intake. *Yoga, Tai Chi* and *biofeedback* may be appropriate relaxation interventions. *Aquatic exercises* may also be helpful.
- ◆ **Weakness** may be alleviated to some extent with *strengthening exercises* specific to those muscles identified as being weak. General conditioning can also help to strengthen weak and deconditioned muscle groups and increase endurance and cardiovascular conditioning. Strengthening can be achieved in a variety of ways, using free weights, machines, theraband, Swiss Balls, or aquatic exercises. Strength training can also assist with the timing of movements, depending on the strength or weakness of the agonist/antagonist muscles. Precaution must be taken to avoid fatiguing muscles or the patient with excessive training. Exercise should be done in a cool environment as overheating can contribute to weakness and fatigue.
- ◆ **Energy expenditure and diminished fluidity of movement** can be addressed by *balance and coordination exercises*. Swiss ball and pool exercises are very effective for balance and coordination, as are yoga and Tai Chi.
- ◆ **Pain** may be alleviated or reduced by *stretching, transcutaneous electrical nerve stimulation (TENS)*, or *thermal modalities* such as cooling. Ergonomic and environmental factors should be evaluated for patients' vocational and avocational activities as these may be contributing to increased pain.

Pharmacologic Interventions

Pharmacologic interventions include the following:

- ◆ Oral *baclofen* is often used as a first line drug for management of spasticity. Many patients get good to excellent reduction in tone with this medication. It is started at a low dose and slowly titrated up to minimize sedation and to identify the lowest effective dose. Patients and family members become adept at making minor dose adjustments to control changes in tone that occur secondary to infection, stress, and other causes previously discussed. Patients may experience fatigue or weakness as a side effect. *Tizanidine (Zanaflex®)*, which can also be sedating, is an effective anti-spasticity medication that may be used alone or in combination with baclofen. *Dantrolene sodium (Dantrium®)*, which works at the muscle level and may cause liver toxicity, may also be considered.
- ◆ Other oral drugs used off label include *diazepam (Valium®)*, which is very sedating at therapeutic levels, and may be habit-forming; *clonazepam (Klonopin®)*, which is a benzodiazepine used in multiple sclerosis primarily for the treatment of tremor, pain, and spasticity; and *gabapentin (Neurontin®)*, an anti-epileptic medication that has had some success in management of spasticity.

- ◆ For more severe spasticity, *phenol nerve blocks* are often effective for up to six months and are especially useful for conditions such as severe adductor spasm. More recently, *botulinum toxin (Botox) injections* have been used successfully for small muscle groups.
- ◆ Implantation of a *pump to deliver baclofen intrathecally* may be helpful for patients who do not respond well to oral medication or cannot tolerate the side effects at the required dosage level. It is also an option for individuals wanting to avoid ongoing nerve injections. Very small amounts of baclofen are required for symptom relief, avoiding the side effects of systemic administration. Problems with the pump include pump failure, infection, and lead displacement.

Summary of pharmacologic interventions:

- ◆ Baclofen (oral or intrathecal)
- ◆ Tizanidine
- ◆ Diazepam
- ◆ Dantrolene sodium
- ◆ Clonazepam
- ◆ Gabapentin
- ◆ Phenol
- ◆ Botulinum toxin

Surgical Procedures for Intractable Spasticity

In rare instances intractable spasticity will necessitate ablative irreversible procedures such as:

- ◆ Tenotomy
- ◆ Neurectomy
- ◆ Rhizotomy

SUMMARY

The treatment of spasticity related to multiple sclerosis is most effective when there is a multi-disciplinary approach to patient care. The patient's abilities and limitations need to be considered in the management plan, as each person's tone and disease are unique. In some cases a single intervention will be effective, but more often a combination of non-pharmacologic and pharmacologic strategies will be needed. These interventions need to be monitored as the course of the MS changes and modifications need to be made accordingly. In rare cases of intractable spasticity, ablative surgical procedures may be required.

ADDITIONAL READINGS

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Physical Therapy in Multiple Sclerosis Rehabilitation

By Patricia G. Provance, PT

Rehabilitation is an essential part of health care delivery for persons with multiple sclerosis (MS). It is important that rehabilitation team members possess knowledge, experience, and sensitivity relating to the unique variation of symptoms between individuals, and to the unpredictable and fluctuating nature of this challenging, progressive disease. A shared understanding of the progressive nature of MS will enable therapists and patients to establish realistic short- and long-term treatment goals over the course of the disease. In addition, rehabilitation therapists need to be aware of the broad range of social, emotional, vocational, and financial issues confronting their patients with MS.

