National Multiple Sclerosis Society

NATIONAL MS SOCIETY

Health Insurance Appeal Letters

— *A Toolkit for Clinicians* —

2ND EDITION

COVERAGE DENIALS & APPEALS

MODEL APPEAL LETTERS

ABSTRACTS OF STUDIES CITED IN LETTERS

NATIONAL MS SOCIETY EXPERT OPINION PAPERS & CLINICAL BULLETINS CITED IN LETTERS

COMMON TERMS & CONCEPTS IN THE APPEAL PROCESS

ADDITIONAL RESOURCES

Edited by Kimberly Calder, MPS

The National MS Society

The National MS Society funds a wide range of research initiatives, drives change through advocacy, facilitates professional education, collaborates with MS organizations around the world, and helps address the challenges of everyone affected by MS.

The National MS Society is the largest nonprofit organization in the United States supporting research for the treatment, prevention and cure of multiple sclerosis. Through its 50-state network of chapters and the combined efforts of volunteers, donors, researchers and health care professionals, the Society provides significant outreach, education and support to individuals and families who are impacted by the disease.

A TOOLKIT FOR CLINICIANS, 2ND EDITION

Health Insurance Appeal Letters

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.

Dedication

This publication is dedicated to the memory of Stephen Cooper, Esq. who served the National Multiple Sclerosis Society from 1997 to 2003, and initiated the Society's professional focus on the health insurance needs of people living with MS. It is an honor to continue his work through the promotion of accessible, affordable and adequate health coverage to every person touched by this disease.

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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
- denials of coverage for off-label use of FDA-approved drugs
- "fail first policies" (a.k.a. "step therapy")
- tiered drug benefits

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 has developed this guide, 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 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, is based on the procedures initially developed by the health insurance industry. Nearly two-thirds of all insured 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 these model appeal letters and materials. Many thanks to the numerous individuals who contributed to this effort. 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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Notes on the Second Edition

Since the launch of the first edition of this Toolkit in 2005, many would say that the US health care system has become even more complex, costly and burdensome for all concerned. Health care costs have continued to rise with no clear consensus on how to contain them. Health plans have responded by shifting more of the cost burden to patients, with even greater scrutiny of providers' clinical decision making. Medicare drug plans, pharmaceutical benefit managers (PBMs), specialty pharmacies, disease management and other entities have emerged as important stakeholders. Although most people with MS have health coverage, rising out-of-pocket costs, (especially co-payments and/or co-insurance for prescription drugs) jeopardize their adherence to treatment and force painful choices between health care and other necessities. Health care professionals specializing in the care of people with MS have expressed fear for the future of their practices, patients' welfare and research endeavors.

Despite these challenges, a common element of various efforts aimed at containing costs and improving the quality of care, such as electronic medical records, standardization of claims procedures and overall transparency, is clear, up-to-date and accessible documentation of patients' status, needs and treatments. The National MS Society has encouraged health care professionals to provide good documentation on their patients' behalf when requested by payers, employers, government agencies, disability and other insurers (provided confidentially is assured). Efforts such as this toolkit have been praised by clinicians for highlighting the types of documentation viewed as most effective by health plans, the Social Security Administration and others.

In addition to new appeal letters and corresponding citations on specific MS therapies, this toolkit includes a new and adaptable model appeal letter requesting a lower co-payment or co-insurance requirement for a patient. Although this letter has been used by people with MS who experienced a dramatic increase in their out-of-pocket cost for their disease modifying therapy, it can be adapted to assist patients' facing unaffordable co-payments for any covered service, treatment or equipment. Although a successful outcome is not guaranteed, filing an appeal of this type for patients with extraordinary needs and costs is a legitimate method of advocating for people with MS.

We hope the content and format of this toolkit encourages providers and their practice colleagues to pursue productive interactions with health plans and others committed to quality MS care.

AN OVERVIEW

Coverage Denials & Appeals

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, Medicare drug plans 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 drugs, dosages, quantities or routes of administration excluded from the formulary; for drugs or devices prescribed off-label; for services that are not covered, have exceeded the coverage limit 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 successful* 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. By law, Medicare prescription drug plans must provide for exceptions and appeals.

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.*

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 treatment, service or item medically necessary and indicated for this patient, at this point in time?
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 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.
4. Has the patient's co-payment or co-insurance amount for a covered service, drug or item recently risen and become un-affordable to the patient? *(See page 5)*

WHEN THE PROBLEM IS UN-AFFORDABLE COSTS TO THE PATIENT

As health plans shift more of the cost of care on to patients in the form of higher co-payments or co-insurance amounts for covered benefits, adherence to care suffers as patients' cost burdens become unaffordable. It is important for MS patients, caregivers and clinicians to know that appealing to a health plan for a lower co-payment or co-insurance amount is appropriate and encouraged when non-adherence is the alternative. Such appeals are most likely to succeed when the patient or clinician's letter accurately details exactly how and when a co-payment or co-insurance amount increased due to a formulary, tiering or policy change by the health plan. In such instances, a request for a return to the former, affordable cost-sharing arrangement (aka "grandfathering in") is warranted, especially when supported by details of the likely result on the patient if the exception is not granted. A model appeal letter requesting a lower co-payment or co-insurance amount for the patient is included in this toolkit.

THE ROLE OF PATIENTS, & HEALTH CARE PROFESSIONALS, IN THE APPEAL PROCESS

In most health plans, 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 is best viewed as a collaboration between patient and clinician. However, requests for exceptions to Medicare drug plan formularies and rules must be filed by the prescribing physician. 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, patients and providers should be aware that health plans have no legal obligation to accept appeals received after the timeframe spelled out in the insurance contract.

The role of HCPs in the appeal 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 it also provides 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.

THE APPEAL PROCESS

In general, the appeal process is similar in all plans, except Medicare prescription drug plans, which include additional rules and some different terminology. (See "Appealing to a Medicare Prescription Drug Plan" below.) 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) conducts this level appeal. Some plans allow the member or his/her representative to attend a meeting of the group and 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. *Remember, first and second level appeals must be exhausted first.*

EXCEPTIONS & APPEALS

Medicare Prescription Drug Plans

The following information and procedures for filing an exception or appeal is the same for stand-alone prescription drug plans (PDPs) and Medicare Advantage (managed care) plans that include drug coverage (MA + PD).

Note that by law, Medicare prescription drug plans must cover certain drugs, but are prohibited from covering many others. With a few exceptions, Medicare drug plans are prohibited from covering treatments for anorexia, fertility, cosmetic purposes or hair growth, cold relief, erectile dysfunction, as well as barbiturates, benzodiazepines, vitamins, minerals and other over-the-counter drugs. Additionally, drugs prescribed for off-label uses are likely to be denied unless its use is listed in one of three Medicare-approved drug compendia.

REQUEST AN EXCEPTION TO A MEDICARE PRESCRIPTION DRUG PLAN UNDER THE FOLLOWING CIRCUMSTANCES

- The medically necessary drug, preferred route of administration or dose is not on the plan's formulary;
- The prescribing physician believes the generic substitution provided in place of a prescribed brand name drug will be ineffective or cause harm;
- The plan imposes restrictions on the prescribed drug, including a prior authorization request, step therapy, or limits on the prescribed quantity.
- The prescribed drug is in a higher (more costly) "tier" than similar drugs on the formulary. Note that Medicare drug plan members will not be granted an exception for a request that a drug in a "specialty tier" be moved to a lower, less costly tier.

1. Your Medicare patient may not be aware that the drug you prescribed falls into one of the categories above until they attempt to fill or re-fill it. Your options will then be to either change the prescription, request an exception, or request an *expedited exception* in an emergency. Only clinicians licensed to prescribe medications can request an exception.
2. If you and your patient choose to request an exception, you (the prescriber) must state in writing that *your originally prescribed drug* is medically necessary, and you must include a justification for the specific exception request. Be sure to ask for an exception for the rest of the plan year or even indefinitely if the drug is for a chronic condition. To request an exception to a restriction (quantity limit, prior authorization request or step therapy for the rest of the year), state that the patient requires an *override to the restriction.*
3. You or your patient can find out where to send the exception request by calling the drug plan, checking their website, or the patient's member handbook (aka "Evidence of Coverage"). Make a copy for your patient, and keep one on file.
4. The plan must respond to your exception request within 72 hours, or 24 hours for an epedited exception. If the plan does not respond on time, the exception request is considered *denied.*
5. If the plan denies, or does not respond to your exception request on time, you may then file an *appeal.* Your patient may also wish to file a complaint with the plan if they did not respond on time.

See the section "Additional Resources on Health Insurance and Appeals" for additional help.

MODEL APPEAL LETTERS

Templates for Common Multiple Sclerosis 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 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. Remember that you and your patient only have two or three opportunities to win an appeal. It is easy to "waste" one of these opportunities through not coordinating all appeal efforts with your patient, or accidentally "appealing" to the health plan over the phone.

Note that all template letters are marked with italicized type wherever the prescriber needs to insert individualized text. For your convenience, all template letters are available on the enclosed CD in an easy-to-edit and user-friendly format.

Avonex

MODEL APPEAL LETTER

Today's date

Name (if known)
Company
Address

RE: NAME OF PATIENT, PATIENT'S INSURER ID NUMBER

Dear Sir or Ms.:

This is to support an appeal of your denial of Avonex, an interferon beta-1a, for my patient Mr./Ms. _____. 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 (or was referred to me) with symptoms including _____, 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[1]. 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. 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.

Finally, I include for your information, the National Multiple Sclerosis Society's "Disease Management Consensus Statement". Note the statement "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
CC: *(patient's name)*

Enclosure: "Disease Management Consensus Statement"

[1] Jacobs LD et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996, 39(3): 285–294.

Avonex Following First Demyelinating Event

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for *(review of your denial of coverage, prior authorization)* for Avonex for my patient *(patient's 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 immuno-modulating therapy for select patients with a first attack who are at high risk of MS.

Sincerely,
John Smith, MD
CC: *(patient's name)*

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[1] Jacobs LS, Beck, RW, Simon JH and the CHAMPS Study Group, *NEJM* vol. 343:13; 898–904.

[2] Kinkel RP, Kollman C, Glassman A, et al. Inferferon 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.

Betaseron

MODEL APPEAL LETTER

Today's date

Name *(if known)*
Company
Address

RE: NAME OF PATIENT, PATIENT'S INSURER ID NUMBER

Dear _____:

It has come to my attention that you have denied coverage for Betaseron to my patient Ms./Mr. _____, 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.)* Betaseron is the preferred therapy for him/her because: _____.

Unfortunately for people living with MS, each of these therapies causes side effects in most people. The range of clinical responses and side effects to these drugs 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 National MS 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

Enclosure: "Disease Management Consensus Statement"

[1] The IFNB Multiple Sclerosis Group, University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995, 45: 1277–1285.

Betaseron After First Demyelinating Event

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a *(request for pre-authorization, continued authorization or appeal of your denial)* for Betaseron *(interferon beta Ib)* for my patient _____ who experienced a documented episode of *(optic neuritis, paralysis, numbness, other—describe with detail)* suggestive of multiple sclerosis.

An 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 Interferon Beta 1b at this stage is the delay of a second event and diagnosis of clinically definite multiple sclerosis.

A multicenter, double-blind, placebo-controlled trial of 468 patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions randomized patients to either 250 mg IFNB-1b subcutaneously, or placebo until clinically definite MS (CDMS) was diagnosed or they had been followed for 24 months[1]. The treatment group showed delayed conversion to clinically definite multiple sclerosis.

A follow-up study of the same patients after three years showed 99 patients (37%) in the early treatment group developed CDMS compared with 85 patients (51%) in the delayed treatment group. Early treatment reduced the risk of CDMS by 41%[2].

I have enclosed for your information the treatment recommendations of the National Multiple Sclerosis Society's "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.

Sincerely,
John Smith, MD
CC: *(patient's name)*

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1 Kappos L, Polman CH, Freedman MS, Et. al., Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology.* 2006 Oct 10;67(7):1242–9. Epub 2006 Aug 16.

2 Kappos L, Freedman MS, Polman CH, et.al., Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet.* 2007 Aug 4;370(9585):389–97

Cooling Vests

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for *(appeal of your denial, pre-authorization, other)* for a cooling vest for my patient, *(patient's name)*, who lives with *(type)* multiple sclerosis. I prescribed this device to relieve *(him/her)* of various symptoms induced or exacerbated bv heat, including _____.

The ability of heat to aggravate symptoms in patients with definitive MS is well-established.

Cooling studies as early as 1959 have revealed positive symptomatic outcomes for patients with MS. Cooling can result in objective clinical improvements in several functional systems of heat-sensitive MS patients, according to a clinical study performed by P.K. Coyle, M.D. and colleagues[1]. The effects of cooling reinstate energy in heat-blocked axons, allowing neural activity restoration, enabling remyelination to provide protection for axons from further degeneration; and potentially slowing the destructive progression of MS.

In a double-blind, randomized study to determine the effect of daily cooling garment use, 84 patients with definite MS received either high-dose or low-dose cooling for one hour per day for one month. The high-dose cooling group demonstrated a small but significant improvement in function and reported less fatigue on standardized, objective measures in comparison to the lower-dose group[2].

Therefore, after careful consideration of *(patient's name)*'s needs, functional capability and symptoms including *(fill in specific details of relevant symptomatology and personal complaints)*, it is my conclusion that a cooling device would assist in improving *(patient's name)*'s overall quality of life as well as functional abilities.

I hope this information is helpful to you and others, and encourages you to think about the beneficial outcome for *(patient's name)* by *(reconsidering/authorizing) (him/her)* as a recipient of a cooling garment.

I look forward to your prompt response in this pressing matter.

Very Truly Yours,
John Smith, MD
CC: *(patient's name)*

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[1] Coyle P.K., Krupp L.B., Doscher C., et.al. Clinical and Immunological Effects of Cooling in Multiple Sclerosis. *Neurology* 1996; 10;1: 9–15.

[2] Schwid SR, Petrie MD, Murray R, et. al., A randomized controlled study of the acute and chronic effects of cooling therapy for MS. *Neurology,* 2003 June 24; 60(12): 1955–60.

Copaxone

MODEL APPEAL LETTER

Today's Date

Plan Name
Plan Address
Plan Address

Dear _____:

This is to support an appeal of your denial of Copaxone *(glatiramer acetate)* for my patient. 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 *(patient's name)* sought my assistance with symptoms including *(provide details from chart),* and has been definitively diagnosed with relapsing MS. Copaxone 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[1].

In 2009, a review of data from a 10 year extension of the trial mentioned above led to the conclusion that "The cumulative evidence for the long-term clinical efficacy of glatiramer acetate is consistent with its dual mechanism of action, reassures the physician that glatiramer acetate can really help improve patient care over the long term, and may contribute to a more positive view of prognosis for patients with multiple sclerosis[2]."

Finally, I include for your information the National Multiple Sclerosis Society's "Disease Management Consensus Statement". Note the statement "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 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
CC: *(patient's name)*

Enclosure: "Disease Management Consensus Statement"

[1] Johnson KP, Brooks BR, Cohen JA et. al., Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995; 45:1268–1276.

[2] Moreau T. Link of the mechanism of action of glatiramer acetate to its long-term data. *J Neurol Sci*. 2009 Feb 1; 277 Suppl 1:S12–5.

Copaxone After First Demyelinating Event

MODEL APPEAL LETTER

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, an exception to your formulary tier)* for my patient *(patient's name)*. I prescribed Copaxone *(glatiramer acetate)* for this patient after *(he/she)* experienced an episode of *(optic neuritis, numbness, other)* as documented in *(his/her)* medical record.

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 Copaxone is the delay of a second event and diagnosis of clinically definite multiple sclerosis.

In February, 2009, the US Food & Drug Administration approved an expansion of the Copaxone label indication to include "the treatment of patients with clinical isolated syndrome suggestive of multiple sclerosis". This expansion was pursued following initial results from a Phase III multi-center, double-blind clinical trial of 481 patients randomized to either Copaxone or placebo. After three years, the proportion of PreCISE study patients on placebo that developed clinically definite multiple sclerosis was 43% compared to 25% in the treatment group. The drug was well tolerated with 84% of participants completing the three year study. Known as the PreCISE Study, Dr. Giancarlo Comi and colleagues present results of this study at the Annual Meeting of the American Academy of Neurology in 2008 *(Abstract #LBS.003),* and their article is currently in publication.

Thank you for your consideration.

Sincerely,
John Smith, MD
CC: *(patient's name)*

Erectile Dysfunction Drugs for Men with MS*

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for *(a re-determination of your denial, or request for pre-authorization)* for the erectile dysfunction drug *(Cialis/tadalafil, Viagra/sildenafil or Levitra/vardenafil)* for my patient *(patient's name).* The erectile dysfunction he experiences is directly related to his multiple sclerosis, which was originally diagnosed in *(year of diagnosis).* As such, the prescription of *(Cialis, Viagra or Levitra)* is medically necessary and appropriate for reimbursement or coverage under his prescription drug benefits.

Sexual dysfunction is a common symptom of MS, affecting up to 80% of men[1]. Erectile dysfunction is the most common symptom of sexual dysfunction among men with the disease, attributable to neurologic impairment, side effects of disease modifying therapy, psychological factors, fatigue, or other factors[2].

Pharmacologic treatment for ED in men with multiple sclerosis is considered appropriate by experts in MS and sexual dysfunction. In a double blind, randomized study comparing sildanefil *(Viagra)* to placebo in men with MS, 95% of the treatment group reported improved erections. The drug was well-tolerated and resulted in significant improvement in general and disease-specific outcome measures[3].

Sincerely,
John Smith, MD
CC: *(patient's name)*

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1 Zorzon M, Zivadinov R, Bosco A, et. al Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. *Mult Scler.* 1999 Dec;5(6):418–27

2 Foley, frederick W., Ph.D., *'Assessment and treatment of sexual dysfunction in multiple sclerosis'.* National Multiple Sclerosis Society Clinical Bulletin, 2008.

3 Fowler CJ, Miller JR, Sharief MK, et. al. *A double blind, randomized study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. J Neurol Neurosurg Psychiatry.* 2005 May;76(5):700–5

* *NOTE: Medicare prescription drug plans are prohibited by law from covering drugs for erectile dysfunction, even when secondary to a diagnosed disease or condition. This letter is not recommended for use with Medicare drug plans.*

IntraVenousImmunoGlobulin (IVIG)

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is an appeal *(for re-consideration of your denial, request for pre-authorization, other)* of IntraVenousImmunoGlobulin (IVIG) for my patient *(patient's 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 (w/o 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 Oct;6 Suppl 2:S9–13,* Karl-Franzens University, Department of Neurology, Graz, Austria

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 Univ Hospital, Dept of Neurology, Rigshospitalet, Denmark

3 Treatment of corticosteroid refractory optic neuritis in multiple sclerosis patients with intravenous immunoglobulin, A. Tselis, J. Perumal, C. Caon et. al., European Journal of Neurology 2008

Sincerely,
John Smith, MD
CC: *(patient's name)*

Lower Co-insurance or Co-pay

MODEL APPEAL LETTER

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 on behalf of my patient, *(patient's name),* who lives with *(insert type of MS)* multiple sclerosis. This is a request for an exception to *(the co-insurance or co-payment amount of $_____)* for this drug for this patient only, to assure her/his continued adherence to treatment.

This patient has been taking *(insert DMD or other Rx here)* to manage *(his/her)* disease since *(date),* but is no longer able to afford the increased co-payment amount of *($_____).* There is no generic equivalent or lower-cost alternative to this drug at this time. Treatment with a disease modifying therapy for MS is standard therapy, and its termination at this time would be premature, harmful and truly substandard clinical management.

As highlighted by the enclosed publication of the National Multiple Sclerosis Society, lack of adherence to treatment with disease modifying therapy in MS is a serious problem attributed to many factors. Only recently have patients' out-of-pocket costs become a major contributing factor to this growing problem. As this patient's medical record will demonstrate, *(he/she)* has been adherent to treatment until this time; cost is the only reason for *(his/her)* inability to continue with this important treatment regimen.

Thank you for your consideration of this request.

Sincerely,
John Smith, MD

Enclosure

Neurontin

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is a request for reconsideration of your *(denial of coverage/pre-authorization, other)* for neurontin *(gabapentin)* for *(patient's name)*. 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 is 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 *(his/her) (examples: pain level, mobility, disability, quality of life, sleep, other—explain).*

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 demonstrated a 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 Feb;81(2):164–9,* U. of CO Health Sciences Center, Denver, PMID# 10668769; UI# 20132203 Abstract).

