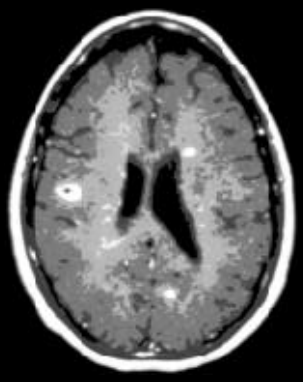
CLINICAL PRACTICE GUIDELINES



Fatigue and MULTIPLE SCLEROSIS

Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis

Administrative and financial support provided by Paralyzed Veterans of America

FATIGUE

Multiple Sclerosis Council
for Clinical Practice Guidelines

MEMBER ORGANIZATIONS

American Academy of Neurology

American Academy of Physical Medicine and Rehabilitation

American Congress of Rehabilitation Medicine

American Neurological Association

American Occupational Therapy Association

American Physical Therapy Association

American Psychological Association

American Society of Neuroradiology

American Society of Neurorehabilitation

American Speech-Language-Hearing Association

Association of Academic Physiatrists

Association of Rehabilitation Nurses

Canadian Neurological Association

Consortium of Multiple Sclerosis Centers

Eastern Paralyzed Veterans Association

International Federation of Multiple Sclerosis Societies

Kaiser-Permanente Health Maintenance Organization

National Institute of Neurological Disorder and Stroke

National Multiple Sclerosis Society

Paralyzed Veterans of America

Rehabilitation in Multiple Sclerosis

U.S. Department of Veterans Affairs

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October 1998

This guide has been prepared based on scientific and professional information available in 1998. Users of this guide should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice.

CONTENTS

FOREWORD

Professional organizations from all sectors of the health-care community have embraced the development, use, and evaluation of practice guidelines through which they collate and evaluate empirical evidence and expert opinion. Generally, the goals of these practice guidelines are to reduce inappropriate care and improve patient outcomes, reduce health-care costs, enhance quality assurance, and improve medical education. Their benefit is in documenting the advice of clinical experts, documenting the clinical research, and assessing the clinical significance of conflicting research findings.

Many public and private health-care organizations are involved in developing practice guidelines, and the scope of topics researched and methodologies used is quite diverse. The choices of topics and methods reflect each organization's major practice concerns, the empirical evidence available on those topics, and, just as importantly, the resources available to the organization for developing the guidelines. Whenever possible, clinical practice guidelines are based on empirical evidence and in those cases the recommendations are graded on the quality of evidence. Nonetheless, expert opinion remains an integral part of guideline development "because reliable scientific evidence is lacking for most clinical practices" (Woolf, 1992).

I am pleased to present these clinical practice guidelines on multiple sclerosis (MS) fatigue management to the health-care community. These guidelines and others developed by the Multiple Sclerosis Council for Clinical Practice Guidelines reflect both the published research on this topic as well as the expert opinion of the panel members. That expert opinion has been supported in turn by the expert consensus of a broad range of clinicians who are MS specialists.

These guidelines are written for health-care professionals to assist them in clinical decision making. A consumer version will soon be available. We anticipate that the two documents will be useful to both consumers and clinicians in discussing MS and its symptoms and in making treatment decisions. We also expect the publications will be useful to individuals and organizations responsible for allocating health-care resources.

People with MS come from all walks of life and live with a broad range of disability. Their care is provided by many types of health-care professionals in varied settings. For this reason, the guidelines have been developed for a range of patients, clinicians, and treatment settings. Adaptability has been a guiding principle of the Multiple Sclerosis Council for Clinical Practice Guidelines, whose members represent the major professional and consumer MS groups, and of the members of the Guidelines Development Panel, who also reflect this provider and consumer diversity.

These guidelines will be of benefit only if they are studied, used, evaluated, and updated. The council welcomes the responsibility of ensuring the current and future value of these guidelines as part of its ongoing activities. However, we will be successful in this effort only with the participation of you, the health-care providers who use this document. We look forward to your comments on these guidelines and encourage you to undertake the investigations for future research recommended in this publication.