In all care delivery models—inpatient (acute, transitional, rehabilitation, or long term care), home care, or outpatient—physical therapists (PTs) must understand and respect the physiological fatigue associated with MS. The goal is to establish corrective exercises and activity programs that are appropriate, realistic, and meaningful, with a strong focus on *improving and maintaining* function. PTs must be prepared to:

- ◆ Educate
- ◆ Develop effective home programs for managing symptoms
- ◆ Promote safe independence
- ◆ Provide resources for equipment and community programs
- ◆ Train family and caregivers

A UNIQUE APPROACH TO MANAGING MS

Physical therapy of persons with MS in the outpatient setting typically varies from the “traditional” (orthopedic or fixed deficit neurological condition) model. Instead of scheduling PT appointments two or three times a week, effective outpatient therapy can be provided as needed, with dedicated one-on-one sessions. This prevents or minimizes depletion of the patient’s energy

and insurance benefits, since the need for rehabilitation follow-up is life long and likely to increase with age. Weekly follow-up is appropriate when regular professional assistance is needed following an exacerbation, progression of disability, or other illness or injury, or when skilled passive stretching, gait training, corrective exercise, and/or family teaching are required.

When symptoms are well controlled and an effective home/community exercise program has been established, follow-up sessions every 1–3 months, or as needed, can work very well. Community programs such as MS aquatic exercise (pool temperature < 85 degrees), hippotherapy (therapeutic horseback riding), gentle yoga, low-level or water-based Tai Chi, adaptive bowling, and day programs can provide needed therapeutic recreational and social outlets.

PHYSICAL THERAPY EVALUATION

Ambulation/Mobility

For the ambulatory individual, the desire to continue walking or “to walk better” is usually a primary goal. Vision, sensation, vestibular or cerebellar deficits, and muscle weakness need to be considered, all within the context of optimizing safety, when assessing balance. Evaluation and training are important to determine the most appropriate ambulation aid(s) to normalize the gait pattern with optimal alignment, and to improve stability with minimal energy expenditure. A person’s needs often vary with level of fatigue, temperature, distance to be walked, or time of day. Ambulatory patients may use a cane, one or two *lightweight* forearm crutches, or a four-wheel rolling walker (preferably with large swivel wheels, a flip-up seat, backrest and handbrakes) at different times of the day, week, or year. An ankle-foot orthosis (AFO), preferably custom-made, can effectively correct foot-drop secondary to weakness and/or fatigue. A motorized mobility aid, such as a scooter or a power wheelchair, is often appropriate for the ambulatory person with fatigue, when long distances must be covered and energy conservation is required. A motorized scooter is also useful for individuals with paraparesis or gait ataxia who retain good sitting balance, transfer skills, and trunk control. A power wheelchair would be more appropriate for individuals who are non-ambulatory and require additional seat and trunk support.

Posture/Trunk Control/Balance/Transfers

It is important to assess seated and standing posture as well as balance in static and dynamic conditions. Unsupported trunk control and good upper extremity strength are essential to maintaining functional transfer abilities. Wheelchair users or primarily sedentary individuals will develop problems with alignment, muscle imbalances, and poor endurance secondary to inactivity. The therapist needs to evaluate transfer control to and from bed, chair, toilet, car, and floor—noting quality, safety, and level of assistance needed for maximally independent function.

Range of Motion (ROM)

Both passive and active functional ROM should be assessed in the extremities and trunk.

Sedentary or inactive persons with MS often present with:

- ◆ Significant hip flexor, adductor, hamstring, and heel cord tightness
- ◆ Limited overhead upper extremity reach due to tightness in the pectoralis minor, major, and latissimus dorsi caused by slumped posture
- ◆ Poor head control due to postural and substitution patterns leading to tightness in the upper trapezius and posterolateral cervical musculature

Motor Function

The therapist should assess gross strength, with emphasis on *function*, in the extremities and trunk. Quality and control of movements, as well as substitution patterns, need to be noted. A key goal is to prevent or correct “secondary” or “disuse” weakness, commonly encountered by people with MS who have assumed a sedentary lifestyle or embraced compensatory movement patterns due to fatigue.