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 Mult Scler 1997 Aug;3(4):250–253 NeuroVirology Research Laboratory, VAMC, Salt Lake City, Utah, UI # 98039778 Abstract)

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
CC: *(patient's name)*

Enclosure

Neuro-Psych Evaluation

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is an appeal of your *(denial of claim, denial for pre-authorization)* dated _____ for a neuro-psychological evaluation of my patient *(patient's name),* who was diagnosed with definite multiple sclerosis in *(year).* As this patient's *(neurologist/treating physician)* I referred *(him/her)* for an assessment of possible cognitive impairment upon the patient's report of *(describe problems such as "difficulty with memory, simple tasks or household chores, at work or school, etc.).* It is my strong opinion that a thorough evaluation by an appropriate provider is necessary to determine the presence of cognitive impairments, their relation to the MS, and possible interventions.

Cognitive impairment is thought to occur in as many as 64% of people living with MS, and can include problems with learning and memory, impaired executive functions *(e.g., the ability to plan and prioritize),* slowed information processing, problems with attention and concentration, and impaired spatial relations. In some cases, severe cognitive impairment can pose a significant threat to a person's safety and independence. Neuro-psychological impairments in people with MS are manifestations of the disease process—just like the physical symptoms. Evaluations to determine their presence and severity are correctly processed by third party payers as medical, not mental health expenses.

The issues surrounding cognitive impairments in MS are more fully described in the enclosed Expert Opinion Paper on the *Assessment and Management of Cognitive Impairment in Multiple Sclerosis* by the National MS Society. Most significantly, the Society asserts "Because of the high incidence of cognitive impairment in MS, its potentially devastating consequences, as well as the advent of new therapies, periodic screening (e.g., every 1–2 years) is recommended." The Expert Opinions of the National MS Society are based on extensive literature review and reflect a consensus of opinion by the leading specialists and academics in the field of MS.

Effective interventions for cognitive deficits now exist. These include training in compensatory measures, counseling to address any behavioral changes and/or emotional responses, and medications to help manage symptoms and modify the progression of the MS itself.

I trust that this letter will address your need for additional information about the critical role of neuro-psychological testing for my patient. Please do not hesitate to contact me if I may be of further assistance.

Sincerely,
John Smith, MD
CC: *(patient's name)*

Enclosure

Novantrone

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is a request for *(prior authorization, re-authorization, or appeal of your denial of coverage)* of Novantrone *(Mitoxantrone)* for my patient *(patient's 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 _____.

As a clinician experienced in treating patients with various forms of multiple sclerosis, I believe it timely and medically necessary for *(patient's name)* 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. Evaluation of cardiac *(will be/was)* performed 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 (*The Lancet,* Vol. 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 *Journal of Neurology, Neurosurgery and Psychiatry* 1997; 62: 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
CC: *(patient's name)*

Enclosure: "Disease Management Consensus Statement"

Plasmapheresis

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for appeal of your *(denial/request for pre-authorization)* for plasmapheresis as second-line therapy for my patient *(patient's name)*, who suffers from a severe form of multiple sclerosis.

Plasma exchange or plasmapheresis is a successful method for treating autoimmune diseases, such as myasthenia gravis and Guillain-Barre Syndrome, because it removes the circulating antibodies that are thought to be responsible for them.

There are no established treatments for patients with acute, severe neurological deficits caused by MS or other inflammatory demyelinating diseases of the central nervous system (CNS) who fail to recover after treatment with high-dose corticosteroids. A controlled clinical trial followed by several confirmatory, prospective, non-randomized studies provides strong evidence for the effectiveness of plasmapheresis for acute attacks of multiple sclerosis, as I describe below. The prevailing opinion among leaders in the treatment of multiple sclerosis is that this procedure should be considered only in patients who have experienced acute, severe attacks of MS or other inflammatory demyelinating disease of the central nervous system AND who have failed corticosteroid treatment.

My records indicate that (*patient's name*) suffered an acute exacerbation of her disease on (*date*) including a worsening of *(list symptoms and describe deficits).* Standard corticosteroid therapy (*describe dosage, route of administration*) was initiated on (*date*), with little or no impact. I prescribed a course of plasmapheresis on (*date, other details as necessary*) as it is my professional judgment that it offers the greatest likelihood of benefit for my patient.

In 1999, Weinshenker and colleagues reported on their randomized trial of plasma exchange in actute CNS inflammatory demyelinating disease in the Annals of Neurology (1999;46:878–886). They concluded: "plasma exchange leads to functionally important neurological recovery in an important proportion of severely disabled patients with acute attacks of idiopathic inflammatory demyelinating disease."

A 2003 prospective, observational study of inpatients with severe demyelinating disease unresponsive to steroid therapy conducted in Spain also showed significant improvement when patients were treated with plasmapheresis. (Meca-Lallana JE et. al., Rev Neurol.2003 Nov 16-30;37(10)917–26.) The authors concluded "We consider plasmapheresis to be a safe, effective therapeutic procedure in the management of patients with MS and other demyelinating processes affecting the CNS."

Similarly, favorable results have been reported by Benneto L et al, J. Neurol 2004; 251: 1515–1521 in a variety of different acute attacks of multiple sclerosis in the U.K., and by Ruprecht K et al Neurology 2004; 63: 1081–1083 in German patients with severe, corticosteroid-refractory optic neuritis, which is a common type of attack that occurs in multiple sclerosis.

Please feel free to contact me at (*phone number*) if I may provide further details.

Sincerely,
John Smith, MD
Cc: *(patient's name)*

Enclosures

Power Scooter

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is *(a request for pre-authorization, an appeal of your denial, other)* for a power operated vehicle, POV or scooter for my patient *(patient's name)* who has been living with multiple sclerosis since *(date of diagnosis).*

The medical record on this patient will show reports of consistent and increasing difficulty with fatigue, the most common symptom of MS. His/her treatment for fatigue currently includes *(e.g., modafinil, amantadine, ritalin, other at "x" dose)* as well as *(e.g., use of cooling devices, reduced workload, exercise, use of cane or walker, other).* These have resulted in improvement based on *(patient self-report including _____, objective measures such as Modified Fatigue Impact Scale, and/or MS Quality of Life Inventory, other).* But *(his/her)* fatigue is worsening, and we have discussed the need for more advanced energy conservation strategies, and specifically the use of a scooter to allow *(him/her)* to *(maintain her job, improve quality of life, maintain ability to live independently, other).*

Currently, on days when *(patient's name)* is experiencing a "bad day" including more severe fatigue and weakness, *(he/she)* is unable to safely negotiate mobility inside *(his/her)* home. This includes the ability to safely evacuate the home during an emergency, thus posing a serious threat of harm until a suitable mobility device is provided.

In their review of the numerous issues involved in choosing an appropriate wheeled mobility device for a person with MS, Canning and Sanchez assert "Several physical, cognitive, and psychological issues unique to people with MS complicate their seating and mobility needs, including the changing and progressive nature of their impairments and the resulting fluctuations in physical performance, psychological adjustment to disability, and cognitive impairment[1]."

As the enclosed Expert Opinion Paper of the National Multiple Sclerosis Society on the Management of MS-Related Fatigue highlights, conserving energy is a cornerstone of managing MS-related fatigue. Such strategies allow the patient to save their energy for times when it is most needed, such as at work, performing activities of daily living, etc.

This patient is an excellent candidate for a power scooter, as *(he/she)* is ambulatory, is able to get in and out of a scooter unassisted and maintains sufficient upper body strength and arm/hand coordination to operate a scooter safely. *(Include objective measures).*

Address any remaining specific reasons mentioned in the denial notice, if applicable.

Thank you.
John Smith, MD
CC: *(patient's name)*

Enclosure

* *NOTE: If the denial suggests coverage is only provided for 'in the home use', add the following statement:*

[1] Canning, B and Sanchez, G. Manual Versus Power Wheeled Mobility for Clients with MS, *International Journal of MS Care,* Vol. 7, #3, Fall 2005 (Special Issue), 87–92.

Power Wheelchair, Enhancements to Current Power Chair

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for *(pre-authorization, appeal of your denial, other)* for a power wheelchair for my patient *(patient's name)* who was diagnosed with multiple sclerosis in *(date of dx). (Comment here on presence of co-morbidities as appropriate/relevant to power chair need).*

As the medical record will show, this patient has utilized a progression of mobility aides including *(cane, Canadian crutches, walker, standard wheelchair, scooter, etc.)*, which are no longer sufficient. The patient has experienced worsening *(spasticity, balance, pain—describe severity and location, upper body strength, other)* resulting in *(falls or fear of falling, lack of sensation, inability to transfer, other—describe fully).*

Currently, on days when *(patient's name)* is experiencing a "bad day" including more severe fatigue and weakness; *(he/she)* is unable to safely negotiate mobility inside the home. This includes the ability to safely evacuate the home during an emergency, thus posing a serious threat of harm until/unless an appropriate power mobility device is made available.

Add objective measures of physical functionality and cognition, including documented deterioration over time. Address patient's ability to more safely perform activities of daily living and instrumental activities of daily living when using a power chair.

(Patient's name) is not a candidate for a scooter for several reasons including *(e.g., poor upper extremity or trunk strength, fatigue, limited manual dexterity, inability to transfer safely, etc.)* A power chair allows *(patient)* to support *(his/her)* forearm while operating a joystick to control both the speed and direction of the chair.

The importance of selecting specific components to meet individual patients' needs are well supported by experts in MS[1,2]. The patient's specific power chair components were chosen for the following reasons. *(Provide rationale for any relevant items listed below including why any lower cost option does not address patient's functional need).*

- Type/model of chair
- Type of controller *(Joystick or another method used to drive the chair such as: Head array, Mini joystick, Electronic display, Gatlin midline or any alternative mount for joystick*
- Foot and arm support
- Types of wheels and tires, anti-tippers
- Accessories including wheelchair tray, tie down modification

If this is an appeal of a denial, address any specific issues included in denial notice that haven't already been addressed.

Sincerely,
John Smith, MD
CC: *(patient's name)*

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1 Canning B and Sanchez G. 'Manual Versus Power Wheeled Mobility for Clients with MS', *International Journal of MS Care* Vol 7:3, Fall 2005 (Special Issue), 87–92.

2 Save FS, Maximizing Comfort and Function: Positioning Intervention, Mobility for Clients with MS', *International Journal of MS Care* Vol 7:3, Fall 2005 (special Issue), 93–100.

Provigil

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is an appeal for re-consideration of your denial of coverage of modafanil *(Provigil)* for my patient *(patient's 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 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 200mg/day of modafinil significantly reduced fatigue and was well tolerated[1].

A review of *(patient's name)*'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 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 number or e-mail)* if I may be of further assistance.

Sincerely,
John Smith, MD

Enclosures

[1] Rammohan KW, Rosenberg JH, Lynn DJ, et. al, *Journal of Neurology, Neurosurgery, and Psychiatry 2002*; 72: 179–183.

Rebif

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

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 *(patient's 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 that compared 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 *(patient's 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
CC: *(patient's name)*

Enclosures: "Disease Management Consensus Statement"

1 PRISMS Study Group "Randomized double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; 352: 498–1504.

2 PRISMS 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.

Rebif After First Demyelinating Event

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

To whom it may concern:

This is a request for *(review of your denial of coverage, prior authorization)* for Rebif for my patient *(patient's 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 immuno-modulating therapy for select patients with a first attack who are at high risk of MS.

Sincerely,
John Smith, MD
CC: *(patient's name)*

Enclosure: National Multiple Sclerosis Society "Disease Management Consensus Statement"

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

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

Rehabilitation (PT)

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is a request for review of your denial of *(coverage, continuation of benefits, prior authorization, pre-approval)* for physical rehabilitation for my *(patient's 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. 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. *(See enclosed "Clinical Bulletin: Physical Therapy in Multiple Sclerosis Rehabilitation")*

The effectiveness of physical therapy in the MS population has been demonstrated. In 2008, Khan and colleagues reported MS patients randomized to individualized rehabilitation showed reduced disability and statistically significant differences in post-treatment Functional Independence Measure (FIM) scores, compared to the non-treatment group[1].

A study on risk of falls among persons with MS 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[2]."

Sincerely,
John Smith, MD
CC: *(patient's name)*

Enclosure

[1] Khan F, Pallant JF, Brand D et. al. Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomized controlled trial. *Journal of Neurological and Neurosurgical Psychiatry,* 2008 Nov;79(11): 1230–5.

[2] Cattaneo, DeNuzzo, et. al., Risk of Falls in Subjects with Multiple Sclerosis, *Arch Phys Med Rehabil* Vol 83, June 2002

Sterile Intermittent Catheterization

MODEL APPEAL LETTER

Today's date

Plan Name
Plan Address
Plan Address

Dear _____:

This is a *(request for pe-authorization, appeal of your denial, other)* for my patient *(patient's name)* who suffers from bladder dysfunction related to *(his/her)* multiple sclerosis. A medically necessary intervention of intermittent catheterization is the standard of care for this patient who has a history of recurring urinary tact infections (UTIs), and is required to avoid further complications.

In June 2008, Medicare updated the local coverage determination for urological supplies for beneficiaries with a history of recurring UTIs, as described in the following guidance to clinicians. Notably, the updated benefit provides for one sterile urological catheter and one packet of lubricant for each catheterization, up to 200 catheters per month.

www.medicarenhic.com/dme/medical_review/mr_bulletins/mr_bulletin_current/Urological_Physician_Letter_0608.pdf

This request is for supplies is necessary for *(patient's name)* to maintain a prescribed regimen of intermittent catheterization. Specifically, the supplies requested are:

#14 French *(Male or Female)* with coude tip urinary catheters and lubrication *(insert amount required per day or month)*

If this patient does not follow his/her schedule of catheterizations, *(he/she)* will be at risk of chronic bladder and kidney infections requiring medical intervention, and/or insertion of a permanent catheter. 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 *(phone number)* for further information.

Sincerely,
John Smith, MD
CC: *(patient's name)*

Tysabri

MODEL APPEAL LETTER

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 to request a *(reconsideration of your previous denial, pre-authorization, other)* for my patient, *(patient's name),* who lives with *(type)* multiple sclerosis to receive treatment in the form of intravenous infusion therapy with the drug Tysabri *(natalizumab).*

The "Indications and Usage" section of the United States FDA approved label for Tysabri is as follows: *"Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations... Tysabri is generally recommended for patients who have had inadequate response to, or are unable to tolerate, alternate MS therapies."*

(Patient's full name) is enrolled in the TOUCH *(Tysabri Outreach: Unified Commitment to Health)* Prescribing Program, a comprehensive risk management program developed in conjunction with the FDA to facilitate the appropriate use for Tysabri. Tysabri's distribution and administration is limited to TOUCH registered infusion centers. It is provided exclusively by trained clinicians who administer Tysabri in an ongoing assessment to specific patients who meet all requirements of the TOUCH Prescribing Program.

Tysabri was assessed over a two-year period in a randomized, multi-center, placebo-controlled, double blind study of 942 patients conducted in 99 sites worldwide. Known as the AFFIRM Study, overall reported results showed 92% fewer lesions detected by MRIs, a reduced risk of disability progression by 42% and an annual relapse rate decreased by 68%; in comparison to the placebo[1].

In another randomized, double-blinded, placebo-controlled trial performed by the International Natalizumab MS Trial Group, 213 patients with relapsing-remitting or relapsing secondary progressive MS received Tysabri over a course of 6 months; yielding an overall reduction rate of 50–80% in lesion formation[2].

Tysabri is the preferred therapy for this patient at this time as I believe it offers the greatest likelihood of delaying physical disability, reducing the frequency of shown relapses and inflammatory brain lesions. As the medical record will show, *(he/she has previously been treated with X, resulting in Y).*

I urge your *(reconsideration/authorization)*, and encourage you to refer to the MS Society's Disease Management Consensus Statement during your review of this claimant's file. I look forward to your prompt response in this urgent matter.

Very Truly Yours,
John Smith, MD

Enclosure: "Disease Management Consensus Statement"

[1] Polman CH, O'Connor PW, Havrdova E, et.al. AFFIRM Investigators, A Randomizes, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *NEJM* 2006; 354: 899–910.

[2] Miller DF, Khan OA, Sheremata WA, et.al. International Natalizumab Multiple Sclerosis Trial Group, A Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *NEMJ* 2003; 348;1: 15–23.

Avonex (Interferon Beta-1a)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Annals of Neurology 1996; 39: 285–294.

TITLE

Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis

AUTHORS

Jacobs LS, Cookfair DL, Rudick RA, et. al.

ABSTRACT

The accepted standard treatment of relapsing multiple sclerosis consists of medications for disease symptoms, including treatment for acute exacerbations. However, currently there is no therapy that alters the progression of physical disability associated with this disease. The purpose of this study was to determine whether interferon beta-1a could slow the progressive, irreversible, neurological disability of relapsing multiple sclerosis. Three hundred one patients with relapsing multiple sclerosis were randomized into a double-blinded, placebo-controlled, multicenter phase III trial of interferon beta-1a. Interferon beta-1a, 6.0 million units (30 micrograms), was administered by intramuscular injection weekly. The primary outcome variable was time to sustained disability progression of at least 1.0 point on the Kurtzke Expanded Disability Status Scale (EDSS). Interferon beta-1a treatment produced a significant delay in time to sustained EDSS (p=0.02). The Kaplan-Meier estimate of the proportion of patients progressing by the end of 104 weeks was 34.9% in the placebo group and 21.9% in the interferon beta-1a-treated group. Patients treated with interferon beta-1a also had significantly fewer exacerbations (p=0.03) and a significantly lower number and volume of gadolinium-enhanced brain lesions on magnet resonance images (p-values ranging between 0.02 and 0.05). Over 2 years, the annual exacerbation rate was 0.90 in placebo-treated patients versus 0.61 in interferon beta-1a treated patients. There were no major adverse events related to treatment. Interferon beta-1a had a significant beneficial impact in relapsing multiple sclerosis patients by reducing the accumulation of permanent physical disability, exacerbation frequency, and disease activity measured by gadolinium-enhanced lesions on brain magnetic resonance images. This treatment may alter the fundamental course of relapsing multiple sclerosis.

Avonex (Interferon Beta-1a)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Annals of Neurology 1996: 49: 285–294.

TITLE

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

AUTHORS

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

BACKGROUND & OBJECTIVE

A phase III double-blind, placebo-controlled clinical trial demonstrated that interferon beta-1a (IFN B-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 B-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 B-1a recipients who reached the primary study outcome.

3 Significantly fewer IFN B-1a recipients progressed to ESDD milestones of 4.0 (relatively severe impairment) or 6.0 (unilateral assistance needed to walk.)

4 Cox proportional hazards models demonstrated that the only bseline characteristic strongly correlated with longer time to disability progression was IFN B-1a treatment.

CONCLUSIONS

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

Avonex Therapy After First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

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; P50.002). 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.

Avonex Following First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

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 b-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 b-1a 30 micrograms IM once weekly in patients who experienced a first clinical demyelinating event. Results showed that IFNb-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 b-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 b-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 (n5100, IT group; n5103, 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 b-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 50.65; 95% CI, 0.43 to 0.97; p50.03). These results remain significant after adjusting for baseline variables independently associated with outcome (adjusted rate ratio 50.57; 95% CI, 0.38–0.86; p50.008). Overall, 36% of the IT group and 48% of the DT group developed CDMS by 5 years. Mean number of relapses over 5 years (6SD) was 0.9 (61.3) in the IT group compared with 1.7 (62.7) in the DT group (p50.008), representing a 47% reduction in the IT group. In both groups combined 13% of patients had an EDSS of > 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, p5–.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.

Betaseron (Interferon Beta-1b)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology 1993; 43: 655–661.

TITLE

Interferon Beta-1b is effective in relapsing-remitting multiple sclerosis

AUTHOR

The IFNB Multiple Sclerosis Group

ARTICLE 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.

Betaseron (Interferon Beta-1b)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology 1995; 45: 1277–1285.