We are grateful to the Paralyzed Veterans of America for convening and providing ongoing support to the representatives of the 22 organizations that constitute the Multiple Sclerosis Council for Clinical Practice Guidelines. PVA's concern for the well-being of people with MS and its commitment to ensuring that appropriate care is available to every person with MS are an example to us all.

Deborah M. Miller, PhD, LISW
Comprehensive Care Director
Mellen Center for Multiple Sclerosis/U-10
Cleveland Clinic Foundation

ACKNOWLEDGEMENTS

The chair and members of the Fatigue Management Panel wish to express special appreciation for the leadership and encouragement shown by the 22 individuals who make up the Multiple Sclerosis Council for Clinical Practice Guidelines and the organizations they represent. We especially appreciate the contributions of the 152 health-care professionals who participated in the consensus conference conducted at the 1997 annual meeting of the Consortium of Multiple Sclerosis Centers and of the 42 professionals who provided expert review of the final draft.
The efforts of all of these groups have been crucial in establishing the expert consensus that underpins these recommendations.

Assistance in conducting the literature review was provided by the staff of the Cleveland Clinic Foundation Medical Library, especially Judith Janes, BA, MSLS, AHIP, and Gretchen A. Hallerberg, MS, MSLS, AHIP. Their aid was essential to the successful completion of these guidelines.

We greatly appreciate the early efforts of the American Academy of Neurology, the Consortium of Multiple Sclerosis Centers, and the National Multiple Sclerosis Society, especially June Halper, RN, MSN, and Jay Rosenberg, MD, in initiating the MS guidelines development process. Financial support provided by the Eastern Paralyzed Veterans Association, Inc., Medtronics, and Berlex through unrestricted educational grants was essential to the inauguration of this project.

The Guidelines Development Panel is indebted to the leaders and staff of the Paralyzed Veterans of America, who provided organizational, administrative, and financial support to the Guidelines Development Panel. In particular, the panel recognizes Steve Shindell, Ph.D., program coordinator, and Jennifer Podulka, MPAff, project administrator of the Health Policy Department, who demonstrated their organizational and management skills throughout this project; John Carswell, associate executive director of that department, who championed the cause of PVA members who have MS; Fred Cowell, staff director of the Health Policy Department, who made sure that the project was appropriately staffed; James A. Angelo, Patricia E. Scully, and Nina Schwartz of the Communications and Information Services Department who provided expert guidance in editing, formatting, and creating artwork; medical editor Joellen Talbot, who provided excellent technical and editorial review; and the PVA staff and consultants who developed the glossary and index and standardized the nomenclature. Finally, we are grateful for the steadfast commitment and advocacy of PVA's senior officers, including National President Kenneth C. Huber, Executive Director Gordon H. Mansfield, Deputy Executive Director John C. Bollinger, and the entire PVA board of directors.

FATIGUE GUIDELINES DEVELOPMENT PANEL MEMBERS

R. Philip Kinkel, MD (Chair)
Medical Director
Mellen Center for MS Treatment and Research
Cleveland Clinic Foundation
Cleveland, Ohio

Kathleen Conway, RN, BSN
Nursing
University of Maryland
Maryland Center for MS
Baltimore, Maryland

Lois Copperman, OT, PhD
Occupational Therapy
Oregon Health Sciences University
Department of Rehabilitation
Portland, Oregon

Sue Forwell, MA, OT
Occupational Therapy
University of British Columbia
School of Rehabilitation Sciences
Vancouver, British Columbia, Canada

Cinda Hugos, MS, PT
Physical Therapy
Oregon Health Sciences University
Portland, Oregon

David C. Mohr, PhD
Psychology
University of California
Mt. Zion MS Center
San Francisco, California

Linda Morgante, RN, MSN
Nursing
Maimonides MS Center
Brooklyn, New York

Judith Rosenberg, RN
Nursing
La Jolla, California

John A. Schafer, MD
Neurology
Medical Clinic of Sacramento
Sacramento, California