Weakness is commonly found in trunk, abdominal, and gluteal muscles. Poor scapular control, due to middle and lower trapezius weakness, and poor head control, due to weak high anterior neck flexors, are also common. These muscle imbalances frequently respond favorably to simple corrective exercises, including standing with good posture, when the individual is conscientious with his or her home program.

Neurological Function

Assessments of the following are necessary for development of treatment interventions (to supplement pharmacologic therapies) to improve safety, control, and function:

- ◆ Abnormal tone—noting nature and extent of hypertonicity (e.g. constant, fluctuating, or intermittent)
- ◆ Clonus
- ◆ Tremors—noting “resting,” “intention,” or both, and interference with function
- ◆ Coordination—gross, fine, rapid alternating
- ◆ Sensation
- ◆ Proprioception
- ◆ Pain

Referral to a psychiatrist or neurologist for additional treatment interventions may be warranted.

OTHER CONSIDERATIONS

- ◆ **Speech**—Evaluate the effectiveness and function of voice control, respiration, and swallowing. Arrange a consult with a speech-language pathologist, if needed.
- ◆ **Cognition**—Be alert to problems with memory, attention, concentration, and planning, which are common in MS. These must be considered in training, treatment, and home-program planning. Arrange a consultation with a neuropsychologist, occupational therapist, or speech-language pathologist if needed.
- ◆ **Emotional**—Assess verbal and non-verbal (body-language) signs, including anger, fear, frustration, denial, depression – especially unrealistic, inappropriate, or euphoric behaviors. (Feedback from family/caregivers can be very helpful.) There is often a need to promote acquisition of effective coping skills that facilitate successful adaptation to the challenges MS presents.
- ◆ **Social**—Assess the “support system” (family, friends, co-workers) for involvement and effectiveness, as well as the individual’s ability to maintain a balanced social life (outings, entertainment, etc.).
- ◆ **Vocational/Homemaking**—Explore possible limitations from fatigue, motor or sensory dysfunction, and cognitive issues. Ensure that safety is maintained.

TREATMENT PLANS AND GOALS

The primary goals are to develop a plan that is:

- ◆ Appropriate to meet individual needs
- ◆ Attainable
- ◆ Functionally-oriented
- ◆ Consistent with the priority needs identified by the individual

HOME PROGRAMS

The key components of a successful home program are that it is enjoyable, varied, goal-oriented, and realistic. Considerations include a person’s endurance, support-assistance from family and friends, motivation, level of understanding, and time constraints. Emphasis needs to be placed on corrective exercises to: (1) improve and maintain function (restoring alignment, mobility, and strength/ endurance lost due to inactivity/disuse or compensatory movement patterns); (2) manage spasticity (slow stretching, cold packs, controlled position changes); and (3) control energy management (careful pacing/ flexing work schedules, proactive resting vs. reactive “collapse,” avoiding overexertion/overheating, substitution of less stressful activities).

OPTIMAL FOLLOW-UP

Optimal follow-up will vary according to individual needs. It is always critical to consider physical and emotional needs, as well as family support, finances, insurance constraints, transportation, and weather.

SUMMARY

- ◆ Understanding, assessing, and managing the unique set of symptoms in each person with MS necessitates careful evaluation and appropriate follow-up.
- ◆ Recognizing the individual needs of each person with MS (physical, emotional, social, and vocation) is essential to a positive outcome.
- ◆ Setting individualized, realistic, appropriate, and functionally-oriented short- and long-term goals is essential to the rehabilitation process.
- ◆ Establishing home/community activity programs that are flexible, varied, appropriate, and effective is essential.
- ◆ Developing a current file of community resources for referral (equipment and programs, including helpful websites) is invaluable, including National Multiple Sclerosis Society (NMSS) programs, equipment, *cool* (<85 degrees) pools, and therapeutic recreational options. In most cases, the NMSS chapter will have resource lists that may be useful to both the PT and the clients.
- ◆ Empowering individuals to understand that MS is a challenging lifelong disease that, like arthritis or diabetes, requires lifestyle adaptations aimed at careful symptom management and basic good health. The greatest service health professionals can provide is to educate and assist each individual to optimize *control* and *quality* of his/her life, resulting in increased *safe independence*. Being available for consultations, and follow-ups as needed, reassures each individual with MS that the PT is a very important member of the health care *support* team.