TITLE

Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial

AUTHORS

The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group

ARTICLE ABSTRACT

Our previously reported multicenter, blinded, randomized, controlled study of two doses of interferon beta-1b (IFNB) in 372 patients demonstrated a reduction in relapse frequency and severity and in MRI activity. We now report the results of the continuation of that study. The median time on study was 46.0 months for the placebo arm, 45.0 months for 1.6 million international units (MIU), and 48.0 months for 8 MIU. IFNB had a persistent beneficial effect on exacerbation rate in the 8-MIU treatment arm, compared with placebo, in each of 5 years. Serial annual MRI was done in all patients, and 217 of the patients had either a fourth-or fifth-year scan. There was no significant progression of lesion burden in the 8-MIU arm in each successive year compared with baseline (at 4 years, p=0.917), whereas a highly significant increase in lesion area occurred in the placebo arm (p=0.001). Among the 154 non-completers, there was no systematic bias recognized that favored either treatment arm for the outcome measures of exacerbation rate, disability, or MRI activity. Dropouts in the placebo group had higher exacerbation rates and accumulation of MRI lesion burden than did dropouts in the other treatment arms, which probably reduced the power of the study to demonstrate treatment effects on these measures in the later years of the trial. Neutralizing antibodies to IFNB were detectable in 38% of patients by the third year and were associated with a significant attenuation of treatment effect on exacerbation rate. However, the reduction in exacerbation rate approached 50% in the antibody-negative 8-MIU group. For all patients, both baseline and endpoint lesion burden significantly correlated with disability. Increase in MRI lesion area was also significantly correlated with increase in disability over the course of the study, validating serial MRI as an outcome measure with clinical relevance. Since the 8-MIU treatment arm had significantly less lesion accumulation by MRI, a reasonable expectation is that IFNB will limit progression of disability. Confirmed disease progression occurred in fewer patients in the high-dose treatment arm (35%) than in the placebo arm (46%) (p=0.096). These results support but do not establish an effect of INFB in limiting progression of disability. This study was not originally powered to demonstrate a treatment effect on disease progression. At these levels of disability, more patients or longer follow-up, or both, would be required. Accordingly, additional clinical trials will be necessary to evaluate the role of IFNB in preventing disability.

Betaseron After First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology. 2006 Oct 10;67(7):1242–9. Epub 2006 Aug 16.

TITLE

Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes

AUTHORS

Kappos L, Polman CH, Freedman MS, Et. al.

OBJECTIVE

To assess efficacy, safety, and tolerability of every-other-day interferon beta-1b treatment in patients with a first clinical event suggestive of multiple sclerosis (MS) (clinically isolated syndrome).

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial. Patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions were randomized to interferon beta-1b (IFNB-1b) 250 mug subcutaneously (SC) every other day (EOD) (n=292) or placebo (n=176), until clinically definite MS (CDMS) was diagnosed or they had been followed for 24 months.

RESULTS

After 2 years, 45% of placebo patients had converted to CDMS (Kaplan-Meier estimate; primary outcome measure) and 85% fulfilled the McDonald criteria (co-primary outcome measure). Overall interferon beta-1b delayed the time to diagnosis of CDMS ($p < 0.0001$) and McDonald MS ($p < 0.00001$). Hazard ratios (95% CI) were 0.50 (0.36 to 0.70) for CDMS and 0.54 (0.43 to 0.67) for McDonald MS favoring treatment with IFNB-1b. Treatment was well tolerated, as indicated by the low rate of patients dropping out of the study before CDMS was reached (6.6% overall, 7.2% in the IFNB-1b group).

CONCLUSIONS

Interferon beta-1b 250 mug subcutaneously every other day delayed conversion to clinically definite multiple sclerosis, and should be considered as a therapeutic option in patients presenting with a first clinical event suggestive of multiple sclerosis.

Betaseron After First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Lancet. 2007 Aug 4;370(9585):363-4.

TITLE

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study

AUTHORS

Kappos L, Freedman MS, Polman CH, et. al.

BACKGROUND

Several controlled studies provide evidence that treatment with interferon beta in patients with a first event suggestive of multiple sclerosis (MS) delays conversion to clinically definite MS (CDMS). Our aim was to determine whether early initiation of treatment with interferon beta prevents development of confirmed disability in MS. METHODS: In the initial placebo-controlled phase of the double-blinded BENEFIT study, patients with a first event suggestive of MS and a minimum of two clinically silent lesions in MRI were randomized to receive either interferon beta-1b 250 microg (n=292) or placebo (n=176) subcutaneously every other day for 2 years, or until diagnosis of CDMS. Patients were then eligible to enter the follow-up phase with open-label interferon beta-1b. In the current prospectively planned analysis 3 years after randomization, the effects of early interferon beta-1b treatment were compared with those of delayed treatment initiated after diagnosis of CDMS or after 2 years on the study. The primary outcomes of this ITT analysis were time to diagnosis of CDMS, time to confirmed expanded disability status scale (EDSS) progression, and score on a patient-reported functional assessment scale (FAMS-TOI). This trial is registered with ClinicalTrials.gov, number NCT00185211. FINDINGS: Of the 468 patients originally randomized, 418 (89%) entered the follow-up phase; 392 (84%) completed 3 years' post-randomization follow-up. After 3 years, 99 (37%) patients in the early group developed CDMS compared with 85 (51%) patients in the delayed treatment group. Early treatment reduced the risk of CDMS by 41% (hazard ratio 0.59, 95% CI 0.44-0.80; p=0.0011; absolute risk reduction 14%) compared with delayed treatment. Over 3 years, 42 (16%) patients in the early group and 40 (24%) in the delayed group had confirmed EDSS progression; early treatment reduced the risk for progression of disability by 40% compared with delayed treatment (0.60, 0.39–0.92; p=0.022; absolute risk reduction 8%). The FAMS-TOI score was high and stable in both groups over the 3-year period (p=0.31). INTERPRETATION: Our data suggest that early initiation of treatment with interferon beta-1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS.

Cooling Vest

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurorehabilitation and Neural Repair, Vol. 10, No. 1, 9–15 (1996).

TITLE

Clinical and Immunological Effects of Cooling in Multiple Sclerosis

AUTHORS

Coyle P.K., Krupp L.B., Doscher Carol, Deng Zhidian, Milazzo Anthony

ARTICLE ABSTRACT

Multiple sclerosis (MS) patients often report that heat makes their symptoms worse. There is anecdotal evidence that the opposite, body cooling, may make MS symptoms better. The goal of this study was to determine whether core body temperature cooling compared to placebo treatment produced objective changes on the neurologic examination, and affected immune parameters, in MS patients. Eleven relapsing-remitting patients who reported heat sensitivity underwent cooling or sham cooling using a commercially available active liquid flow cooling garment. Clinical parameters of visual acuity, timed walk, muscle strength, and coordination, and immune parameters of cytokine production were examined one hour before and after treatment. Cooling produced a significant improvement in acuity, timed walk, and muscle strength compared to sham cooling. Cooling, but not sham cooling, also decreased cytokine production by MS peripheral blood cells. These results suggest that cooling can result in objective clinical improvements in several functional systems of heat-sensitive MS patients. In addition to a clinical effect, cooling may also have an immune effect on MS.

Cooling Vest

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology. 2003 Jun 24;60(12):1955–60.

TITLE

A randomized controlled study of the acute and chronic effects of cooling therapy for MS

AUTHORS

Schwid SR, Petrie MD, Murray R, Leitch J, Bowen J, Alquist A, Pelligrino R, Roberts A, Harper-Bennie J, Milan MD, Guisado R, Luna B, Montgomery L, Lamparter R, Ku YT, Lee H, Goldwater D, Cutter G, Webbon B; NASA/MS Cooling Study Group

BACKGROUND

Cooling demyelinated nerves can reduce conduction block, potentially improving symptoms of MS. The therapeutic effects of cooling in patients with MS have not been convincingly demonstrated because prior studies were limited by uncontrolled designs, unblinded evaluations, reliance on subjective outcome measures, and small sample sizes.

OBJECTIVE

To determine the effects of a single acute dose of cooling therapy using objective measures of neurologic function in a controlled, double-blinded setting, and to determine whether effects are sustained during daily cooling garment use. METHODS: Patients (n=84) with definite MS, mild to moderate disability (Expanded Disability Status Scale score < 6.0), and self-reported heat sensitivity were randomized into a multicenter, sham-treatment controlled, double-blind crossover study. Patients had the MS Functional Composite (MSFC) and measures of visual acuity/contrast sensitivity assessed before and after high-dose or low-dose cooling for 1 hour with a liquid cooling garment. One week later, patients had identical assessments before and after the alternate treatment. Patients were then re-randomized to use the cooling garment 1 hour each day for a month or to have observation only. They completed self-rated assessments of fatigue, strength, and cognition during this time, and underwent another acute cooling session at the end of the period. After 1 week of rest, they had identical assessments during the alternate treatment.

RESULTS

Body temperature declined during both high-dose and low-dose cooling, but high-dose produced a greater reduction ($p < 0.0001$). High-dose cooling produced a small improvement in the MSFC (0.076 +/- 0.66, $p=0.007$), whereas low-dose cooling produced only a trend toward improvement (0.053 +/- 0.031, $p=0.09$), but the difference between conditions was not significant. Timed gait testing and visual acuity/contrast sensitivity improved in both conditions as well. When patients underwent acute cooling following a month of daily cooling, treatment effects were similar. Patients reported less fatigue during the month of daily cooling, concurrently on the Rochester Fatigue Diary and retrospectively on the Modified Fatigue Impact Scale.

CONCLUSIONS

Cooling therapy was associated with objectively measurable but modest improvements in motor and visual function as well as persistent subjective benefits.

Copaxone (glatiramer acetate)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology 1995 Jul; 45 (7): 1268–76.

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. The Copolymer 1 Multiple Sclerosis Study Group

AUTHORS

Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB

ARTICLE 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 > or = 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)

Copaxone (glatiramer acetate)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

J Neurol Sci 2009 Feb 1;277 Suppl 1:S12– 5.

TITLE

Link of the mechanisms of action of glatiramer acetate to its long-term clinical data

AUTHOR

Moreau T

ARTICLE ABSTRACT

A consequence of the long-term nature of progression in multiple sclerosis is that treatment needs to be provided over the long term. Gathering evidence for long term clinical efficacy, safety and patient acceptance of immunomodulatory therapies is thus a critically important issue. However, pivotal trials, which generally last no more than two years, cannot address this issue. Glatiramer acetate is the only immunomodulatory treatment for which prospective data is available covering a treatment period of over a decade. In the long-term extension of the pivotal trial of glatiramer acetate, 108 patients have been followed for a mean treatment duration of 10.1 years. At the end of the treatment period, patients were experiencing a relapse only once every five years and 92% remained ambulatory throughout. Similar findings have been made in observational studies in the long-term follow-up of patients with relapsing remitting multiple sclerosis treated with glatiramer acetate under a compassionate use programme in France and in a patient registry in Argentina. Such data strongly suggest that a reduced risk of relapse represents a real long-term treatment effect. The cumulative evidence for the long-term clinical efficacy of glatiramer acetate is consistent with its dual mechanism of action, reassures the physician that glatiramer acetate can really help improve patient care over the long term, and may contribute to a more positive view of prognosis for patients with multiple sclerosis.

Erectile Dysfunction Drugs

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Clinical Neurology, University of Trieste, Trieste, Italy.

TITLE

Title: Sexual dysfunction in multiple sclerosis: A case-control study. L Frequency of groups.

AUTHORS

Zorzon M, Zivadinov R, Bosco A, Bragadin LM, Moretti R, Bonfigli L, Morassi P, Iona LG, Cazzato G

ARTICLE ABSTRACT

Sexual dysfunction is a very important but often overlooked symptom of multiple sclerosis. To investigate the type and frequency of symptoms of sexual dysfunction in patients suffering from multiple sclerosis, we performed a case-control study comparing 108 unselected patients with definite multiple sclerosis, 97 patients with chronic disease and 110 healthy individuals with regard to sexual function, sphincteric function, physical disorders impeding sexual activity and the impact of sexual dysfunction on social life. Information has been collected from a face-to-face structured interview performed by a doctor of the same gender as the patient. The disability, the cognitive performances, the psychiatric conditions and the psychological profile of patients and controls have been assessed. Sexual dysfunction was present in 73.1% of cases, in 39.2% of chronic disease controls and in 12.7% of healthy controls ($P < 0.0001$). Male cases reported symptoms of sexual dysfunction more frequently than female cases ($P < 0.002$). Symptoms of sexual dysfunction more commonly reported in patients with multiple sclerosis were anorgasmia or hyporgasmia (37.1%), decreased vaginal lubrication (35.7%) and reduced libido (31.4%) in women, and impotence or erectile dysfunction (63.2%), ejaculatory dysfunction and/or orgasmic dysfunction (50%) and reduced libido (39.5%) in men. Seventy-five percent of cases, 51.5% of chronic disease controls and 28.2% of healthy controls ($P < 0.0001$) experienced symptoms of sphincteric dysfunction. In conclusion, a substantial part of our sample of patients with multiple sclerosis reported symptoms of sexual and sphincteric dysfunction. Both sexual and sphincteric dysfunction were significantly more common in patients with multiple sclerosis than in either control group. Our findings suggest that a peculiar damage of the structures involved in sexual function is responsible for the dysfunction in patients with multiple sclerosis, but the highly significant lower frequency of symptoms of depression and anxiety in healthy controls may also imply a possible causative role of psychological factors.

Erectile Dysfunction Drugs

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery.

TITLE

A double blind, randomized study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis

AUTHORS

Fowler CJ, Miller JR, Sharief MK, Hussain IF, Stecher VJ, Sweeney M

OBJECTIVE

Identifying and effectively treating erectile dysfunction (ED) can result in an improvement of the quality of life (QoL) in men with multiple sclerosis (MS).

METHODS

This randomized, double blind (DB), placebo controlled, flexible dose study with an open label extension (OLE) assessed efficacy, QoL, and safety of sildenafil citrate in men with MS and ED. Overall, 217 men received sildenafil (25–100 mg; n=104) or placebo (n=113) for 12 weeks. Efficacy was assessed by the International Index of Erectile Function (IIEF) questionnaire that includes questions on achieving (Q3) and maintaining (Q4) an erection as well as a global efficacy question (GEQ). QoL was also assessed.

RESULTS

After 12 weeks, patients receiving sildenafil had higher mean scores for IIEF Q3 and Q4 compared with those receiving placebo ($p < 0.0001$), and 89% (92/103) reported improved erections compared with 24% (27/112) of patients receiving placebo ($p < 0.0001$). At the end of the OLE phase, 95% of men reported improved erections. Patients receiving placebo during the DB phase showed a nearly fourfold increase in improved erections (97% v 26%). Men receiving sildenafil also showed improvements in five of the eight general QoL questions compared with men receiving placebo ($p < 0.05$). The total mean score for the QoL questionnaire improved by 43% for the sildenafil group versus 13% for the placebo group ($p < 0.0001$). Treatment related AEs were predominantly mild in nature, and no patient discontinued due to an AE.

CONCLUSION

Sildenafil treatment for ED in men with MS was effective and well tolerated, and resulted in significant improvements in both general and disease specific QoL variables.

IntraVenousImmunoGlobulin (IVIG)

ABSTRACTS OF STUDIES CITED IN LETTERS

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

ARTICLE 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 body weight over 2 years was associated with a significantly more favorable course of disability as measured by the EDSS (20.23 vs. 0.12; p50.008) and caused a significant reduction of the frequency of relapses (0.52 vs. 1.26; p50.011). 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.

IntraVenousImmunoGlobulin (IVIG)

ABSTRACTS OF STUDIES CITED IN LETTERS

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; p50.03). During IVIG treatment, 15 patients were exacerbation free compared with only 7 (p50.02). 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.

IntraVenousImmunoGlobulin (IVIG)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Eur J Neurol. 2008 Nov;15(11):1145.

TITLE

Treatment of corticosteroid refractory optic neuritis in multiple sclerosis patients with intravenous immunoglobulin

AUTHORS

Tselis A, Perumal J, Caon C, et. al.

BACKGROUND

Patients with severe visual loss because of optic neuritis refractory to high dose corticosteroids have limited therapeutic options. The use of intravenous immunoglobulin (IVIG) has been advocated in the past, but data are scarce. In this study, we use a protocol different from those used in other studies, with different timing and dosage.

METHODS

Consecutive patients with corticosteroid-refractive optic neuropathy were treated with IVIG and compared with control patients who received only corticosteroids in an open-label, non-randomized, controlled prospective study.

RESULTS

Twenty-three patients received treatment with IVIG and 24 matched patients who did not receive treatment with IVIG were followed as controls. All patients had visual acuity 20/400 or worse in the affected eye. There was significant improvement in the IVIG group with 18/23 (78%) subjects reaching near normal vision (20/30 or better), compared with the control group with only 3/24 (12.5%) responding similarly.

CONCLUSIONS

The use of IVIG, following corticosteroids, may be useful using the protocol described herein, with sustained pulsed dosing. A larger controlled trial is indicated to confirm these results.

Neurontin (gabapentin)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Arch Phys Med Rehabil 81, February 2000.

TITLE

Gabapentin Effect on Spasticity in Multiple Sclerosis: A Placebo-Controlled, Randomized Trial

AUTHORS

Nancy C. Cutter, Dan D. Scott, Jane C Johnson, Gale 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 900mg 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 regiment.

MAIN OUTCOME MEASURES

The outcome measures were divided into two categories: subject self-report scales physician-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 gabepentin-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.

Neurontin (gabapentin)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Multiple Sclerosis (1997) 3, 250–253.

TITLE

Open label gabapentin treatment for pain in multiple sclerosis

AUTHORS

Maria K. Houtchens, John R. Richert, Arif Sami and John W. 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.

Novantrone (mitoxantrone)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Lancet 2002 360 (9350): 2018–25.

TITLE

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

AUTHORS

Hartung, HP, Gonsette R, Konig N, 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).

Novantrone (mitoxantrone)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Journal of Neurology, Nuerosurgery, and Psychiatry 1997; 62: 112–118.

TITLE

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

AUTHORS

Edan G, Miller D, Clanet M 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%v 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 (-1.1v + 0.3; $p < 0.001$). There was a significant reduction in the number of relapses (7 v 31; $p < 0.01$), and an increase in the number of patients free of exacerbation (14 v 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.

Plasmapheresis

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Ann Neurol. 1999 Dec;46(6):878–86.

TITLE

A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease

AUTHORS

Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, Pineda AA, Stevens LN, Rodriguez M

ABSTRACT

There are no established treatments for patients with acute, severe neurological deficits caused by multiple sclerosis or other inflammatory demyelinating diseases of the central nervous system who fail to recover after treatment with high-dose corticosteroids. We conducted a randomized, sham-controlled, double-masked study of plasma exchange without concomitant immunosuppressive treatment in patients with recently acquired, severe neurological deficits resulting from attacks of inflammatory demyelinating disease, who failed to recover after treatment with intravenous corticosteroids. Patients who did not achieve moderate or greater improvement after the first treatment phase crossed over to the opposite treatment. Moderate or greater improvement in neurological disability occurred during 8 of 19 (42.1%) courses of active treatment compared with 1 of 17 (5.9%) courses of sham treatment. The primary analysis was positive. Improvement occurred early in the course of treatment, and was sustained on follow-up. However, 4 of the patients who responded to the active treatment experienced new attacks of demyelinating disease during 6 months of follow-up. Moderate or greater improvement occurred during follow-up in only 2 of 13 patients who failed to improve during the treatment phase. Plasma exchange leads to functionally important neurological recovery in an important proportion of severely disabled patients with acute attacks of idiopathic inflammatory demyelinating disease.

Plasmapheresis

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Rev Neurol 2003 Nov 16–30;37(10)917–26.

TITLE

Plasmapheresis: its use in multiple sclerosis and other demyelinating processes of the central nervous system

AUTHORS

Meca-Lallana JE, Rodríguez-Hilario H, Martínez-Vidal S, et.al.

INTRODUCTION

We present a retrospective observation study aimed at analyzing the value of plasmapheresis in the management of patients with multiple sclerosis (MS) and other acute demyelinating processes affecting the central nervous system (CNS) who show severe exacerbations that do not respond well to conventional therapy with corticoids.

PATIENTS & METHODS

A total of 11 patients were included in the study: nine with MS, one disseminated acute encephalomyelitis and one case of transverse myelitis. All of them presented an acute or subacute neurological deficit, which prevented them from carrying out their day to day activities, with or without repercussions on the EDSS, and with the risk of suffering a severe residual disability after not responding to intravenous methylprednisolone pulses. Each patient was submitted to three exchanges per week, for 2 weeks, with association of orally administered prednisone and they were then evaluated after the last session and at one, six and twelve months.