Michael Seidle, MD, CMD
Medical Consumer
Muncie, Indiana

Jane Kent-Braun, PhD (Consultant)
Exercise Physiology
University of California
San Francisco, California

CONTRIBUTORS

MS Council for Clinical Practice Guidelines Member Organizations and Representatives

American Academy of Neurology
Michael Greenberg, MD

American Academy of Physical Medicine and Rehabilitation
George Kraft, MD

American Congress of Rehabilitation Medicine
Doug Jeffrey, MD, PhD

American Neurological Association
Fred Lublin, MD

American Occupational Therapy Association
Lois Copperman, PhD

American Physical Therapy Association
Cinda Hugos, MS, PT

American Psychological Association
David Mohr, PhD

American Society of Neuroradiology
Craig Bash, MD, MBA

American Society of Neurorehabilitation
Jack Burks, MD

American Speech-Language-Hearing Association
Pam Sorensen, MA, CCC-SLP

Association of Academic Physiatrists
Ronald Taylor, MD

Association of Rehabilitation Nurses
Ismari M. Clesson, RN

Canadian Neurological Association
T.J. Murray, MD

Consortium of Multiple Sclerosis Centers
Deborah M. Miller, PhD (Chair)

Eastern Paralyzed Veterans Association
Vivian Beyda, DrPh

International Federation of Multiple Sclerosis Societies
Robert Herndon, MD

Kaiser-Permanente Health Maintenance Organization
Jay Rosenberg, MD

National Institute of Neurological Disorder and Stroke
Henry McFarland, MD

National Multiple Sclerosis Society
Nancy Holland, RN, EdD

Paralyzed Veterans of America
Suzanne Diffley, RN

Rehabilitation in Multiple Sclerosis
Michele Messmer Uccelli, BA

U.S. Department of Veterans Affairs
John Booss, MD

Expert Reviewers

Donna Jo Blake, MD
R. Henry Bodenbender, MD
Karen Bridges, RN
Patricia Coyle, MD
John DeLuca, PhD
Pierre Duquette, MD
Greg Farmer, PT
Jill Fischer, PhD
Fred Foley, PhD
Donna Fry-Welch, PhD, PT
Gloria Furst, OTR
Barbara Geisser, MD
Andrew Goodman, MD
June Halper, MSN, RN, CS
Joe Herbert, MD
Nancy J. Holland, RN, EdD
Bruce L. Hughes, MD
Brian Hutchinson, MS, PT
C.S. Kim, MD
Lauren Krupp, PhD
Laura Lennihan, MD
William Likosky, MD
Laurie McClearen, RN, MSN, CRRN
Donna Jensen Manugen, OT
Jeanne Melvin, OTR
Linda Morgante, RN, MSN, CRRN
Ib. R. Odderson, MD, PhD
Joel Oger, MD
Hillel Panitch, MD
Jack Petajan, MD, PhD
Paul Ritvo, PhD
Brian J. Rosenthal, MD
Michael Saffir, MD
Andrea Serdar, PT
Randall T. Shapiro, MD
James A. Sliwa, DO
Kate Stolp-Smith, MD
George Szollar, MD
Susan Vesmarovich, RN, MSN, CRRN
John Whitaker, MD
Jerry Wolinsky, MD
Louise Zingeser, PhD

THE MULTIPLE SCLEROSIS COUNCIL

Two separate organizational efforts stimulated the 1997 formation of the Multiple Sclerosis Council for Clinical Practice Guidelines. The first of these efforts was formalized in 1995 when the American Academy of Neurology, the Consortium of Multiple Sclerosis Centers, and the National Multiple Sclerosis Society established the inter-organizational Collaborative Group for Multiple Sclerosis Management Strategies (CGMSMS). The term "management strategies" was used in this collaboration because of concern that although the recommendations would be based on all available empirical evidence, development of the recommendations would be largely dependent on expert consensus. In that same year, CGMSMS formed a steering committee, which established criteria for topic selection and management strategy development, and convened management strategies development panels on two topics–fatigue and bladder dysfunction.