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Bladder Dysfunction in Multiple Sclerosis

by Nancy J. Holland, RN, EdD

In dealing with individuals with multiple sclerosis (MS), it is important to note:

- ◆ **Bladder dysfunction is common in MS**, both in patients with minimal symptomatology and those with major impairments.
- ◆ **Bladder symptoms are often responsible for withdrawal from social and vocational activities.** Frequency, urgency, and incontinence are problematic for all types of interpersonal contact.
- ◆ **Bladder involvement may pose a serious threat to the individual's health**, and complications may be life threatening. Untreated bladder dysfunction can lead to serious morbidity.
- ◆ **Bladder symptoms are often mismanaged.** Incorrect treatment can precipitate acute urinary retention with damage to the detrusor (the primary bladder muscle), and urinary tract infections.
- ◆ **Support from health practitioners**, in both professional and social roles, is a major determinant in compliance with bladder management regimens.

NORMAL BLADDER FUNCTION

The involuntary detrusor muscle of the bladder provides the force needed to expel urine. The external sphincter, which contracts to hold back urine until voiding occurs, is voluntary muscle. At a volume of about 300–500 ml, simultaneous contraction of the detrusor and relaxation of the sphincter allow bladder emptying to occur.

NEUROGENIC BLADDER DYSFUNCTION IN MS

Dysfunction may occur in the detrusor, external sphincter, or coordination of their functions. The detrusor can be hyperactive, signaling the urge to void at very low urinary volume, or hypoactive, allowing a dangerously large amount of urine to accumulate before signals to void

are initiated. The external sphincter may contract during attempted urination, inhibiting urinary flow. Relaxation of the external sphincter is crucial, since even strong detrusor contractions will not empty the bladder if the exit is blocked by a tight sphincter.

ANALYSIS AND MANAGEMENT OF BLADDER SYMPTOMS

Begin by obtaining a detailed bladder history. Recurrent or persistent urinary tract infections (UTIs) and/or history of renal or bladder calculi require early consultation with a urologist. The algorithm below provides guidelines for assessment, including post-void residual (PVR) measurement, and intervention:

Algorithm for Analysis and Management of Bladder Symptoms (see following page)

Notes for the Algorithm

1. Testing for urinary tract infection (UTI)

- ◆ Use urinalysis/culture and sensitivity to test for UTI; have appropriate antibiotic therapy initiated if UTI is present.

2. Evaluation of post-void residual (PVR)

- ◆ Have patient well hydrated.
- ◆ When the patient experiences a desire to void, have him/her urinate and measure the volume.
- ◆ Measure the residual volume by ultrasound determination; use catheterization when ultrasound is not available.
- ◆ Add voided and residual volumes to determine the bladder capacity.