RESULTS

Following plasmapheresis all the patients experienced a significant drop in disability and seven of them (77.7% of the total number with MS) even improved during the first month with respect to their basal situation (an extension of the Lazarus effect). After a year s follow up, 100% of the patients still maintained the basal situation that was recovered from before exacerbation, and only two relapses were recorded. The patients with MS presented a transient exacerbation after the second exchange. New therapy with immunosuppressants, immunomodulators or both was associated in eight cases.

CONCLUSIONS

We consider plasmapheresis to be a safe, effective therapeutic procedure in the management of patients with MS and other demyelinating processes affecting the CNS. Its use should be considered as first choice in severe relapses and in swiftly progressing forms that do not respond to intravenous methylprednisolone.

Plasmapheresis

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Rev Neurol 2003 Nov 16– 0;37(10)917–26.
Journal of Neurology. 2004 Dec;251(12):1515–21.

TITLE

Plasma exchange in episodes of severe inflammatory demyelination of the central nervous system. A report of six cases.

AUTHORS

Bennetto L, Totham A, Healy P, Massey E, Scolding N

ABSTRACT

The standard therapy for episodes of severe acute inflammatory demyelinating disease of the central nervous system is high dose intravenous corticosteroids. A small proportion of patients fail to improve with this regime and their prognosis can become grave. A recent sham controlled double blind crossover trial in this group of patients demonstrated a significant benefit from plasma exchange. We report six patients with severe acute steroid-insensitive inflammatory demyelinating disease of the central nervous system treated with plasma exchange. We observed a clear improvement in five of these six patients. Whilst complications of plasma exchange occurred these did not outweigh the benefits. Our study supports the use of plasma exchange in severe acute steroid-insensitive inflammatory disease of the central nervous system.

Provigil (modafinil)

ABSTRACTS OF STUDIES CITED IN LETTERS

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.

Rebif (Interferon B-1a)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Lancet 1998; 352: 498–1504.

TITLE

Randomized double-blind placebo-controlled study of interferon B-1a in relapsing/remitting multiple sclerosis

AUTHORS

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

BACKGROUND

Previous trials of interferon B in multiple sclerosis (MS) have shown efficacy, but the degree of clinical benefit remains uncertain, and the optimum dose is knot known. We undertook a double-blind, placebo-controlled study in relapsing/remitting MS to investigate the effects of subcutaneous interferon B-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 B-1a 22 micrograms (n=189) or 44 micrograms (n=18;4), 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 B-1a than with placebo (mean number per patient 1–82 for 22 microgram 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 microgram groups respectively, and the proportion of relapse-free patients was significantly increased ($p < 0.05$). Interferon B-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 B-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.

Rebif (Interferon B-1a)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Neurology 2001; 56: 1628–1636.

TITLE

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

AUTHORS

The PRISMS (Prevention of Relapses and Disability by Interferon B-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-B-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 B-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-B-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.

Rebif After First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

NEJM, 2000 Sep 28;343(13):898–904.

TITLE

Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group.

AUTHORS

Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW.

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 brain-stem or cerebellar syndrome) and evidence of prior subclinical demyelination on magnetic resonance imaging (MRI) of the brain. After initial treatment with corticosteroids, 193 patients were randomly assigned to receive weekly intramuscular injections of 30 microg 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 ($P < 0.001$), 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.

Rebif After First Demyelinating Event

ABSTRACTS OF STUDIES CITED IN LETTERS

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. Normalized 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

I41 (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.

Rehabilitation (PT)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

J Neurol Neurosurg Psychiatry, 2008 Nov: 79(11):1230–5.

TITLE

Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomized controlled trial.

AUTHORS

Khan F, Pallant JF, Brand C. et. al

OBJECTIVE

A stratified, randomized, waitlist controlled study over 12 months assessed the effectiveness of rehabilitation in persons with multiple sclerosis (MS) in an Australian community cohort.

METHODS

Patients with definite MS (n=101) recruited from a tertiary hospital database, randomized to a treatment group (n=49) for individualized rehabilitation programme or a control waitlist group (n=52). Functional Independence Measure (FIM) was used to assess "activity" while the Multiple Sclerosis Impact Scale (MSIS-29) and General Health Questionnaire (GHQ-28) assessed "participation" and quality of life (QoL). Assessments were at baseline and 12 months.

RESULTS

Analysis of data from 98 patients (treatment n=48, control n=50) showed reduced disability in the treatment group, with statistically significant differences in post-treatment FIM motor scores for the two groups ($p < 0.001$). There was a clinical and statistically significant improvement in FIM (motor) total scores ($p < 0.001$), and the FIM motor domains of: transfer ($p < 0.001$), locomotion ($p < 0.001$), self-care ($p < 0.001$) and the FIM cognitive subscale ($p < 0.016$). In the treated group, 70.8% improved compared with 13% of controls. Significantly more patients in the control group deteriorated over the study period (58.7% vs 16.7%; $p < 0.001$). There were no differences between the control and treatment group scores on the MSIS-physical ($p=0.18$), MSIS-psychological ($p=0.45$) or GHQ subscales.

CONCLUSION

An individualized rehabilitation programme reduces disability in persons with MS compared with no intervention. The impact of rehabilitation on QoL needs further evaluation. More information on the effectiveness of the various components of the multidisciplinary rehabilitation programmes are now needed. Australian clinical trials registry: Trials registration number: ACTRNO12605000676617.

Rehabilitation (PT)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

Arch Phys Med Rehabilitation 2002, 83: 854–7.

TITLE

Risks of Falls in Subjects with Multiple Sclerosis

AUTHORS

David Cattaneo, PT, Carmela De Nuzzo, PT, Teresa Fascia, PT, Marco Macalli, Ivano Pisoni, Ph.D.

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.

Tysabri (natilazumab)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

N Engl J Med. 2006 Mar 2;354(9):899–910.

TITLE

A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis

AUTHORS

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators

BACKGROUND

Natalizumab is the first alpha4 integrin antagonist in a new class of selective adhesion-molecule inhibitors. We report the results of a two-year phase 3 trial of natalizumab in patients with relapsing multiple sclerosis.

METHODS

Of a total of 942 patients, 627 were randomly assigned to receive natalizumab (at a dose of 300 mg) and 315 to receive placebo by intravenous infusion every four weeks for more than two years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability, as measured by the Expanded Disability Status Scale, at two years.

RESULTS

Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77; $P < 0.001$). The cumulative probability of progression (on the basis of Kaplan-Meier analysis) was 17 percent in the natalizumab group and 29 percent in the placebo group. Natalizumab reduced the rate of clinical relapse at one year by 68 percent ($P < 0.001$) and led to an 83 percent reduction in the accumulation of new or enlarging hyperintense lesions, as detected by T2-weighted magnetic resonance imaging (MRI), over two years (mean numbers of lesions, 1.9 with natalizumab and 11.0 with placebo; $P < 0.001$). There were 92 percent fewer lesions (as detected by gadolinium-enhanced MRI) in the natalizumab group than in the placebo group at both one and two years ($P < 0.001$). The adverse events that were significantly more frequent in the natalizumab group than in the placebo group were fatigue (27 percent vs. 21 percent, P=0.048) and allergic reaction (9 percent vs. 4 percent, P=0.012). Hypersensitivity reactions of any kind occurred in 25 patients receiving natalizumab (4 percent), and serious hypersensitivity reactions occurred in 8 patients (1 percent).

CONCLUSIONS

Natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing multiple sclerosis. Adhesion-molecule inhibitors hold promise as an effective treatment for relapsing multiple sclerosis. (ClinicalTrials.gov number, NCT00027300.).

Tysabri (natilazumab)

ABSTRACTS OF STUDIES CITED IN LETTERS

CITATION

N Engl J Med, 2003 Jan 2; 348(1): 15–23

TITLE

A controlled trial of natalizumab for relapsing multiple sclerosis

AUTHORS

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Connor PW; International Natalizumab Multiple Sclerosis Trial Group.

BACKGROUND

In patients with multiple sclerosis, inflammatory brain lesions appear to arise from autoimmune responses involving activated lymphocytes and monocytes. The glycoprotein alpha4 integrin is expressed on the surface of these cells and plays a critical part in their adhesion to the vascular endothelium and migration into the parenchyma. Natalizumab is an alpha4 integrin antagonist that reduced the development of brain lesions in experimental models and in a preliminary study of patients with multiple sclerosis.

METHODS

In a randomized, double-blind trial, we randomly assigned a total of 213 patients with relapsing-remitting or relapsing secondary progressive multiple sclerosis to receive 3 mg of intravenous natalizumab per kilogram of body weight (68 patients), 6 mg per kilogram (74 patients), or placebo (71 patients) every 28 days for 6 months. The primary end point was the number of new brain lesions on monthly gadolinium-enhanced magnetic resonance imaging during the six-month treatment period. Clinical outcomes included relapses and self-reported well-being.

RESULTS

There were marked reductions in the mean number of new lesions in both natalizumab groups: 9.6 per patient in the placebo group, as compared with 0.7 in the group given 3 mg of natalizumab per kilogram ($P < 0.001$) and 1.1 in the group given 6 mg of natalizumab per kilogram ($P < 0.001$). Twenty-seven patients in the placebo group had relapses, as compared with 13 in the group given 3 mg of natalizumab per kilogram ($P=0.02$) and 14 in the group given 6 mg of natalizumab per kilogram ($P=0.02$). The placebo group reported a slight worsening in well-being (a mean decrease of 1.38 mm on a 100-mm visual-analogue scale), whereas the natalizumab groups reported an improvement (mean increase of 9.49 mm in the group given 3 mg of natalizumab per kilogram and 6.21 mm in the group given 6 mg of natalizumab per kilogram).

CONCLUSIONS

In a placebo-controlled trial, treatment with natalizumab led to fewer inflammatory brain lesions and fewer relapses over a six-month period in patients with relapsing multiple sclerosis.

NATIONAL MS SOCIETY

Expert Opinion Papers & Clinical Bulletins Cited in Template Letters

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

Including a copy of the relevant Society Clinical Bulletin or Expert Opinion Paper 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 NATIONAL CLINICAL ADVISORY BOARD

- "Disease Management Consensus Statement"
- Changing Therapy in Relapsing Multiple Sclerosis: Considerations & Recommendations
- Assessment & Management of Cognitive Impairment in Multiple Sclerosis
- Management of MS-Related Fatigue
- Rehabilitation: Recommendations for Persons with Multiple Sclerosis
- Patient Access to Tysabri

CLINICAL BULLETINS ARE DISCUSSIONS OF TOPICS OF IMPORTANCE IN THE CLINICAL ASSESSMENT & MANAGEMENT OF MS & ITS SYMPTOMS

- Bladder Dysfunction in Multiple Sclerosis
- Cognitive Loss in Multiple Sclerosis
- Pain in Multiple Sclerosis
- Assessment & Treatment of Sexual Dysfunction in Multiple Sclerosis
- Spasticity

Disease Management Consensus Statement

EXPERT OPINION PAPER

National Clinical Advisory Board Of The National Multiple Sclerosis Society
Treatment Recommendations For Physicians

RECOMMENDATIONS

The Executive Committee of the National Clinical Advisory Board of the National Multiple Sclerosis Society has adopted the following recommendations regarding use of the current MS disease-modifying agents *(in alphabetical order):*

1. glatiramer acetate (Copaxone®)
2. interferon beta 1a—intramuscular (Avonex®)
3. interferon beta 1a—subcutaneous (Rebif®)
4. interferon beta 1b (Betaseron®)
5. mitoxantrone (Novantrone®)
6. natalizumab (Tysabri®)

- The Society recognizes that the factors that enter into a decision to treat are complex and best analyzed by the individual patient's neurologist.
- Initiation of treatment with an interferon beta medication or glatiramer acetate should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease, and may also be considered for selected patients with a first attack who are at high risk of MS.*
- Natalizumab is generally recommended by the Food and Drug Administration (FDA) for patients who have had an inadequate response to, or are unable to tolerate, other multiple sclerosis therapies.
- Treatment with mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with secondary-progressive multiple sclerosis who are worsening, whether or not relapses are occurring.
- Patients' access to medication should not be limited by the frequency of relapses, age, or level of disability.
- Treatment is not to be stopped while insurers evaluate for continuing coverage of treatment, as this would put patients at increased risk for recurrent disease activity.
- 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.

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* A relapse (also known as an *exacerbation* or *attack*) is conventionally defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month.

- 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; failure to do so is unethical and discriminatory.
- Movement from one disease-modifying medication to another should occur only for medically appropriate reasons.
- 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 glatiramer acetate and interferon beta 1a and 1b, mitoxantrone, and natalizumab. A number of positive outcomes have been demonstrated in people with relapsing disease: reduction in the frequency of relapses[1] [Betaseron[2–5]; Avonex[6–9]; Copaxone[10–11]; Rebif[12–14]; Novantrone[15]; Tysabri[16]]; reduction of brain lesion development, as evidenced by magnetic resonance imaging (MRI) [Betaseron2,[17–18]; Avonex[6–9]; Copaxone[19–21]; Rebif[12–14,22–23]; Novantrone[24]; Tysabri[16]] and the possible reduction of disability progression[25] [Betaseron[2,17–18]; Avonex[6–9]; Copaxone[10–11]; Rebif[12–14]; Novantrone[15,24]; Tysabri[16]].

Based on several years of experience with glatiramer acetate, interferon beta 1a and 1b and mitoxantrone, and the more recent experience with natalizumab, it is the consensus of researchers and clinicians with expertise in MS that these agents are likely to 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[26].

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 glatiramer acetate, interferon beta 1a, or interferon beta 1b, 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 mitoxantrone and natalizumab be available for judicious use in aggressive relapsing disease and for those not responding to other disease-modifying therapies.

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 interferon beta 1b. Since then, five additional agents that modify the underlying disease process have been approved by the FDA: glatiramer acetate, interferon beta 1a (intravenous and subcutaneous formulations), mitoxantrone, and natalizumab. The benefits of these agents include direct evidence of disease modification[1–24], 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 each may 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 "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 National MS Society's "Disease Management 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, 43% are not on disease-modifying therapy (National MS Society-funded Sonya Slifka Longitudinal MS Study, unpublished data).
- This is of particular concern in light of numerous studies[27–30] 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[31–32] 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 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 disease-modifying therapies, 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 National Clinical Advisory Board (formerly called the National 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 Society's National Clinical Advisory Board's Executive Committee provided final review of the document. The document has been updated as needed, with all revisions reviewed by the Executive Committee.

ROLE OF THE NATIONAL MULTIPLE SCLEROSIS SOCIETY

The mission of the National MS Society 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 National MS Society 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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Changing Therapy in Relapsing Multiple Sclerosis

Considerations & Recommendations of a Task Force of the National Multiple Sclerosis Society

EXPERT OPINION PAPER

National Clinical Advisory Board of the National Multiple Sclerosis Society
Treatment Recommendations for Physicians

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

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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Assessment & Management of Cognitive Impairment in Multiple Sclerosis

EXPERT OPINION PAPER

National Clinical Advisory Board of the National Multiple Sclerosis Society
Treatment Recommendations for Physicians

INTRODUCTION

This document is based on existing literature and expert opinion derived from clinical practice and experience. It is designed to help clinicians be sensitive to the possibility of cognitive deficits in their patients with MS, be more aware of the impact of such deficits, and learn about potential interventions to alleviate the negative consequences of these deficits.

SUMMARY

- Cognitive deficits appear to be present in more than half of MS patients, *however the majority of persons with MS do not have impairments that significantly impair daily functioning.*
- Learning/memory, speed of information processing, working memory, cognitive flexibility and other executive functions appear to be most commonly impaired.
- Periodic screening for such deficits is recommended.
- Intervention for such deficits is recommended:
  - Training in strategies to compensate for deficits
  - Counseling/psychotherapy for patients and family to address accompanying behavioral changes and emotional responses, and develop realistic expectations
  - Treatment with medications (disease-modifying and/or symptomatic therapies)

BACKGROUND

- Prevalence of Cognitive Dysfunction and MS: Studies suggest that cognitive impairment may occur in up to 50% of all MS patients *although the prevalence has not been adequately determined by prospective, population-based studies*[1,2,3,4]. The most common cognitive impairments are:
  - Impaired learning and memory[5,6,7,8], i.e., encoding, storage, manipulation, retrieval of information, especially episodic memory (experiential knowledge of events)
  - Slowed information processing[9,10,11,12], i.e., reductions in speed of thinking that can affect efficiency of cognitive function
  - Impaired working memory[13,14], especially alternating attention (or shifting attention back and forth between two stimuli—cognitive flexibility) and complex attention (simultaneously attending to multiple stimuli)

- While less common, deficits in spatial abilities and higher executive function are recognized and are detrimental to adaptive behavior[15,16].

IMPACT OF COGNITIVE FUNCTION

Studies have clearly shown that individuals with cognitive decline are at greater risk for employment problems[17]. Those with moderate to severe cognitive dysfunction also have difficulty with activities of daily living, may require personal assistance, and may experience problems in social situations[18,19,20]. The impact on family relationships is also significant[21,22]. Furthermore, the impact on driving may be great enough that the individual is no longer safe behind the wheel[23,24].

Often patients require cognitive evaluation to determine the extent to which their complaints, or the concerns of others, are related to actual MS related cognitive decline, or other confounding factors such as fatigue[25,26,27], and/or mood disorder[28,29,30]. Adherence to medication and other therapeutic regimens may also be affected by cognitive dysfunction; for example, training in injection techniques for disease modifying agents may present greater challenges in patients with cognitive dysfunction[31].

CORRELATION BETWEEN COGNITIVE DYSFUNCTION & OTHER MS CHARACTERISTICS

Cognitive impairment is difficult to predict on the basis of clinical presentation alone.

- Heterogeneity in cognitive deficits related to different disease courses is well established[32,33,34].
- Based on several studies[35,36,37], no or minimal correlation has been found between physical disability and cognitive deficits. In fact, some studies have shown defective cognitive function in patients with minimal physical disability[38,39,40].
- Depression can give rise to deficiency in working-memory capacity[41].
- Correlation between cognitive dysfunction and fatigue has been observed in some studies although not consistently[42,43]. In one study, subjective fatigue across the workday increased more for MS patients than for a control group but cognitive test performance was equal for the two groups[44].
- There is an ambiguous relationship between disease duration and cognition. Some researchers find correlation between length of disease and cognitive status, while others find no relationship[45,46,47].
- A recent study showed a gender-related effect of clinical and genetic variables on cognitive impairment in MS. Cognitive decline was predominant in men and was associated with clinical and genetic variables while cognitive dysfunction in women was independent of these variables[48].

MRI FINDINGS & COGNITIVE DYSFUNCTION

While many factors can contribute to cognitive impairment (e.g., depression, premorbid ability), the strong relationship between neuropsychological testing and brain MRI demonstrates that much of the problem is due to cerebral disease (recent studies show large effects on the order of r=0.71[49,50].).

- Many studies have shown that lesion volume is correlated with cognitive dysfunction in MS[51,52,53,54,55].
- Stronger correlations have emerged with measures of brain atrophy[56,57], and cognitive deterioration depends more on the development of brain parenchymal atrophy than on the extent of lesion burden in the brain[58].

- There are other promising MRI indicators that account for cognitive declines in MS, such as regional brain atrophy[59], diffusion-tensor imaging[60], and N-acetylaspartate (NAA—indicative of axonal integrity) levels[61], to name a few.

A goal for future research is to develop reliable neuroimaging methods that may be used to identify patients at risk for cognitive impairment[62,63,64].

RECOMMENDATIONS

Recommendations for Screening and Assessment

- *Providers should consider periodic screening and/or assessment for cognitive deficits in MS, as such deficits may not be always be apparent or reported.* Cognitive dysfunction may be difficult to detect because language skills and intellectual function are generally preserved[65]. Because of the high incidence of cognitive impairment in MS, its potentially devastating consequences, as well as the advent of new therapies, periodic screening (e.g., every 1–2 years) is recommended. Screening refers to the application of a simple, inexpensive test that attempts to identify patients that (a) may have a specified illness or condition and (b) would benefit from further evaluation (and in turn, treatment).
- Recommended approaches:
  - Query the patient as well as the family regarding cognitive function. Report by family members is closely correlated to cognitive deficits in the individual with MS[66]. Note that patient reports that are not confirmed by the family may reflect elevated depressive symptoms (e.g., poor self image) rather than true or measurable cognitive deficits. On the other hand, patients may not report symptoms that the family recognizes.
  - Utilize self- and informant-report questionnaires The most appropriate self-report instrument available at this time is the MS Neuropsychological Screening Questionnaire (MSNQ). This is a brief (5-minute) questionnaire that is completed by the patient and by a family member, and does not require a neuropsychologist or rehabilitation professional to administer or score[67].
  - Several other methods for screening for cognitive impairment have been proposed. Table 1 & 2 (see page 98–99) Financial and time constraints in an outpatient practice may limit the use of these instruments.