The second organizational effort was initiated by the Paralyzed Veterans of America. To better serve the approximately 30 percent of PVA members who experience multiple sclerosis, the organization made a board-level decision in 1997 to commit resources for developing practice guidelines for MS. This commitment paralleled the guidelines support PVA had been providing to the spinal cord injury community since 1995, through the Consortium for Spinal Cord Medicine. In making these resources available, PVA also ensured that its only influence on the recommendations generated through the MS guidelines effort would be through its one voting member on the council. In 1997 the two organizational efforts were integrated, and the Multiple Sclerosis Council for Clinical Practice Guidelines was established. This merger allowed a greater number of organizations to participate and a more ambitious schedule for producing the guidelines to be set.

The Multiple Sclerosis Council for Clinical Practice Guidelines is made up of 22 representatives from key MS professional and consumer organizations. A multidisciplinary group, it includes civilian and military representatives who have experience in fee-for-service and managed care payment systems, as well as in academic, group, and individual practice settings. These representatives and their organizations are listed above. Each member organization is responsible for providing the following:

- Appointment to the council of one member with expertise in the topic area.
- High-level professional and technical peer review of the guidelines materials.
- Dissemination and application of the guidelines through the organization's educational offerings.
- Organizational endorsement of the completed practice guidelines and related products.

In addition, each member of the council participates in one of three advisory subcommittees: the Methodological and Scientific Review Advisory Subcommittee; the Topic Selection and Panel Recruitment Advisory Subcommittee; or the Peer Review, Dissemination, and Outcomes Evaluation Advisory Subcommittee.

The preparation of individual guidelines is completed by a Guidelines Development Panel that includes multidisciplinary experts in the field. The Fatigue Guidelines Development Panel followed a process that integrates the methodologies of the Collaborative Group for MS Management Strategies and the Consortium for Spinal Cord Medicine. The first phase of the work process was setting the parameters of the guidelines. The framework for the guidelines was established when the panel developed a potential cause-and-effect diagram that allowed the panel to identify a comprehensive list of factors that can have either a positive or negative impact on the target condition. This technique, taken from the continuous quality improvement literature, helped the Fatigue Guidelines Development Panel to specify the scope of care for inclusion in the guidelines.

Next, the analytic framework, specifying the direct, surrogate, and intermediate outcomes, both positive and negative, that were expected from the guidelines was outlined. The Fatigue Guidelines Development Panel then constructed a proto-algorithm of the treatment process that members believed, based on their expert opinion, would maximize the preferred outcomes and minimize the negative ones.

The literature review strategy was subsequently developed and documented by the Fatigue Guidelines Development Panel and by process methodologists who have expertise in medical literature review, data extraction, and data synthesis. Potentially relevant original research articles were collected through electronic search procedures, reviews of research and survey article bibliographies, and recommendations from experts in the field. Relevant original research articles were identified, and levels of evidence were assigned. The levels of evidence and strength of recommendations used in this process are listed in Table 1. All members of the Fatigue Guidelines Development Panel read all relevant articles.

The guidelines writing process occurred as the Fatigue Guidelines Development Panel expanded the proto-algorithm and wrote the supporting annotations, based on the available literature. This process took several iterations between the Fatigue Guidelines Development Panel and the process methodologist.

In the second phase of the development process, members of the Fatigue Guidelines Development Panel identified aspects of care that were recommended based on experience, though not supported by empirical research. This documenting of the Fatigue Guidelines Development Panel's expert opinion was the first step in the expert consensus process.

The second step was to present these expert opinions at a consensus conference held in conjunction with the 1997 annual meeting of the Consortium of Multiple Sclerosis Centers in Calgary, Alberta, Canada. A total of 152 MS specialists participated in this conference. Twenty-one percent of those specialists were physicians; 44 percent were nurses; 10 percent were mental health professionals; 14 percent were rehabilitation therapists; and 11 percent worked in various fields. Only those recommendations that received a 90 percent endorsement rating at the consensus conference were retained.