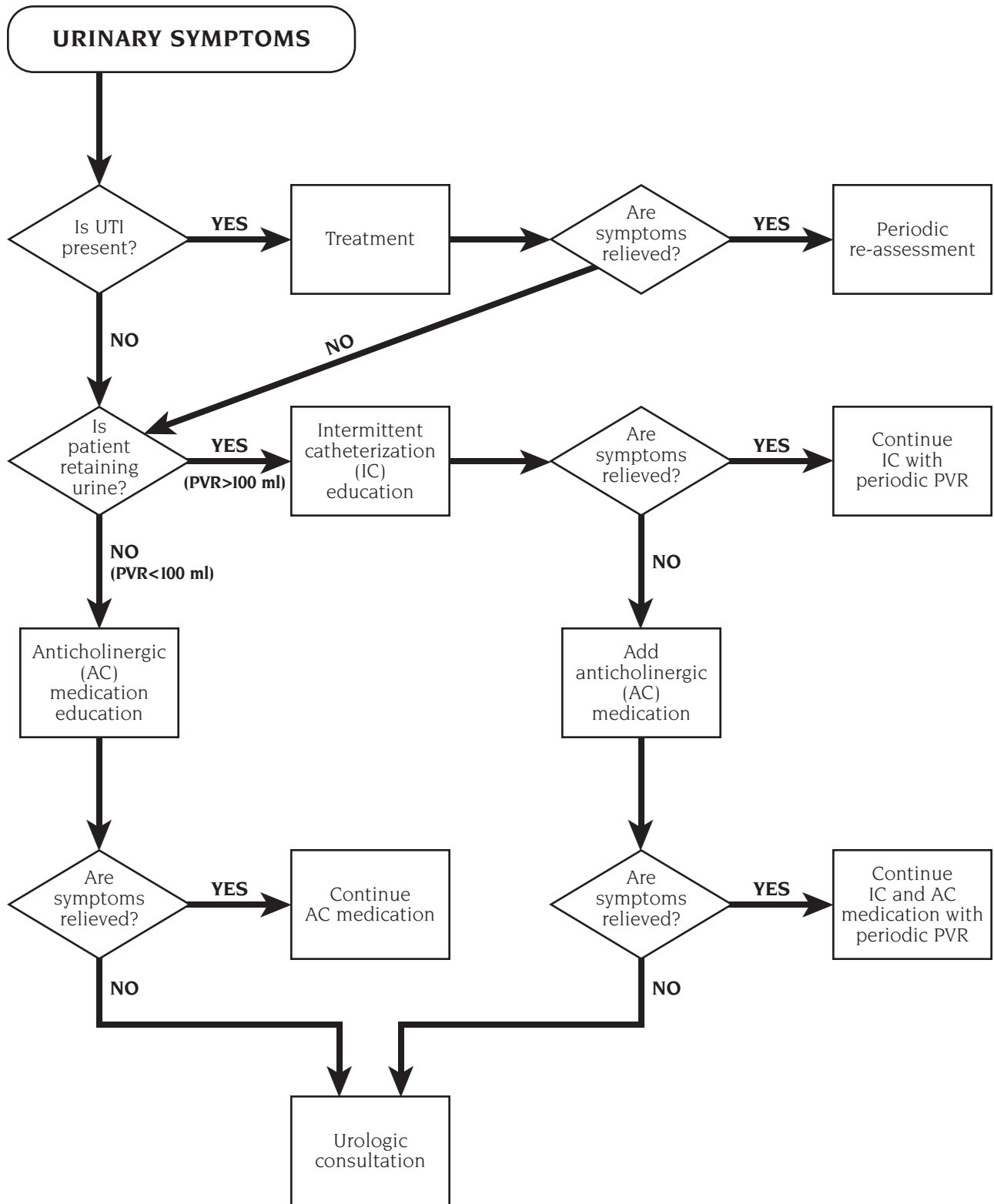
3. Intervention

- ◆ With the following information the experienced practitioner can estimate pathology and initiate therapy:

<i>Dysfunction</i>		<i>Management</i>
Storage	Capacity below 200 ml and/or residual less than 100 ml	Anticholinergic medications (e.g., Ditropan XL®, Detrol®)
Emptying	Residual greater than 100 ml	Intermittent catheterization
Combined	Residual greater than 100 ml; symptoms persist despite intermittent catheterization	Intermittent catheterization & anticholinergic medications

- ◆ It is important to re-assess bladder status periodically, including PVR.

Algorithm for Analysis and Management of Bladder Symptoms



4. Urologic consultation

- ◆ Inability to relieve symptoms by following this protocol requires urologic consultation. More serious interventions, such as surgery, may be needed for these individuals with advanced urologic impairment.
- ◆ Recognition of symptoms suggestive of neurogenic bladder dysfunction, and active participation in assessment, management, and patient teaching in this area, are important nursing responsibilities within a comprehensive team approach.



Additional Resources

National MS Society—Our website section on Planning & Independence (<http://www.nationalmssociety.org/Planning%20and%20Independence.asp>) includes a wealth of information about Health Insurance and Medicare, as well as Social Security Disability Insurance (see “Facilitating the SSDI Application Process: A Kit for Healthcare Professionals”).

Kaiser Family Foundation—The Kaiser Family Foundation provides in-depth information on key health policy issues including health insurance, the uninsured, Medicaid, Medicare, prescription drugs, global HIV/AIDS and more. www.kaiserfamilyfoundation.org

Families USA—Families USA is a national nonprofit, non-partisan organization dedicated to the achievement of high-quality, affordable health care for all Americans. www.familiesusa.org

Health Assistance Partnership—Health Assistance Partnership is a program of Families USA, and serves as an information and training resource for community-based Medicare and insurance consumer counseling services. www.healthassistancepartnership.org

Health Insurance Consumer Guides—The Georgetown University Health Policy Institute maintains a website of state-specific information on getting and keeping health insurance in all 50 states, plus Washington, DC. www.healthinsuranceinfo.net

For a glossary of health insurance terminology, see <http://www.insweb.com/learningcenter/glossary/health-a.htm>

RESOURCES ON MEDICARE

The Centers for Medicare and Medicaid Services—www.medicare.gov or 1-800-MEDICARE

The Center for Medicare Advocacy—www.medicarerights.org

The Medicare Rights Center—www.medicarerights.org

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