The evaluation approach should be tailored to the clinical needs of the patient or clinic. Brief objective testing batteries have been proposed for MS patients with known or suspected cognitive deficits[68,69]. There is also increasing interest in the use of single neuropsychological tests that can be administered to identify patients who are cognitively impaired[70,71].

Neuropsychological data can help identify areas of cognitive or behavioral change for such at-risk patients, and provide baseline data for later comparisons. However, before neuropsychological deficits are ascribed to multiple sclerosis, the influence of other medical conditions and medications should be considered.

In certain circumstances, *comprehensive* neuropsychological evaluation is appropriate to consider, including detailed exploration of deficits commonly associated with multiple sclerosis[72]. Other forms of cognitive evaluation may be administered by occupational and speech/language therapists (as well as other health care providers) as part of the assessment process, and to guide clinical care.

The most common indicators for comprehensive neuropsychological evaluation are:

- Maintenance of employment: Patients struggling to maintain competitive employment. These patients need a detailed review of residual strengths as well as weaknesses, so effective treatment can be designed and delivered, and appropriate accommodations made in the workplace. Some patients may be denied disability benefits on the basis of normal IQ testing, which lacks sensitivity to MS-associated cognitive impairment. It is important to evaluate higher executive functions in such patients.
- Independence in home and community: Patients struggling with family or household management, and/or activities of daily living benefit from a clear delineation of neurocognitive and neurobehavioral strengths and weaknesses.
- Educational attainment: Students of all ages whose educational activities require cognitive acumen, and who would benefit from knowing how their residual abilities and difficulties are likely to impact success in school, are also well served by more comprehensive neuropsychological evaluation. Test results also help guide recommendations for accommodation in the classroom.
- Differential diagnosis, and/or co-morbid conditions: Consider additional testing where it is necessary to rule out other neurological conditions such as Alzheimer's disease or depression. In addition, for some patients, the level of psychiatric distress or symptoms they develop may interfere with effective cognitive function, even though major cognitive deficits are not present. Cognitive re-evaluation is often recommended to ascertain whether there is evidence of cognitive decline. Other clinical problems related to longitudinal analysis include:
  - Significant cognitive worsening has occurred, accompanied by a major depressive episode; testing is needed to differentiate probable neurocognitive changes from mood disorder, to help guide pharmacologic and other treatments.
  - Cognitive function has continued to worsen in an older patient with MS, despite disease modifying therapies that have helped maintain physical function; there are concerns about a new, underlying cortical dementia such as Alzheimer's disease.
  - A patient, placed on medical leave from work secondary to cognitive problems at the time of a major exacerbation, has improved, and the employer requests documentation of current abilities to assist with successful return to work efforts.

RECOMMENDATIONS FOR INTERVENTION & MANAGEMENT

- *Intervention and management of cognitive dysfunction in MS is ideally performed by certified and/or licensed health professionals experienced in cognitive rehabilitation,* with medication management provided by physicians or other appropriate health care providers, e.g., nurse practitioners. Cognitive rehabilitation professionals include neuropsychologists, psychologists, speech-language pathologists, and occupational therapists. The physicians involved in medication management for cognitive problems are typically neurologists, psychiatrists, or physiatrists (rehabilitation medicine physicians). Ideally, these professionals should have an understanding of MS, including the disease process, common symptoms and findings, and medical treatments (and their side effects). In addition, an understanding of factors that may aggravate or complicate assessment, treatment and function of people with MS— especially temperature-sensitivity, fatigue, and affective disturbance—is desirable.

- *Interventions should be designed to improve the person's ability to function in all meaningful aspects of family and community life. Intervention should involve systematic, functionally oriented, therapeutic activities that are based on understanding of specific deficits.* Most commonly, compensatory strategies (i.e., utilizing intact skills and/or external aids) are used to improve daily functioning. Examples include: cognitive structuring (a learned, practiced approach used to routinize cognitive tasks); substitution strategies (the learned use of intact cognitive abilities to circumvent or bolster impaired abilities, such as using intact visual memory in place of impaired verbal memory function); scheduling and timelines; use of recording devices; memory strategies (e.g., lists, mnemonics, clustering, visualization techniques); templates for repeated tasks; organizational strategies; assistive technology (e.g., hand held computers, electronic calendars and memory logs), creating a structured environment; conducting conversations and activities in quiet places to minimize distraction; etc. Solution-focused, practical training in how to maximize function in spite of deficits, which can be generalized to the individual's everyday environment, is most desirable.

  Therapeutic activities designed to restore function (e.g., direct retraining) have also been attempted. However, evidence of effectiveness is ambiguous and controversial. Although the main body of literature suggests some benefit of intervention for people with MS[73,74,75,76,77,78,79,80,81], other studies have not demonstrated a benefit[82,83,84]. Furthermore, improvement of scores on standardized tests may not necessarily be correlated with improved function in everyday work or avocational situations.

- *In some circumstances, interventions should be accompanied by counseling/psychotherapy to address grief, decreased self-esteem, anxiety, and other emotional responses that may accompany cognitive deficits*. Concurrent emphasis on helping the individual redefine him/her-self, develop effective coping strategies, increase communication skills, and learn to take fullest advantage of his/her strengths to compensate for new areas of difficulties is paramount. Involvement of family members in counseling is critical; in order to facilitate the individual's accommodation to deficits, families need to adjust their expectations toreflect those deficits.

- *Like other clinical manifestations of MS, cognitive impairment—and especially worsening cognitive impairment as indicated by cognitive testing—is a sign of active disease, and should be viewed as justification for using disease modifying therapy or changing to a different immunomodulator, as well as other medications that may address cognitive symptoms.* (For further clarification on the use of disease modifying agents, see the Society's "Disease Management Consensus Statement"[85].) In patients who have dementia (some 10%–20% of MS patients[86]), medications shown to be effective for Alzheimer's disease and other types of dementia are appropriate[87,88,89]. These same medications show promise for mild cognitive impairment more often seen in patients with MS. A recent trial with Donepezil HCl suggested improvement in many aspects of cognitive function[90,91] though a smaller, earlier trial did not[92]. No benefit was found with the use of Amantadine® or 4-Aminopyridine in some studies[93,94] while improved attention was found in another[95]. Symptomatic treatment of fatigue and depression may also yield improvement in functional cognitive abilities.

RECOMMENDATIONS FOR FUTURE RESEARCH

More research is needed to further evaluate cognitive rehabilitation and intervention in people with MS across the spectrum of the illness.

Issues to be addressed include:

- Better outcome measures
- The role that individualized assessment might play before treatment
- Specific evaluation and treatment techniques
- Duration of treatment
- Duration of benefits

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Table 1

EXAMPLES OF MS SCREENING METHODS
(IN ORDER OF TIME REQUIREMENTS)

FIRST AUTHOR	DESCRIPTION	RECOMMENDED ADMINISTRATOR
Screening Examination for Cognitive Impairment in MS		
W. Beatty (1995)	*Brief selection of NP tests emphasizing tests of attention, memory and problem-solving requiring 25-30 minutes*	*Neuropsychologist, or other qualified rehabilitation specialist (e.g., occupational therapist, speech/ language pathologist, nurse practioner, etc.)*
Neuropsychological Screening Battery for MS		
S. Rao (1991)	*Brief selection of NP tests emphasizing processing speed and memory requiring 30–35 minutes*	*Neuropsychologist, or other qualified rehabilitatin specialist (e.g., occupational therapist, speech/ language pathologists, nurse practioner, etc.)*
Automated Neuropsychological Assessment Metrics—ANAM		
J. Wilken (2003)	*A computerized selection of NP tasks emphasizing tests of reaction time, processing speed, working memory, recognition memory, visual reasoning, and fine motor coordination requiring approximately 30 minutes*	*Neuropsychologist, or other qualified rehabilitation specialist (e.g., occupational therapist, speech/ language pathologist, nurse pracitioner, etc.)*

Table 2

EXAMPLES OF MS BRIEF NP TEST BATTERIES (IN ORDER OF TIME REQUIREMENTS)

FIRST AUTHOR	DESCRIPTION
Brief Repeatable Battery of Neuropsychological Tests in MS (BRB)	
S. Rao (1991)	*Tests were empirically derived from a larger battery of NP tests. Included are the Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, Selective Reminding Test, 10/36 Spatial Recall Test, and the Controlled Oral Word Association Test. Approximate administration time 60 minutes*
Minimal Assessment of Cognitive Function in MS (MACFIMS)	
R. Benedict (2002)	*Tests were rationally derived based on a consensus conference sponsored by the Consortium of MS Centers. Included are the Paced Auditory Serial Addition Test, Symbol Digit Modalities Test, California Verbal Learning Test—II, Brief Visuospatial Memory Test—Revised, Judgment of Line Orientation Test, Controlled Oral Word Association Test, and the Sorting Test from the Delis-Kaplan Executive Function System. Approximate administration time 90 minutes.*

Management of MS-Related Fatigue

EXPERT OPINION PAPER

National Clinical Advisory Board of the National Multiple Sclerosis Society
Treatment Recommendations for Physicians

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:
  - Management and elimination of any secondary causes of fatigue:
    - Treatment of any co-existing medical conditions (including depression) that are causing fatigue.
    - 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.
    - 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.

- 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.
- 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).
  - Appropriate rest to activity ratio
  - Use of assistive devices to conserve energy (motorized scooters are particularly useful for ambulatory people who experience fatigue when walking)
  - Environmental modifications to make activities more energy-efficient
  - Cooling strategies to avoid the fatigue caused by elevations in core body temperature due to heat, exercise-related exertion, and fever
  - Regular aerobic exercise, geared to the person's ability, to promote cardiovascular health, strength, improved mood, and reduce fatigue
  - Stress management techniques

- Treatment of primary MS fatigue:
  - 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:
    - 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.
    - 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.
    - 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.
  - 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.

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* Symmetrel is a registered trademark of Endo Pharmaceuticals
Provigil is a registered trademark of Cephalon, Inc.
Ritalin is a registered trademark of Novartis Corp.

Rehabilitation

Recommendations for Persons with Multiple Sclerosis

EXPERT OPINION PAPER

National Clinical Advisory Board of the National Multiple Sclerosis Society
Treatment Recommendations for Physicians

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.
- 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.

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* or nurse practitioner or physician's assistant

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

- 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
- 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.
- 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.

*** 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.

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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Patient Access to Tysabri

EXPERT OPINION PAPER

National Clinical Advisory Board of the National Multiple Sclerosis Society
Treatment Recommendations for Physicians

In June 2006, the U.S. Food and Drug Administration (FDA) approved the return to market of Tysabri (natalizumab), produced by Biogen Idec and Elan Pharmaceuticals, to delay the accumulation of physical disability and reduce the frequency of relapses (clinical exacerbations) in those with relapsing multiple sclerosis. The approval is based on positive results from two clinical trials showing that Tysabri significantly reduced the risk of sustained progression of disability and the rate of clinical relapse in those with relapsing MS[1,2].

The approval included creation of a mandatory registration program for patients and prescribing physicians, known as the TOUCH™ Program. The Food and Drug Administration describes the TOUCH Program as "a distribution program designed to assess the risk of progressive multifocal leukoencephalopathy (PML) associated with Tysabri, minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding TYSABRI use." While it is not clear that TOUCH can actually reduce the risk of PML, or death and disability due to PML, the program should lead to a better understanding of the incidence of PML among MS patients exposed to TYSABRI. Of the three people in clinical trials involving Tysabri who developed PML, two died and one had permanent, serious neural damage. The drug, which is taken by monthly IV infusion, is only dispensed at registered infusion centers across the country.

The Indications and Usage section of the FDA-approved label for Tysabri reads as follows:

"Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations... Tysabri is generally recommended for patients who have had inadequate response to, or are unable to tolerate, alternate MS therapies."

Tysabri should not be used in combination with any other immunomodulatory agent, and is not recommended for individuals who have compromised immune systems. Although the FDA has generally recommended Tysabri for use in patients with an inadequate response to other approved MS therapies, there is no present evidence-based standard for defining such an inadequate treatment response. This wording thus appears to give physicians considerable leeway in exercising their judgment when determining if Tysabri is an appropriate therapeutic option for a given patient. The Society's Expert Opinion Paper, "Changing Therapy in Relapsing Multiple Sclerosis" (*www.nationalMSsociety.org/docs/HOM/Exp_ChangTherapy.pdf*), outlines several possible markers of treatment failure as guidance for clinicians.

The label's reference to "relapsing forms of MS" has been misconstrued and may benefit from clarification. The four Disease Course Classifications (Relapsing-Remitting MS, Secondary-Progressive MS, Primary-Progressive MS, and Progressive-Relapsing MS) represent the results of an international survey of disease patterns in MS[3] and are now recognized worldwide as the standard approach to the description of MS at any stage. A relapse is conventionally defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least one month. The term "relapsing forms of MS" includes:

- Relapsing-Remitting MS (RRMS), which involves periodic relapses, followed by partial or complete recovery.
- Secondary-Progressive MS (SPMS) in those patients who were initially diagnosed with RRMS and convert to a course of steady progression several years later, but continue to have relapses.
- Progressive-Relapsing MS (PRMS), which is characterized by disease progression from onset with relapses superimposed along the way.

Patients in all three of these groups are considered candidates for Tysabri as long as they continue to have relapses. Patients with Primary-Progressive MS (which is progressive from onset and has no relapses) and those with SPMS and PRMS who are no longer experiencing relapses are not considered candidates for Tysabri. *(NOTE: The term chronic progressive MS is outdated and no longer recognized.)*

The Society encourages continued studies and analyses of existing data to help better predict favorable or unfavorable course of treatment. Until such time as additional evidence on Tysabri is available, decisions regarding the appropriate use of Tysabri should be made collaboratively—by the individual physician with expertise in MS and the patient—in order to ensure informed consent based on all known evidence of its safety and efficacy.

Clinicians are also encouraged to consider this Expert Opinion Paper, along with the Expert Opinion of the National Clinical Advisory Board entitled "Changing Therapies in Relapsing Multiple Sclerosis" as part of a process to determine a treatment plan.

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Bladder Dysfunction in Multiple Sclerosis

CLINICAL BULLETIN

Information for Health Professionals
by Nancy J. Holland, EdD, RN and Nancy C. Reitman, MA, RN

Effective bladder management strategies make it possible for people with multiple sclerosis (MS) to pursue daily activities of living and participate in the world of work with comfort, dignity and confidence. With appropriate diagnosis and treatment, the incidence of bladder complications is greatly diminished.

When treating people with MS, it is important to note that:

- *Bladder dysfunction is common in MS,* in people with minimal symptoms and those with major impairments.
- *Bladder symptoms may be responsible for withdrawal* from social and vocational activities. Frequency, urgency, and incontinence may negatively affect interpersonal interaction.
- *Bladder involvement may threaten the individual's health,* with complications leading to serious morbidity.
- *Bladder symptoms are often mismanaged,* precipitating such problems as acute urinary retention, dam age to the detrusor (primary bladder muscle) and urinary tract infections (UTIs).

NORMAL BLADDER FUNCTION

The bladder wall consists of three main layers: the mucosa, submucosa, and detrusor muscle. The detrusor, a thick layer of smooth muscle, expands to store urine and contracts to expel urine. Storage and emptying of the bladder are regulated by the internal and external urethral sphincters. Sphincters are normally in a closed position, needing stimulation to open. Continence depends on sphincter-detrusor coordination.

When approximately 250 to 300 cc of urine fill the bladder, the internal pressure activates stretch receptors in the bladder wall. The stretch receptors signal the nervous system, small contractile waves occur in the detrusor muscle, and the internal urethral sphincter automatically relaxes. The external sphincter is consciously tightened and the urge to urinate becomes apparent. Voluntary voiding occurs when two actions occur simultaneously: the detrusor muscle contracts to expel the urine and the external sphincter relaxes and opens to allow the urine to pass freely into the urethra and out of the body.

NEUROGENIC BLADDER DYSFUNCTION IN MS

The demyelination of MS interferes with signals between the bladder, the spinal cord, and brain, causing urination to become less controlled. Dysfunction may occur in the detrusor, external sphincter, or in the 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.

- Storage Dysfunction: Storage dysfunction may be caused by an over-active detrusor muscle that contracts prematurely, as soon as a small amount of urine enters the bladder, continually signaling the need to void. The bladder does not fill to normal capacity, which results in the following symptoms:
  - Urgency: inability to delay urination
  - Frequency: need to urinate repeatedly
  - Nocturia: need to urinate during the night
  - Incontinence: inability to control time and place of urination

EMPTYING DYSFUNCTION

Demyelination in the spine interrupts signals to the voiding reflex, resulting in failure to empty the bladder. The bladder fills, but the spinal cord is unable to send the signal to the brain to relax the sphincter, causing the bladder to retain urine and sometimes fill beyond normal capacity. Emptying dysfunction can lead to:

- Urgency
- Dribbling: uncontrolled leaking of urine
- Hesitancy: delay in ability to urinate, though need to void is experienced
- Incontinence
- Infection

COMBINED DYSFUNCTION

Detrusor–external sphincter dyssynergia—or failure to store combined with failure to empty—occurs as a result of the lack of coordination between muscle groups. Urine is trapped in the bladder, leading to:

- Urgency
- Hesitancy
- Dribbling
- Incontinence (detrusor hyperreflexia)
- Infection

URINARY TRACT INFECTION

People with MS who are unable to empty their bladder because of bladder emptying dysfunction increase their risk for UTI development. Retained urine may encourage the growth of bacteria and allows mineral deposits to settle and form stones that irritate bladder tissues. The symptoms of a UTI are:

- Urgency
- Frequency
- Dysuria: burning sensation during urination
- Abdominal or lower back pain
- Fever
- Increased spasticity
- Dark, foul-smelling urine

Because sensory loss may prevent people with MS from noticing some of these symptoms, they should pay particular attention to any significant changes in the color or smell of their urine, or any abrupt increase in other MS symptoms.

An abrupt increase in symptoms could signal a pseudoexacerbation, defined as a temporary flare-up of symptoms—unrelated to new damage in the central nervous system—which is typically caused by an elevation in core body temperature resulting from an infection, heat and/or humidity, or strenuous exercise. The elevated body temperature interferes with nerve conduction, resulting in symptoms such as muscle weakness, tingling, blurred or double vision and more spasms. The symptoms generally return to baseline without treatment once the body temperature returns to normal. Since pseudoexacerbations are common with UTIs, it is important to check for a bladder infection when a patient reports a sudden worsening of MS symptoms.

ANALYSIS AND MANAGEMENT OF BLADDER SYMPTOMS

Obtain a detailed bladder history. Recurrent or persistent urinary symptoms require early consultation and assessment by a urologist, most appropriately one who is experienced in MS.

ALGORITHM FOR ANALYSIS AND MANAGEMENT OF BLADDER SYMPTOMS, DIAGRAM 1 (SEE PAGE 119)

Notes for the Algorithm:

- Testing for UTI
  - Use urinalysis/culture and sensitivity to test for UTI. Have appropriate antibiotic therapy initiated if UTI is present.
- Evaluation of post-void residual (PVR)
  - Person must be well-hydrated.
  - When person needs to void, have him/her urinate and measure volume.
  - Measure residual volume in bladder by ultrasound or catheterization.
  - Add voided and residual volumes to determine bladder capacity.
- Intervention
  - Storage dysfunction
    - Capacity below 200 ml and/or residual less than 200 ml
      - Ditropan XL, Detrol, Oxytrol (transdermal system), Pro-Banthine (anticholinergics) and Vesicare, Sanctura, Enablex (antimuscarinics) are first-line medications
      - DDAVP or desmopressin acetate, a hormone nasal spray, temporarily reduces amount of urine produced, allowing more restful sleep
      - Pelvic floor exercises
      - Behavioral techniques—limiting caffeine, maintaining adequate fluid intake during day
      - Absorbent pads (men and women) and for men a condom-like sheath that connects to drainage
      - Assess mobility issues (proximity to toilet)

- Emptying dysfunction
  - Residual greater than 200 ml
    - Intermittent self catheterization (ISC)
    - Dietary changes to increase acidifying urine Assess mobility issues (proximity to toilet)
    - Antispasmodic medications, such as Lioresal or Zanaflex
    - Flomax, Hytrin, Minipress (sympatholytics) that increase urine flow
- Combined or detrusor–external sphincter dyssynergia (DESD)
  - Residual greater than 200 ml
  - Symptoms persist despite intermittent catheterization
    - Intermittent catheterization
    - Anticholinergic medications, e.g. Detrol
    - Antispasmodic medications, such as Lioresal, Zanaflex
    - Minipress, Flomax,or Hytrin to promote urine flow
    - Botox or botulinum toxin, injected into the sphincter or bladder wall has been found to be safe and effective in clinical trials, but is not yet FDA approved for this purpose.