The final step in the consensus process consisted of a review of the document by the 22 members of the Multiple Sclerosis Council for Clinical Practice Guidelines and by as many as 3 additional reviewers from each member organization. Endorsement of the guidelines was made by each organization of the Multiple Sclerosis Council for Clinical Practice Guidelines according to their own rules of governance.

Dissemination of the guidelines is through the member organizations and other key societies. Evaluation of the guidelines is the responsibility of the Multiple Sclerosis Council for Clinical Practice Guidelines, which will consider the guidelines' utility, their impact on clinical outcomes, and the need for revision as new information becomes available.

Table 1. Grades of Recommendations and Levels of Evidence

Class A Recommendations require

one **Level I Study:** randomized control trial (RCT) with significant statistical power and duration

or

two or more **Level II Studies:** RCTs of smaller magnitude and/or duration

Class B Recommendations require

one or more **Level III Studies:** prospective cohort design

Class C Recommendations require

one or more **Level IV Studies:** cross-sectional controlled studies or retrospective cohort

or

two or more **Level V Studies:** Case series of any size

INTRODUCTION

Fatigue is now recognized as the most common symptom of MS. Surveys and case control studies indicate that 75 to 95 percent of individuals with MS experience fatigue, and 50 to 60 percent report fatigue as one of their worst problems (Freal et al., 1984; Murray, 1985; Fisk et al., 1994). The impact of fatigue on a person's quality of life can not be overstated. Not only does fatigue exacerbate impairment and disability, it is also intimately related to an individual's sense of control over the illness and overall mental health (Ritvo et al., 1996; Monks, 1989; Schwartz et al., 1996; Vercoulen et al., 1996a). In fact, fatigue is one of the two major reasons for unemployment among people with MS. The Social Security Administration responded in 1986 by adding fatigue to the list of causes of MS-related disability in the code for disability impairments (Edgley et al., 1991; Jackson et al., 1991).

Despite more than 10 years of investigation, the pathophysiologic basis of MS-related fatigue remains obscure. Scientists' lack of understanding is in part a result of the biological complexity of fatigue. Physiologic and metabolic studies of people with MS, other neurologic disease states, and normal populations suggest that primary sources of fatigue can emanate from multiple levels within the neural hierarchy, beginning with ideation of an activity within the cortex and ending with the process of muscle contraction and force generation (Enoka and Stuart, 1992; Kent-Braun et al., 1994; Sandroni et al., 1992; Roelcke et al., 1997). Unfortunately, the ability to dissect these physiologic pathways with surrogate measures of fatigue, to develop biologically based paradigms of MS-related fatigue, and to apply this knowledge to specific therapeutic approaches is only in its infancy. More advanced is our understanding of the multidimensional clinical features of fatigue in MS and other disorders. This knowledge has been applied empirically to the management of fatigue, but only infrequently tested using modern clinical investigative methodology. Although there is general agreement on a number of treatments that appear to reduce fatigue and its impact, this agreement is based upon clinical experience and preliminary studies. This state of affairs was recognized by the Guidelines Development Panel at its initial meeting and explicitly addressed in a series of goals established by the panel prior to initiation of work on the project. These goals can be summarized as follows:

- To review and classify the scientific evidence supporting current evaluation and management strategies for MS-related fatigue and to obtain expert consensus where little or no scientific evidence exists.
- To categorize the nature of MS-related fatigue in a framework appropriate for assessment and treatment.
- To identify appropriate care and coping strategies for MS-related fatigue based on scientific evidence or expert consensus.
- To develop guidelines for use by all MS health-care providers and consumers.
- To provide a framework for clinical research that should eventually refine and improve the initial management strategies algorithm.
- To document required resources for the effective management of fatigue.

The panel established a systematic approach to achieve these goals, as outlined below. First and foremost, the algorithm was designed to reflect outcome-based methodology. Only through this approach would clinicians and researchers be able to test the algorithm, assess the response to treatment, and modify the algorithm as new knowledge and treatments become available.