- Urologic consultation
  - Inability to relieve symptoms by following these protocols requires urologic consultation.
  - Additional diagnostic measures may be needed: ultrasound, radioisotope renal scan, intravenous pyelogram (IVP), urodynamic studies, cystoscopy.

UROLOGIC HEALTH

The person with MS and urinary dysfunction may become socially isolated due to fear of bladder difficulties such as incontinence. A thorough assessment and evaluation by the healthcare practitioner is imperative in discerning problems that may be compromising quality of life. It is imperative to re-assess symptoms and repeat tests such as PVR. 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.

RECOMMENDED RESOURCES

Readings:

- De Seze M, Ruffion A, Denys P, et al. The neurogenic bladder in multiple sclerosis: Review of the literature and proposal of management guidelines. *Multiple Sclerosis* 2007 Mar; 13:915.
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ORGANIZATIONS

National Association For Continence
1-800-BLADDER
www.nafc.org

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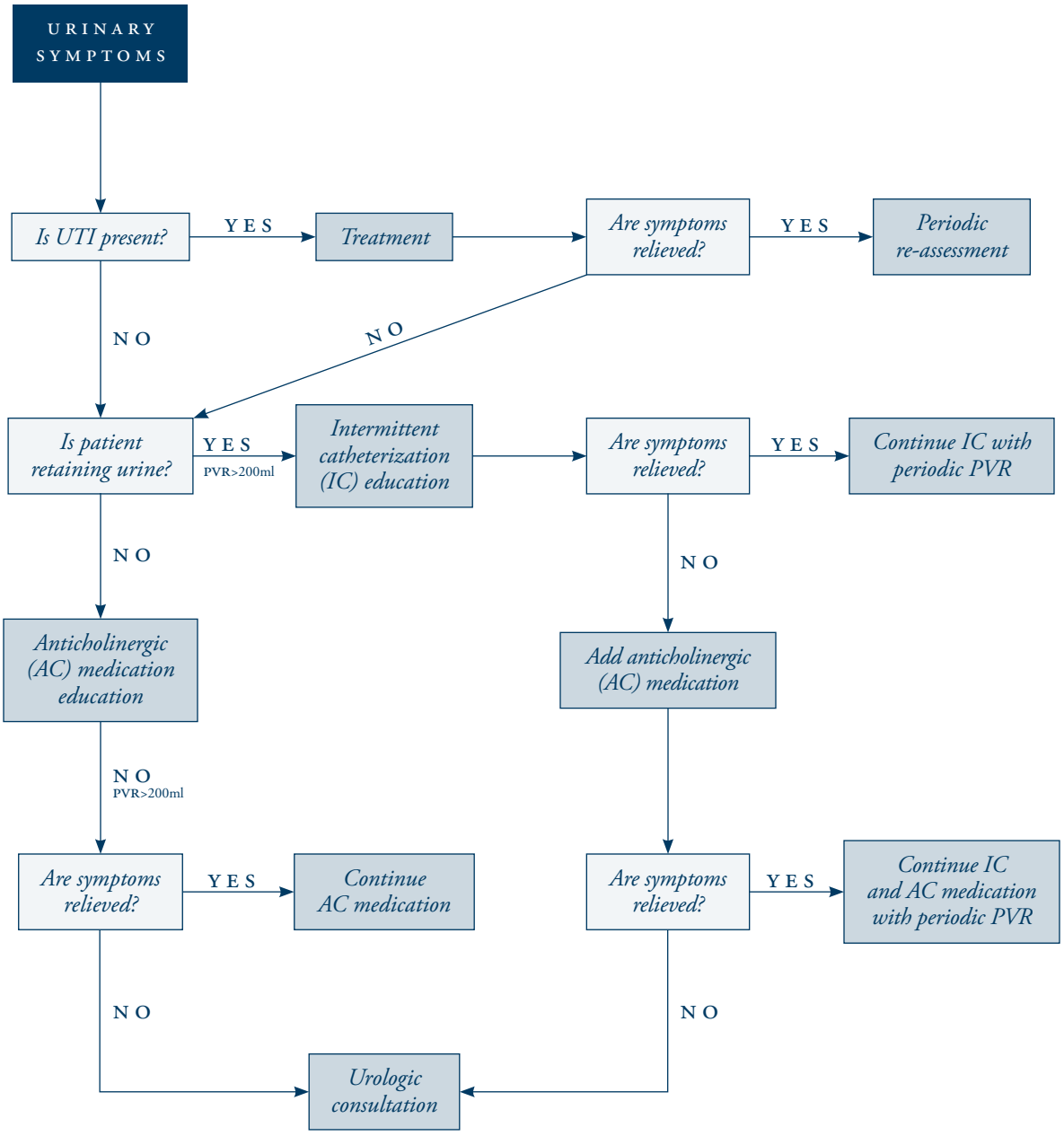
Diagram 1

ALOGORITHM FOR ANALYSIS &
MANAGEMENT OF BLADDER SYMPTOMS



Cognitive Loss in Multiple Sclerosis

CLINICAL BULLETIN

Information for Health Professionals
by Randolph B. Schiffer, MD

Adapted with permission from Schiffer RB. Cognitive loss. In van den Noort S, Holland N (eds): *Multiple Sclerosis in Clinical Practice.* New York: Demos Medical Publishing, 1999.

Neuropsychological studies have provided evidence of disease-based cognitive loss in a substantial number of patients with MS, possibly as many as 50%. These cognitive deficits often go unnoticed by the physician, and may not be recognized even by the patients themselves. They can have an appreciable effect, however, on the lives of the patients and their family members. In addition to causing a significant amount of emotional distress, cognitive deficits are a primary cause of early departure from the workforce.

COGNITIVE FUNCTION AFFECTED BY MS

Though patients vary greatly, the following cognitive impairments have been most commonly reported:

- Slowed information processing
- Impaired attention and concentration, especially "alternating attention" (the need to shift attention back and forth between two stimuli) and "divided attention" (simultaneously attending to multiple stimuli)
- Impaired recent memory, especially "explicit memory" (explicitly instructed information meant for learning and remembering) and "episodic memory" (the memory of events and of information that is seen, read, or heard)
- Impaired executive functions, such as concept formation, reasoning, problem-solving, and planning and sequencing

Cognitive impairment is difficult to predict on the basis of clinical indicators. In general, relapse rates and changes in neurologic disability are poor predictors of the degree of cognitive dysfunction. Patients may be mildly affected physically but present with significant cognitive dysfunction.

Severely disabled persons, on the other hand, may experience no cognitive declines. As a group, secondary progressive patients are more likely to demonstrate cognitive symptoms.

Recent attention has been directed toward MRI predictors of cognitive impairment. Several indices of cerebral damage have been positively correlated with the severity of cognitive loss, including lesion volume scores, third ventricle size, corpus callosum size, and ventricular-brain ratios and overall cerebral atrophy. There is also a correlation between the degree of left frontal lobe plaque involvement and poor performance on tests of abstraction, memory, and word-finding.

ASSESSMENT OF COGNITIVE IMPAIRMENT

Unfortunately, there is no established method for quickly and accurately assessing cognitive loss in MS. The Mini-Mental Status Examination (MMSE) is not sensitive in this diagnosis, and a complete neuropsychological assessment is often unrealistic in the limited managed care setting. When cognitive loss is suspected, the clinician might begin the screening process by posing a series of ad hoc questions, such as whether the patient has noticed a problem with remembering appointments or conversations, understanding or remembering written material, or focusing attention on a task without becoming distracted. A patient who reports recent onset or a worsening of these types of problems should be referred for a brief neuropsychological screening battery to assess performance in the most common areas of deficit, and determine if further intervention is necessary. A screening battery takes approximately one to two hours. Recommended tests include:

COGNITIVE FUNCTION	INSTRUMENT
Processing speed/working memory	*Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT)*
Learning/memory	*California Verbal Learning Test—II (CVLT-II); Brief Visuospatial Memory Test—Rev. (BVRT-R)*
Executive functions	*California Card Sorting Test (CST)*
Visual perception/spatial processing	*Judgment of Line Orientation Test (JLO)*
Language	*Controlled Oral Word Association Test (COWAT)*

TREATMENT OF COGNITIVE LOSS

Data are limited regarding the effects of immunomodulating agents on cognitive dysfunction. However, clinical trials have suggested that they may improve some aspects of performance. The possibility that they may reduce disease progression, and thereby slow cognitive decline, supports the move toward early treatment with these agents. Donepezil (Aricept®), a drug that has been approved by the FDA for the treatment of memory disorders in Alzheimer's disease, was found in a recent study of 69 MS patients with memory deficits to have modest benefits for verbal memory (the ability to remember a list of words). A forthcoming multi-center trial of Aricept® should provide more definitive evidence concerning the effectiveness of this drug for people with MS.

The best management approach at this point appears to be to recognize and diagnose cognitive loss early, and to provide appropriate social or vocational protection. This may include cognitive retraining, and an individualized plan for compensatory strategies utilizing intact functions and external aids such as "memory books." The overall success of cognitive rehabilitation and other specific interventions in MS patients has not been thoroughly assessed, however.

The family plays an important role, both in diagnosis and management. The steady support of family members is key in assisting the patient's process of acceptance and in facing any social or vocational role changes. Family members themselves must become personally involved if the cognitive loss necessitates adaptive changes in social and family roles.

Referral to neuropsychologists for more comprehensive assessment is recommended in many cases. Rehabilitation psychologists, occupational therapists, and speech/language pathologists may also be of great help in assisting the adaptive process.

SOURCES

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Pain in Multiple Sclerosis

CLINICAL BULLETIN

Information for Health Professionals
by Heidi Maloni, DNScc, RN, APRN, BC-ANP, CNRN, MSCN

INTRODUCTION

Pain is a recognized symptom of multiple sclerosis (MS), affecting as many as seventy-five percent of people at some time during the course of their disease[1–4]. However, only twenty-five percent of those who suffer with MS pain are being treated for it—presumably because pain is more difficult to manage than other MS symptoms[5]. Pain is a subjective sensory experience: "Pain is whatever the experiencing person says it is, existing whenever he/she says it does[6]." The subjective nature of pain, coupled with the different causal mechanisms seen in MS, contribute to the treatment challenge.

The most commonly reported pain syndromes in MS are burning dysesthesias in the lower extremities, headache, lower back pain, and painful spasms[1–2]. People with MS describe their pain as having varying levels of severity and intensity, and characterize it as sharp, shooting, dull, or nagging pain that is either continuous or intermittent[7]. Compared to the various types of pain described by the general population, the pain experienced by people with MS is reported as more intense, having greater impact on activities of daily living, and requiring greater use of analgesia[2–4,8–11].

The symptom of pain in MS demands attention, as it impacts activities of daily living and is associated with anxiety, depression, and fatigue[8]. Pain in MS is also, but not exclusively, associated with longer disease duration, advancing age, higher disability scores, and secondary-progressive disease course[2,4,8–11].

CLASSIFICATION OF MS PAIN

The etiology of MS pain is mixed. MS pain can be classified as either *neurogenic* (central) in origin or *nociceptive* (secondary to other factors). Whereas neurogenic pain is a consequence of lesions in the central nervous system (CNS), nociceptive pain is associated with noxious thermal, mechanical, electrical, or chemical stimuli that are generally a consequence of disease-related disability rather than the disease process itself[1,12–15]. Differentiating types of MS-related pain according to the causal mechanism involved facilitates mechanism-tailored treatment strategies[12,16].

Neurogenic Pain

Neurogenic pain results from lesions in the CNS[15]. The neurogenic pain syndromes described in MS include: trigeminal neuralgia; glossopharyngeal neuralgia; painful tonic seizures or spasms; dysesthesias of the extremities; thoracic and abdominal band-like sensations; certain types of headache; episodic facial pain; Lhermitte's sign; and paroxysmal limb pain.

Neurogenic pain is further described by the character, duration, and intensity of symptoms that are experienced. Neurogenic pain often occurs spontaneously—i.e., independent of any stimulus—and may be either *paroxysmal* or *continuous.* Spontaneous paroxysmal pain is typically characterized as shooting, stabbing, shock-like, lancinating, crushing, or searing. The most common forms of spontaneous

continuous pain are dysesthesias—abnormal sensations that are characterized as burning, aching, prickling, tingling, nagging, dull and/or band-like. Dysesthesias are typically less intense than paroxysmal episodes of pain[4,12].

Stimulus-dependent forms of neuropathic pain (i.e., occurring in reaction to a stimulus) include painful spasms and allodynia. Allodynia refers to pain in response to a stimulus that does not normally cause pain, such as gentle touch, massage, the feeling of clothing against the skin, or the weight of bed covers. Stimulus-dependent pain is usually of short duration and normally lasts only for the period of the stimulus[12,15].

The following is a review of the most common neurogenic pain syndromes seen in MS:

- Paroxysmal Pain Syndromes
  - Trigeminal Neuralgia: Trigeminal neuralgia (TN) is experienced by approximately 4% of the MS population (a prevalence 400 times greater than in the general population). It affects one or more branches of the trigeminal nerve that innervates the eye, cheek, and jaw. TN is an intense, severe, sharp, electric-shock like pain, which is generally unilateral but may occasionally present bilaterally.[17] Attacks can be spontaneous, or may be triggered or worsened by touching, chewing, smiling, or any facial movement. Periods in which sharp, shock-like attacks lasting 2 to 3 seconds to several minutes occur at varying frequency are typically interspersed with periods of remission. In rare instances the individual experiences episodes of longer duration (45–60 min) or continuous pain. TN rarely occurs during sleep[18]. The onset of TN in MS occurs at an earlier age than in the general population. Presentation of TN pain in young adults may be diagnostic of MS[19].
    - TN in MS is thought to be associated with a lesion at the trigeminal root entry zone of the pons[20]. Interrupting the pain pathway is the mechanism-tailored treatment strategy for trigeminal neuralgia in MS. Anticonvulsant medications, known to stabilize cell membranes—thereby decreasing the hyperexcitability of sensory neurons via sodium and calcium channel regulation—are the first-line treatment for the pain of trigeminal neuralgia[21–22]. The second generation anticonvulsant agents have gentler side effect profiles; sustained-release, long-acting formulas minimize side effects.
    - When pain relief is not obtained through drug intervention, surgical gamma knife, radiofrequency, or nerve block procedures that interrupt the pain pathway may become an option. Percutaneous radiofrequency or glycerol rhizotomy is a safe and effective treatment, with lower reported risk of facial sensory loss than other invasive therapies[23–25].
  - Headache: Headache is more common in MS than in the general population, with 58% of patients experiencing episodic headache pain[26]. Although the relationship between MS and headache is not clear, MS lesions in the midbrain have been associated with migraine-type headache[27]. The headaches in MS are usually characterized as migraine-like, cluster, or tension-type. Migraine headache is more commonly reported in patients with relapsing-remitting disease. There is some evidence that migraine headaches are associated with exacerbation of MS symptoms[26].

- Headaches should be treated following existing clinical guidelines for headache type. Mechanism-based treatment strategies include increasing the availability of the neurotransmitters serotonin and norepinephrine. The tricyclic antidepressants and the serotonin and norepinephrine reuptake inhibitors have been used with success in some patients. Increasing the availability of serotonin and norepinephrine may be an effective ongoing therapy for MS patients experiencing headache, as migraine is linked to changes in serotonin function and MS patients may have low serotonin levels[28].

- Continuous Pain Syndromes
  - Dysesthetic Pain: The most common type of continuous pain experienced in MS is dysesthetic pain, which is defined as an unpleasant, abnormal sensation that is either spontaneous or evoked[15]. Dysesthetic pain occurs more commonly in people with minimal disability and is characterized by sensations described as burning, prickling, or tingling, nagging, dull, or band-like[1,7]. This persistent pain—often symmetric—typically affects the legs and feet but may also involve the arms, trunk, and perineum (called vulvodynia). Although dysesthetic pain is usually of moderate intensity, its nagging, persistent nature makes it difficult to tolerate. It is typically worse at night, and tends to be aggravated by changes in temperature. Dysesthetic pain can be associated with feelings of warmth or cold in the extremities that are unrelated to actual temperature[29]. Allodynia is considered the hallmark of stimulus-induced dysesthetic pain. The use of a bed cradle and lambskin pads or booties may offer relief.
    - Dysesthetic pain is difficult to treat fully. Mechanism-based strategies include neuromodulation and interruption of pain pathways, with tricyclic antidepressants considered the first-line treatment. There is recent evidence that combination therapy (anticonvulsants plus antidepressants) provides greater effect with lower doses and fewer side effects[30–31]. Topical agents such as capsaicin (Zostrix), applications of heat and cold, and transdermal agents such as clonidine gel or patch (Catapres-TTS) and the lidocaine patch (Lidoderm) are effective management strategies. In the absence of allodynia, stimulation with fitted prescription pressure stockings at night, massage, acupuncture, or transcutaneous electric nerve stimulation (TENS), can also offer relief[21].

Nociceptive Pain

While nociceptive pain can be acute or chronic, the most common experiences in MS are chronic. This type of pain tends to be associated with greater disability and specifically described as low back pain and pain resulting from severe spasticity[1–2,32]. Nociceptive pain can be intermittent or continuous, provoked or spontaneous. Some nociceptive pain can be easily localized—often described as aching, squeezing, stabbing or throbbing. Other nociceptive pain is more variable in intensity and not as well localized—generally described as gnawing or cramping, although sometimes described as sharp.

- Musculoskeletal Pain: Common nociceptive pain experiences in MS, including back pain and painful spasms, involve the musculoskeletal system. MS musculoskeletal pain is a result of weakness, deconditioning, immobility, and stress on bones, muscles, and joints. Steroid use contributes to osteoporosis and possible compromise of the blood supply to large joints (avascular necrosis), with associated pain. Any pain of a musculoskeletal nature requires a thorough assessment for lumbar disc disease, avascular necrosis, or other condition.

- Prevention is critical to the management of musculoskeletal pain. Bone antiresorptive therapies (e.g., calcitonin (Miacalcin), alendronate (Fosamax), raloxifene (Evista), teriperatide (Forteo)), smoking cessation, and calcium and vitamin D supplementation are preventive for pain associated with osteoporosis.
- Physical therapy is essential for assessment and management of safety, gait, positioning, seating, and effective use of mobility aids, and ankle-foot-orthoses. Exercise and weight control are effective in preventing and treating musculoskeletal pain. Frequent position change and proper support relieve stress on muscles, bones, and joints.
- Acetaminophen (Tylenol), salicylates (aspirin), and nonsteroidal anti-inflammatory agents (NSAIDs) such as ibuprofen (Motrin), naproxen (Aleve), and celecoxib (Celebrex) are first line medical treatments for musculoskeletal pain. All types of NSAIDs can cause GI irritation and bleeding. They can also decrease renal blood flow, causing fluid retention and hypertension. NSAID labeling includes a black box warning for the potential risk of cardiovascular events and life-threatening GI bleeding. The U.S. Federal Drug Administration recommends that NSAIDs be dosed exactly as prescribed or listed on the label. The lowest possible dose should be given for the shortest possible time.[33]

- Spasticity: Flexor and extensor muscle cramping, pulling, and subsequent pain occurs as spasticity in MS. Spasticity is evoked by noxious stimulation such as a pressure ulcer, urinary tract infection, full bowel or bladder, or can result spontaneously from a CNS lesion. Management of spastic pain in MS follows standard spasticity medication management with baclofen (Lioresal), tizanidine (Zanaflex), diazepam (Valium), dantrolene (Dantrium), or botulinum toxin (Botox).

MS PAIN MANAGEMENT

Management of pain in multiple sclerosis involves a combination of behavioral, physical, surgical, and medical interventions[32].

Behavioral Mechanisms

Cognitive/behavioral approaches to MS pain management include education, relaxation, behavior modification, distraction, psychotherapy, support groups, imagery, hypnosis, biofeedback, recreation, laugh therapy, music therapy, and, meditation.

Physical Mechanisms

Physical modalities include: physical therapy; stretching; application of heat, cold, and pressure; reconditioning to improve strength, endurance and flexibility; counter irritation; massage; acupuncture; exercise; yoga and Tai Chi; attention to ergonomics and positioning; electroanalgesia such as transcutaneous electric nerve stimulation (TENS); and sound nutrition and weight control.

Medication Management

- Neurogenic Pain: Neurogenic pain is often resistant to therapy, requiring an in-depth and ongoing assessment of pain indicators, sleep, mood, and quality of life. Medication management includes topical agents, anticonvulsants, antidepressants, antiarrhythmics, NMDA-receptor antagonists, and non-narcotic and narcotic opioids.[16,21–22]

- The use of opioids in neurogenic pain remains controversial as studies show equivocal results[34]. A meta-analysis of several randomized controlled trials demonstrated significant efficacy of opioids over placebo for non-MS neurogenic pain[35].Rowbotham and colleagues (2003) randomized eight MS patients to either high-dose or low-dose levorphanol and found a significant effect of the high-dose opioid on pain intensity[36]. Opioids should be considered when other agents become ineffective or are not well tolerated[37]. Clearly, further studies are needed to confirm their long-term efficacy and safety for the treatment of neurogenic pain in MS.
- In April 2005, Health Canada, the drug regulatory agency for Canada, approved the use of the cannabis-derived drug Sativex to treat MS-related pain. The approval was based on a four-week clinical trial conducted in the United Kingdom in 66 people with MS[38]. Sativex contains extracts from the marijuana plant and is administered as a spray into the mouth. This drug is not approved in the United States. Studies of the herbal cannabis, Delta(9)-tetrahydrocannabinol, and the oral form dronabinol (Marinol) indicate a modest analgesic effect on MS pain[39]. Current studies have been short-term and the long-term adverse events of cannabinoid use in MS have not been determined. Modest therapeutic effect must be balanced with disruption in cognitive function, and increases in anxiety and depression[40]. For more information, see Recommendations Regarding the Use of Cannabis in Multiple Sclerosis at: *www.nationalMSsociety.org/ExpertOpinionPapers.*
- The goal of pain management is to enhance comfort, function, mood, sleep, and quality of life. The benefits of the medications used must be weighed against their side effects. The use of combination therapy (low doses of different drug classes and different drugs within classes) may increase efficacy while minimizing the unwanted effects.

- Nociceptive Pain: Medications commonly used to manage musculoskeletal pain include acetaminophen, salicylates and nonsteroidal anti-inflammatory agents, and non-narcotic and narcotic opioids. Spasticity-related pain is treated with baclofen (Lioresal), tizanidine (Zanaflex), diazepam (Valium), dantrolene (Dantrium), or botulinum toxin (Botox).

Table 1 (see pages 131–132) provides information about the medications commonly used to manage neurogenic/neuropathic pain in MS, including dosage, adverse events, and indications for use. The indications for medication use are derived primarily from evidence-based trials in diabetic and post-herpetic neuropathy.

INVASIVE INTERVENTIONS

Invasive procedures include intrathecal medication administration of either baclofen (Lioresal) or morphine, or both in combination; botulinum toxin (Botox) injection; phenol injection of trigger-points; epidural steroids; regional blocks; spinal cord stimulators; and various surgical procedures.

- Deep brain stimulation, which generates a pulse to relieve pain through electrodes planted in the brain, has the advantage of being reversible.
- Neurosurgical procedures include: cordotomy, rhizotomy, percutaneous balloon compression, percutaneous glycerol injection, radiofrequency rhizotomy, and Gamma knife radiosurgery. Microvascular decompression surgery (MVD) has not shown an effect that outweighs side effects for pain in MS[41].

- Neuroablative techniques are considered when medical therapy is not well tolerated or is ineffective in managing pain. Quality of life is balanced with possible adverse effects of localized numbness, pain recurrence, and possible worsening of the underlying pain[18].

SUMMARY

Pain control is an achievable goal that begins with a thorough assessment, including the identification of pain triggers. Recommendations for effective pain management include:

- Use preventive measures and non-drug strategies in conjunction with medications.
- Be familiar with the treatment options and side effects—and treat the side effects promptly.
- Use low doses of several different medications to achieve greater efficacy with fewer adverse effects.
- Begin with low doses and titrate slowly to an effective pain control. If pain free for three months, titrate back the dosage slowly.

Pain is a symptom that demands serious attention, as it has such 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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Table 1

PHARMACOLOGICAL TREATMENT OF NEUROGENIC/NEUROPATHIC PAIN IN MS

CLASS OF MEDICATION	USE IN MULTIPLE SCLEROSIS
Antidepressants	*Chronic neurogenic pain (e.g., dysesthetic extremity pain such as burning, tingling); often prescribed at night, but split dosing is recommended*
▪ Tricyclic Antidepressants ▫ amitriptyline (Elavil) ▫ mipramine (Tofranil) ▫ desipramine (Norpramine) ▫ nortriptyline (Pamelor)	
▪ SNRI Antidepressants	
▫ duloxetine (Cymbalta)	*Migraine; episodic and continuous neurogenic pain (sharp, shooting, burning/dull sensations; nighttime pain)*
▫ venlafaxine (Effexor)	
Antiepileptics	*For use primarily in sharp, lancinating neurogenic pain (e.g., trigeminal neuralgia); also used in dull or burning, continuous neurogenic pain*
▪ carbamazepine (Tegretol; Carbatrol (extended release)	*Trigeminal neuralgia; tonic painful seizures; pelvic pain; intense episodic, lancinating, burning pain*
▪ gabapentin (Neurontin)	*Trigeminal neuralgia; pins/needles sensations; cramping; dysesthetic extremity pain; tonic spasms; nocturnal spasms. Good combination drug with little drug-drug interaction; better tolerated than carbamazepine*
▪ pregabalin (Lyrica)	*Same indications as gabapentin; better tolerated with lower effective doses*
▪ lamotragine (Lamictal)	*Trigeminal neuralgia; continuous and episodic dysesthetic extremity pain; burning; painful tonic spasms. Better tolerated than carbamazepine*
▪ levetiracetam (Keppra)	*Trigeminal neuralgia; painful spasms*
▪ oxcarbazepine (Trileptal)	*Trigeminal neuralgia*
▪ tiagabine (Gabitril)	*Painful tonic spasms*
▪ topiramate (Topamax)	*Trigeminal neuralgia; sharp, episodic paroxysmal pain*
▪ zonisamide (Zonegran)	*Neurogenic pain*

CLASS OF MEDICATION	USE IN MULTIPLE SCLEROSIS
Antiarrhythmic Agents	
▪ mexilitine (Mexitil)	*Neurogenic pain; painful tonic seizures; trigeminal neuralgia; itching, Lhermitte's*
▪ lidocaine	*Not well tolerated; use as add-on therapy*
Transdermal Agents	*Moderate, continuous dysesthetic neurogenic pain. Use to reduce oral medication load or side effects*
▪ clonidine (Catapres-TTS)	*Acts synergistically with morphine*
▪ lidocaine patch (Lidoderm)	*Use for neurogenic, dysesthetic, continuous, burning, tingling pain of recent onset. Less effective for long-term and severe dysesthetic pain*
▪ capsaicin (Zostrix)	*Mild/moderate neurogenic/nociceptive pain*
▪ fentanyl (Duragesic)	*Moderate neurogenic/nociceptive pain not responsive to non-opioid*
Antispasmodic Agents	*Painful spasms*
▪ baclofen	*Painful spasticity; trigeminal neuralgia; glossopharyngeal neuralgia*
▪ tizanidine (Zanaflex)	*Painful spasms*
▪ botulinum-A	*Painful spasms*
Nonsteroidal Antiinflammatories (NSAIDs) (selective representation)	*Nociceptive pain (ineffective for neurogenic pain)*
▪ ibuprofen (Motrin; Advil) ▪ naproxyn sodium (Naprosyn; Aleve) ▪ celecoxib (Celebrex) ▪ aspirin (ASA)	
Non-opioid and Opioid Agents	*Use as add-on for moderate/severe neurogenic/nociceptive pain, or when non-opioids are ineffective—caution in combination with carbamazepine or TCAs*
▪ tramadol (Ultram; Ultracet)	*Neurogenic pain*
▪ methadone (Dolophine HCl)	*Neurogenic pain (continuous and touch-evoked); nociceptive pain*
▪ oxycodone (Oxycontin)	*Moderate/severe neurogenic pain; allodynia, tolerance not developed to side effect, constipation*
▪ hydromorphone (Dilaudid)	
▪ hydrocodone (plus acetaminophen = Vicodin, Lortab)	
▪ levorphanol (Levo-Dromoran)	
▪ morphine sulfate (Kadian; MS Contin; Avinza)	*Nociceptive and neurogenic pain when other agents have failed*

Assessment & Treatment of Sexual Dysfunction in Multiple Sclerosis

CLINICAL BULLETIN

Information for Health Professionals
by Frederick W. Foley, PhD

INTRODUCTION

The Nature and Frequency of Sexual Dysfunction in Women

The few epidemiological studies on sexual dysfunction in women with MS report a wide variety of sexual concerns that range in frequency between 40 and 80 percent[1–4]. The most common complaints are decreases in genital sensation, fatigue, decrease in libido and vaginal lubrication, and difficulties with orgasm. In several studies, a correlation was found between sexual difficulties and overall level of disability. However, in one study, the rates of sexual dysfunction in MS were higher than a non-MS comparison group only on genital numbness interfering with sexuality[5].

The Nature and Frequency of Sexual Dysfunction in Men

Difficulty acquiring or maintaining satisfactory erections seems to be the most common male complaint in MS, with frequencies ranging from 25 percent to 75 percent of those surveyed. These observations are noteworthy in comparison to a 5 percent occurrence rate of erectile dysfunction in healthy 40-year-old men in the general population, and a 15 percent to 25 percent occurrence rate after age 65[1–3, 5–7]. The combined findings of numerous studies on the causes of erectile dysfunction in MS suggest both a physical and a psychogenic (emotional) role in MS-related erectile dysfunction.

In addition to erectile problems, surveys of men with MS have identified decreased genital sensation, fatigue, difficulties with ejaculation, and decreased interest or arousal as fairly common complaints. In one of the most comprehensive and methodologically sound surveys to date, only 35 percent of men reported no sexual problems, and many reported multiple problems[8].

Primary, Secondary, and Tertiary Sexual Dysfunction

The ways in which MS can affect sexuality and expressions of intimacy have been divided into *primary, secondary,* and *tertiary* sexual dysfunction[9]. Primary sexual dysfunction results from central nervous system lesions that directly affect the sexual response. In both men and women, this can include a decrease in, or loss of, sex drive, decreased or unpleasant genital sensations, and diminished capacity for orgasm. Men may experience difficulty achieving or maintaining an erection, and a decrease in, or loss of, ejaculatory force or frequency. Women may experience decreased or absent vaginal lubrication.

Secondary sexual dysfunction stems from nonsexual MS symptoms that can also affect the sexual response, such as bladder and bowel problems, fatigue, spasticity, muscle weakness, body or hand tremors, impairments in attention and concentration, and nongenital sensory paresthesias.

Tertiary sexual dysfunction is the result of disability-related psychosocial and cultural issues that can interfere with one's sexual feelings and experiences.

Screening for Sexual Dysfunction in the Office or Clinic

There are several ways the busy MS practitioner can screen for sexual dysfunction in the office or clinic setting. If a review of physical symptoms is conducted as part of the evaluation, a question about sexual functioning can be asked when inquiring about bladder and bowel function. A 19-item self-report screen developed specifically for persons with MS can be filled out by the patient in about 2 minutes[10]. Following a positive screen for sexual dysfunction, ask the patient if he or she would like help with these symptoms. In one randomized study, simply providing educational materials on MS and sexual dysfunction was associated with improvements in reported symptoms on follow-up[11].

PRIMARY SEXUAL DYSFUNCTION IN MS

Evaluation and Treatment

A more comprehensive evaluation process may include a physical history and examination, a review of current medications for their possible effects on sexual functioning, a detailed sexual history, and perhaps some specialized tests of bladder and/or sexual function. The sexual history thoroughly examines the current problem and investigates both present and prior sexual relationships and behaviors. The specialist may wish to conduct a joint interview of the person who has MS and his or her sex partner in order to gain a better understanding of the problem as it is experienced by both individuals. A number of questions may be asked regarding the couple's communication, intimacy, and sensual or erotic behaviors in order to obtain a balanced view of the strengths and weaknesses of their relationship. Once this interview has been completed, treatment may begin with feedback from the assessment process, education about the effects of physical symptoms of MS, and suggestions for managing these symptoms.

Decreased Vaginal Lubrication

Similar to the erectile response in men, vaginal lubrication is controlled by multiple pathways in the brain and spinal cord. Decreased vaginal lubrication can be addressed by using generous amounts of water-soluble lubricants, such as K-Y Jelly®, Replens®, or Astroglide®. Healthcare professionals do not advise the use of petroleum based jellies (e.g., Vaseline®) for vaginal lubrication, because they greatly increase the risk of bacterial infection.

Sensory Changes

Uncomfortable genital sensory disturbances, including burning, pain, or tingling, can sometimes be relieved with gabapentin (Neurontin®), carbamazepine (Tegretol®), phenytoin (Dilantin®) or divalproex (Depakote®) or by a tricyclic antidepressant such as amitriptyline (Elavil®). Decreased genital sensation can sometimes be overcome by more vigorous stimulation, either manually, orally, or with the use of a vibrator. Exploring alternative sexual touches, positions, and behaviors, while searching for those that are the most pleasurable, is often very helpful. Masturbation with a partner observing or participating can provide important information about ways to enhance sexual interactions.

Orgasmic Dysfunction

MS can interfere directly or indirectly with orgasm. In women and men, orgasm depends on nervous system pathways in the brain (the center of emotion and fantasy during masturbation or intercourse), and pathways in the sacral, thoracic, and cervical parts of the spinal cord. If these pathways are disrupted by plaques, sensation and orgasmic response can be diminished or absent. In addition, orgasm can be inhibited by secondary (indirect physical) symptoms, such as sensory changes, cognitive problems, and other MS symptoms. Tertiary (psychosocial or cultural) orgasmic dysfunction stems from anxiety, depression, and loss of sexual self-confidence or sexual self-esteem, each of which can inhibit orgasm.

Treatment of orgasmic loss in MS depends on understanding the factors that are contributing to the loss, and appropriate symptom management of the interfering problems.

Decreased Libido

Decreased libido is much more common in women with MS than men. To date, there are no published clinical trials of medications that restore libido in MS. Hormone replacement therapy has helped in some post-menopausal women without MS. Testosterone replacement in persons with abnormally low physiological levels has been tried in non-MS populations. However, there is research currently underway that is evaluating medicines that enhance sympathetic arousal, to see if this impacts libido in women with MS. Similarly, there is research evaluating clitoral vacuum devices and vibrators to see if blood flow, libido, and sensation are enhanced in women with MS.

Pelvic floor or Kegel exercises are sometimes prescribed to enhance female sexual responsiveness (although these exercises have not been tested in a clinical trial to determine whether they are helpful in MS). However, in women with significantly reduced sensation, EMG biofeedback is required to help them identify and contract the appropriate pelvic floor muscles in the prescribed manner. The rationale for Kegel exercises is that sensation and contraction of the muscles around the vagina is an important part of the female sexual response.

When loss of desire is due to secondary sexual dysfunction (for example, as a result of fatigue) or tertiary sexual dysfunction (for example, as a result of depression), treatment of the interfering secondary or tertiary symptoms frequently restores libido. When a person's libido is diminished by MS, he or she may begin to avoid situations that were formerly associated with sex and intimacy. Sexual avoidance serves as a source of misunderstanding and emotional distress within a relationship. The partner may feel rejected, and the person with MS may experience anxiety, guilt, and reduced self-esteem. Misunderstandings surrounding sexual avoidance frequently compound the loss of desire and diminish emotional intimacy in relationships.

Some men and women who have sustained loss of libido report that they continue to experience sexual enjoyment and orgasm even in the absence of sexual desire. They may initiate or be receptive to sexual activities without feeling sexually aroused, knowing that they will begin to experience sexual pleasure with sufficient emotional and physical stimulation. This adaptation requires developing new internal and external "signals" associated with *wanting* to participate in sexual activity. In other words, instead of experiencing *libido* or *physical desire* as an internal "signal" to initiate sexual behaviors, one can experience the anticipation of closeness or pleasure as an internal cue that may *lead* to initiating sexual behaviors and the subsequent enjoyment of sexual activity.

Changing one's sexual signals or cues to initiate sexual activity can be assisted by conducting a body mapping exercise, which constitutes modified sensate focus exercises that take into account MS symptoms[12]. Body mapping is typically used to help compensate for primary (genital) or secondary (nongenital) sensory changes, but it can be a useful first step in the enhancement of physical pleasure and emotional closeness, as well as sexual communication and intimacy.

Diminished libido is frequently associated with a decrease in sexual fantasies. Diminished libido can sometimes be stimulated by increasing sexual imagery and fantasy. Historically, most sexual literature, videos, and magazines have been developed to appeal to a male rather than female audience. Recently, however, some sexual videos are being marketed to appeal to couples and women. They typically include fewer close-ups of genitals during orgasm and have more emotional and romantic content and imagery. When libido is partially intact but difficulty sustaining arousal and/or having orgasms occurs, sharing sexual fantasies or watching sexually oriented videos together may help sustain arousal. Similarly, introducing new kinds of sexual play into sexual behavior can help maintain arousal and trigger orgasms.

Erectile Problems

There are a number of oral FDA approved PDE-5 (phosphodiesterase-type-5) inhibitors to treat erectile dysfunction. The mechanism of action involves active inhibition of the PDE-5 enzyme with subsequent increases in cyclic guanosine monophosphate (cGMP), which maintains smooth muscle relaxation and venous compression in the penis. These medicines include sildenafil (Viagra®), vardenafil (Levitra®), and tadalafil (Cialis®). To date, only sildenafil has been evaluated in clinical trials with men who have MS, although the other medicines are very similar and may be prescribed[13]. PDE-5 inhibitors do not improve libido, but are associated with increased frequency and satisfaction of erections and intercourse. These medicines are contraindicated for use with nitrate-based cardiac medicines, since they interact and can lower blood pressure excessively.

In addition to the PDE-5 inhibitors, there are other oral medicines in development for erectile dysfunction. For example, apomorphine SL (Uprima®) is a dopaminergic agonist with affinity for D(2) dopamine receptor sites in the brain known to be involved in sexual function. Apomorphine induces selective activation in the nucleus paraventricularis leading to erection. It has not been tried to date in MS.

Injectable medications for erectile dysfunction in MS include prostaglandin E1 (alprostadil; Prostin VR®), which has been approved by the FDA for the management of erectile problems. Auto-injectors are available that work with a simple pushbutton mechanism. Dose titration is done in the physician's office, to establish the lowest effective dose and minimize the probability of priapism (an overly prolonged erection), a potentially serious side effect. A second potential side effect is scarring at the injection site. Injectable prostaglandin E1 has been widely used in neurologic populations, including MS[14].

Alprostadil can also be delivered via a urethral suppository (Muse®). The drug is then absorbed into the penile tissues, stimulating an erection. However, approximately one-third of the men who tried the drug reported penile discomfort. In rare instances, priapism can occur.

Phentolamine (Regitine® in the United States; Rogitine® in Canada) is sometimes used in combination with either prostaglandin E1 and/or papaverine to heighten medication efficacy. Phentolamine is an alpha-adrenergic blocking agent and will not induce erections without the presence of another medication (most frequently prostaglandin E1 and/or papaverine). Depending on the type of symptoms the man is experiencing, a urologist may prescribe different combinations of these medications.

One noninvasive way to achieve an erection is to use a vacuum assistive device. With this method, a plastic tube is fitted over the flaccid penis, and a pump creates a vacuum that subsequently produces an erection. Then, a latex constriction band is slipped from the base of the tube onto the base of the penis. The band maintains engorgement of the penis for sexual activities, although it cannot be used for more than 30 minutes.

A more invasive form of treatment for erectile problems is the penile prosthesis. There are two types of penile prostheses: semirigid and inflatable. With the semirigid type, flexible rods are surgically implanted in the corpus cavernosa of the penis. These rods can be bent upward when an erection is desired and bent downward at other times. Following insertion of the rods, the penis remains somewhat enlarged, with a permanent semierection. With the inflatable type, a fluid reservoir and pump are surgically implanted in the abdomen and scrotum, with inflatable reservoirs inserted into the penis that inflate when an erection is desired. This type of prosthesis is barely noticeable, but the potential risks are significant. Surgical complications, infection, scarring, and difficulty operating the pump can create long-term problems.

Approximately 80 percent of the men who use these types of prostheses find them satisfactory. In general, a penile prosthesis is only recommended when other efforts to manage erectile dysfunction have not been successful.

The efficacy of any treatment depends on the ability of both partners to communicate openly about sexual issues and decide on methods that are comfortable and enjoyable for both. Education about treatment options provides persons who have MS and their partners with the language and knowledge that enables discussion and informed decision making.

SECONDARY SEXUAL DYSFUNCTION IN MS

In multiple sclerosis, the incidence of fatigue, muscle tightness or spasms, bladder and bowel dysfunction, and pain, burning, or other discomfort can have adverse effects on the experience of sexual activity. The interference of these symptoms with sexual function can often be alleviated by taking an aggressive approach to symptom management.

Fatigue

One of the most common secondary sexual symptoms in MS is fatigue. Fatigue greatly interferes with sexual desire and the physical ability to initiate and sustain sexual activity. Fatigue can be managed in a number of ways. Pharmacologic management generally involves prescribing stimulants such as modafinil (Provigil®), methylphenidate (Ritalin®) or antidepressants with an energizing effect, such as bupropion (Welbutrin®), when they are not contraindicated (e.g., history of cardiac problems or seizures).

Non-pharmcologic management may include setting aside some time in the morning for sexual activity because this is often when MS fatigue is at its lowest ebb. Energy conservation techniques, such as taking naps and using ambulation aids, can preserve the energy needed for sexual activities. Choosing sexual activities and positions that are less physically demanding or weight-bearing for the partner with MS may minimize fatigue during sex.

Bladder and Bowel Symptoms

Pharmacologic interventions have also been used to manage bladder and bowel symptoms in MS. Some common symptoms of bladder dysfunction include incontinence and urinary urgency and frequency. Anticholinergic medications help manage incontinence by reducing spasms of the bladder and the urethra. One side effect of anticholinergics is dryness of the vagina. However, as previously mentioned, vaginal dryness can be alleviated by using generous amounts of a water-soluble lubricant, such as K-Y Jelly®. A physician may be able to help modify daily medication schedules to allow for maximum effectiveness at the time of planned sexual activity.

Restricting fluid intake for an hour or two before sex and conducting self catheterization just before sexual activity will also minimize incontinence. For men who are concerned about small amounts of urinary leakage, wearing a condom during sex is advised.

If an indwelling catheter is used, healthcare providers may be able to offer tips for handling or temporarily removing catheters. If a woman needs to keep the catheter in place, she can move it out of the way by folding it over and taping it to her stomach with paper tape. It is a good idea to experiment with different sexual positions and activities to find those that feel the most comfortable with the catheter in place.

Spasticity

Spasticity can make straightening the legs, or changing leg positions for sexual activity, quite painful. Active symptomatic management of spasticity will minimize its impact on sexuality. Range of motion and other physical therapy exercises are commonly employed, as well as antispasticity medications, such as baclofen (Lioresal®) and tizanidine (Zanaflex®). Exploring alternative sexual positions for intercourse is helpful when spasticity is a problem. Women who have spasticity of the adductor muscles may find it difficult or painful to separate their legs. Changing positions (e.g., lying on one side with the partner approaching from behind) to accommodate this symptom may be important. Taking an antispasticity medication 30 minutes before anticipated sexual activity can be helpful.

Weakness

Weakness is a common MS symptom, and it frequently necessitates finding new positions for satisfactory sexual activities. Reclining (non-weight-bearing) positions do not place as much strain on muscles and are therefore less tiring. Pillows can be used to improve positioning and reduce muscle strain. Inflatable wedge-shaped pillows are specifically designed to provide back support during sexual activity. Oral sex requires less movement than intercourse, and using a hand-held or strap-on vibrator can help compensate for hand weakness while providing sexual stimulation.

Distractibility

Sustained attention and myotonia (increasing muscle tension) are usually required for sexual feelings to build progressively toward orgasm. MS can cause impairment of attention and concentration that may interfere with maintaining sexual desire during sexual activities. The main strategy to deal with distractibility is to minimize nonsexual stimuli and maximize sensual and sexual stimuli. Creating a romantic mood and setting, using sensual music and lighting, talking in sexy ways, and engaging in erotic touching provide multisensory stimuli that minimize "cognitive drift" during sex. Introducing humor at those moments when the person "loses attention" allows mutual acceptance of this frustrating symptom and helps minimize its impact.

TERTIARY SEXUAL DYSFUNCTION IN MS

The physical changes experienced by people who have MS can alter their view of themselves as sexual beings, as well as their perception of the way others view them. The psychological and cultural context in which physical changes occur can adversely affect self-image, mood, sexual and intimate desire, and the ease or difficulty with which persons with MS communicate with their partners.

Self-Image and Body Image

In Western societies, women are particularly susceptible to having a negative body image. The media's depiction of women as unrealistically thin and oozing with sensuality is at odds with the reality of most women's personal experience. The extremely high prevalence of diagnosed eating disorders, the variety of commercially packaged diet programs and cosmetic surgery centers, and the multibillion dollar cosmetics industry targeting women, all reflect the efforts of women to reconcile their sensual and sexual self-image with the unrealistic cultural feminine mystique. Women with MS may have difficulty enjoying their sensual and sexual nature because of the gap between their internalized cultural images of the "sensual woman" and their MS-related physical changes.

Similar cultural pressures affect men. Internalized cultural images of men as potent, aggressive, and powerful are at odds with the illness experience. MS-associated changes in erectile capacity or employment can be associated with an internal sense of failure or defectiveness as the discrepancy between culturally induced self-expectations and one's personal experience grows wider.

Changing Roles

Changes in family and societal roles secondary to disability can affect one's capacity for intimacy and sexuality. The person with MS who has difficulty fulfilling his or her designated work and household roles may no longer feel like an equal partner. The partner of a severely disabled individual may feel overburdened by additional caregiving, household and employment responsibilities. The couple's intimate relationship can be threatened by the growing tension that results from these feelings.

In addition, the caregiving partner (either male or female) may have trouble switching from the nurturant role of caretaker to the more sensual role of lover. As a sexual partner of a woman (or man) with a disability, a man may begin to think of his partner as too fragile or easily injured, or as a "patient" who is ill and therefore unable to be sexually expressive. If it is practical or culturally acceptable, having non-family members perform caretaking activities helps minimize this "role conflict." When caretaking must be performed by the sexual partner, separating caretaking activities from times that are dedicated to romantic and sexual activities can minimize this conflict.

Accompanying these role changes may be an increasing sense of isolation in the relationship and less understanding of the partner's struggles and perspectives. The diminishing capacity to understand and work through these issues creates greater isolation and misunderstanding, leading to increasing resentments.

Cultural Expectations Regarding Sexual Behavior

The religious, cultural, and societal influences in our lives help shape our thoughts, views, and expectations about sexuality. One of the notions about sexuality that prevails in Western culture is a "goal-oriented" approach to sex. In this approach, the sexual activity is done with the goal of having penile-vaginal intercourse, ultimately leading to orgasm. Here, the sexual behaviors labeled as foreplay, such as erotic conversations, touching, kissing, and genital stimulation, are seen as steps that inevitably lead to intercourse rather than as physically and emotionally satisfying sexual activities in their own right. Hence, couples are not thought to be having "real" sex until they are engaging in coitus, and sex is typically not considered "successfully completed" until orgasm occurs.

This Western view of sexuality leads to spending a great deal of time and energy worrying about the MS-related barriers to intercourse and orgasm ("the goal") rather than seizing the opportunity to explore physically and emotionally satisfying alternatives to intercourse. The capacity to discover new and fulfilling ways to compensate for sexual limitations requires that couples be able to let go of preconceived notions of what sex should be and focus instead on openly communicating their sexual needs and pleasures without fear of ridicule or embarrassment.

MS-Related Emotional Challenges

The MS experience is frequently associated with emotional challenges, including grief, demoralization, and clinical depression[15]. These emotional struggles may temporarily dampen interest in sex or the ability to give and receive sexual pleasure. Coping with emotional changes to enhance sexuality has several aspects: assessment, education, professional treatment, and coping interventions. Assessment of clinical depression can be done by a mental health professional who is familiar with MS. Treatment that involves antidepressant medications and psychotherapy typically offers symptom relief, including the restoration of sexual interest. It is important to select an antidepressant that will minimally impact sexual function.

Talking With Your Patients and Acquiring Information

Often, neurologists and other MS healthcare providers do not spontaneously bring up sexual dysfunction. They may ignore sexuality because they perceive this line of questioning as an unwelcome intrusion into their patients' private lives, because they are personally uncomfortable asking about sexuality, or because they lack professional training in this area. Clinical experience and anecdotal evidence strongly suggest that the majority of persons with MS appreciate being asked about this symptom.

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Spasticity

CLINICAL BULLETIN

Information for Health Professionals
by Sue Kushner, MS, PT and Kathi Brandfass, MS, PT

CLINICAL SIGNS & 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 inactivities 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 (see pages 147–148) 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 (see page 149). 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.

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 (see page 150).

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 multidisciplinary 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.

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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 Abductors														
Knee Flexors														
Knee Extensors														
Ankle Dorsiflexors														
Ankle Plantarflexors														
Average for UE														
Average for LE														

Date/Comments:

Table 1

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

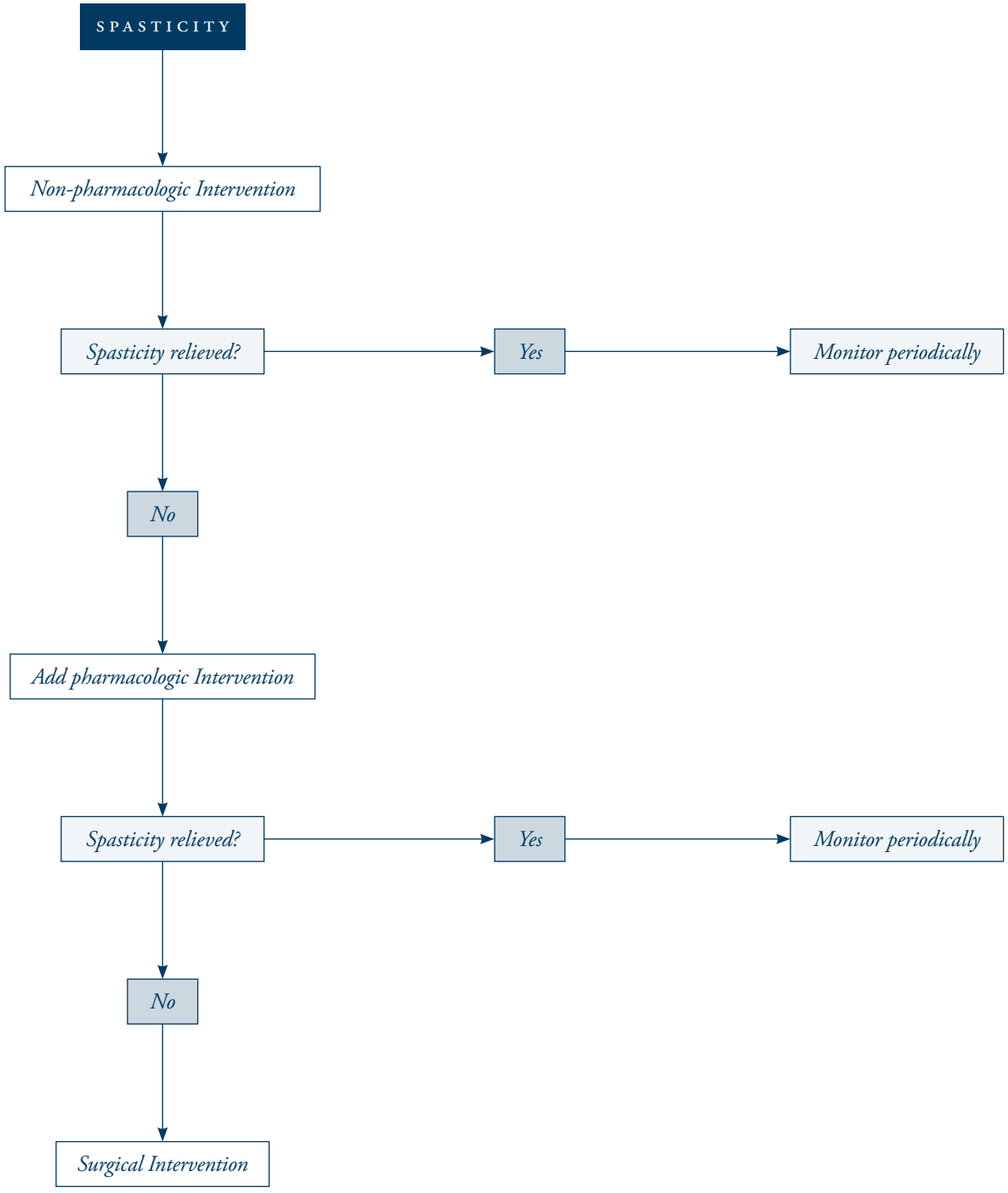
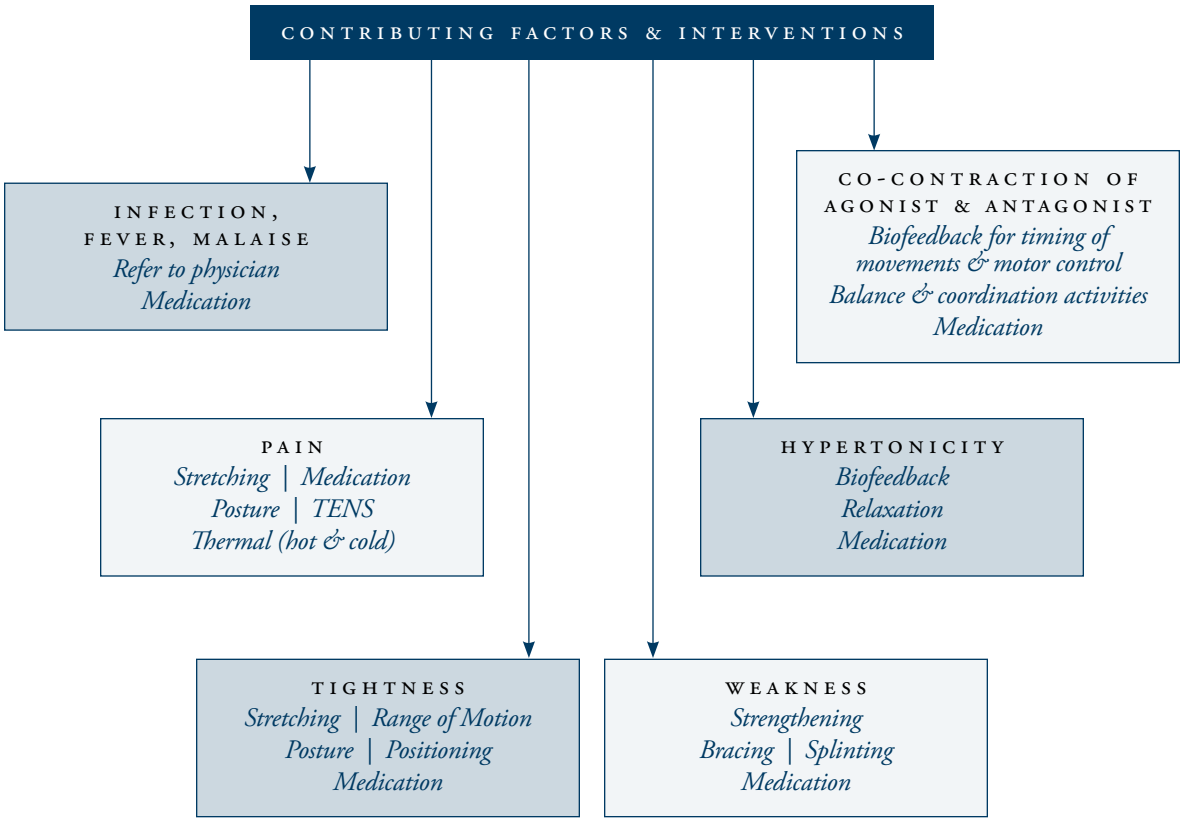


Figure 2

SPASTICITY: CONTRIBUTING FACTORS & RELATED INTERVENTIONS



Common Terms & Concepts in the Appeal 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.

CASE MANAGER

A nurse, doctor, or social worker who arranges all services that are needed to give proper health care to a patient or group of patients.

CARVEOUT

A portion of covered benefits which is 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.

EVIDENCE

Generally referring to published studies and other credible documentation of the effect of a treatment, often used by doctors as evidence that a treatment works or does not work.

EXCEPTION REQUEST

A term describing an appeal to a Medicare prescription drug plan requesting coverage for a drug not covered by the formulary, or for coverage of a "non-preferred drug" at a "preferred drug" cost.

EXPERIMENTAL OR INVESTIGATIONAL TREATMENT

Treatment 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.

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.

EXTERNAL REVIEW

A determination of medical necessity 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 possible fees for the applicant.

GRIEVANCE

A request for re-consideration of an adverse determination concerning an administrative decision, rather than medical necessity, such as a dispute over a network pharmacy's hours of operation, or timeliness of claims processing.

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 USE

Or unlabeled 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 AND T) COMMITTEE

A group of physicians, pharmacists or other health care providers who advise a health 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 purpose of administering prescription drug benefits to plan members.

RETROSPECTIVE REVIEW

A coverage determination or appeal made after a service or item is provided.

STEP THERAPY

A strategy used by health plans, particularly pharmacy benefit managers (PBMs), to manage costs. Step therapy requires that a particular therapy—generally one that is less costly—be tried first. Approval for coverage of a more costly therapy is only provided if the patient fails to respond to the first therapy.

TIER (AS IN TIERED FORMULARIES)

Level of cost-sharing that applies to specific drugs on a plan's formulary. Plans generally have multiple cost-sharing tiers; tiers designated by smaller numbers (e.g. tiers 1 or 2) generally have lower cost-sharing than those designated by larger numbers (e.g. tiers 3 or 4).

UNLABELED USE

Same as off-label use *(see page 152).*

HEALTH INSURANCE & APPEALS

Additional Resources

THE NATIONAL MS SOCIETY

www.nationalMSsociety.org

See the website section on Living with MS >> Insurance and Money Matters, including information about Health Insurance and Medicare, Help for the Uninsured and Under-insured, Social Security Disability Insurance, Other Insurance Helpful to People with MS, and more. Health care professionals are welcome to contact the Professional Resource Center at 1-866-MS TREAT.

KAISER FAMILY FOUNDATION

www.kaiserfamilyfoundation.org

Provides in-depth information on key health policy issues including health insurance, the uninsured, Medicaid, Medicare, prescription drugs, global HIV/AIDS and more. It is a major resource for the media, lawmkers and the health services research community.

FAMILIES USA

www.familiesusa.org

A national consumer-focused nonprofit, non-partisan organization dedicated to the achievement of high-quality, affordable health care for all Americans. Assistance with appeals and other health coverage problems is available for consumers.

COVER THE UNINSURED.ORG

covertheuninsured.org

This site includes state-specific data on health coverage, as well as state-by-state guides to help consumers learn about their state's health insurance programs, legal protections and more. It is a particularly helpful resource for patients with no insurance, and their caregivers.

For a glossary of health insurance terminology: www.familiesusa.org/resources/tools-for-advocates/kits/glossary-health-care.html

RESOURCES ON MEDICARE & MEDICARE PRESCRIPTION DRUG PLANS

The Centers for Medicare and Medicaid Services

www.medicare.gov or 1-800-MEDICARE

The Medicare Rights Center

www.medicarerights.org is a national, nonprofit consumer service organization that works to ensure access to affordable health care for older adults and people with disabilities through counseling and advocacy, educational programs and public policy initiatives. All services are provided free-of-charge, and include counseling hotlines for Medicare beneficiaries or health care professionals (1-800-333-4114).

The Center for Medicare Advocacy

www.medicarerights.org

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.

nationalMSsociety.org
healthprof_info@nmss.org

nationalMSsociety.org/PRC

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