Definition of Fatigue

Fatigue can be defined in a number of ways. For example, a physiologist might define fatigue as a failure to maintain a determined force output. Associated with this failure are a number of properties that can be quantified, such as force generation and recovery time. Although this definition — confined to the properties of muscle fatigue — has advantages, it is of limited utility in the global assessment of fatigue in the clinic. The panel recognized the importance of beginning with a generalized, consumer-oriented definition of fatigue, which could then be clarified and quantified by incorporating various assessments into the algorithm. This approach had the further advantage of not excluding significant fatigue that may be only secondarily related to the MS disease process (e.g., fatigue due to depression or disrupted sleep). With these thoughts in mind, the panel agreed to the following definition of fatigue:

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

The panel recognized that all individuals with MS experience some degree of fatigue from time to time. Specifically, acute episodes of fatigue are frequently associated with disease relapses, intercurrent illnesses such as viral infections or urinary tract infections, or acute changes in weather. Such episodes require a different assessment and management approach than chronic persistent fatigue. Therefore, the panel attached two descriptive modifiers to eliminate nonsignificant or everyday fatigue from the algorithm and to differentiate acute, intermittent fatigue from chronic persistent fatigue.

Chronic persistent fatigue is defined as:

- Fatigue that is present for any amount of time on 50 percent of the days for more than 6 weeks.
- Fatigue that limits functional activities or quality of life.

Acute fatigue is defined as:

- New or a significant increase in feelings of fatigue in the previous 6 weeks.
- Fatigue that limits functional activities or quality of life.

Surveys and case control studies suggest that the modifiers defining chronic fatigue will apply to the 50 percent of people with fatigue who experience the greatest distress and functional impact associated with fatigue, independent of disability or disease course (Freal et al., 1984; Murray, 1985; Krupp et al., 1988; Fisk et al., 1994).

Fatigue Algorithm Outcome Measure

The fatigue measure used should be based on each individual's assessment of fatigue and its impact. This requires use of a self-report measure with psychometric properties, including internal consistency, reliability, and validity. After reviewing the fatigue scales that have been applied to the MS population (Krupp et al., 1989; Krupp et al., 1995; Fisk et al., 1994; Schwartz et al., 1996; Belza et al., 1993; Vercoulen et al., 1994), the panel decided to recommend the Modified Fatigue Impact Scale (MFIS) from the Multiple Sclerosis Quality-of-Life Inventory (MSQLI) as the main outcome measure.

The modified scale assesses the client's perceived impact of fatigue on physical, cognitive, and psychosocial functioning. The MFIS was developed by a panel funded by the National Multiple Sclerosis Society. The Fatigue Guidelines Development Panel used both expert and client peer review to assess all available fatigue scales. Through this process, the Fatigue Guidelines Development Panel selected the 40-item Fatigue Impact Scale (FIS) as most appropriate for assessing the impact of MS-related fatigue on quality of life (Fisk et al., 1994). The MSQLI panel derived the shorter 21-item MFIS through a field test of the original FIS, which identified and eliminated items in the FIS that appeared to be redundant.

Despite the scientific rigor and expert consensus applied to the development of the MFIS, the clinical relevance of all reviewed fatigue scales, including the MFIS, remains to be proven. The Guidelines Development Panel hopes that publication and dissemination of these guidelines will stimulate research on self-report measures such as the MFIS in day-to-day clinical practice.

DEVELOPMENT OF THE ALGORITHM

The evaluation and treatment algorithm for MS-related fatigue is based on the following principles outlined by the panel:

- The order and priorities of evaluation and treatment recommendations are based on the level of scientific evidence and, where lacking, expert consensus.
- The algorithm recognizes the multidimensional nature of fatigue.
- Evaluation and management is designed as an iterative process with multiple loops within the algorithm. This recognizes the uncertain dimensions associated with fatigue at any point in time and the need to reevaluate and adjust the recommendations.
- The algorithm recognizes the importance of multidisciplinary management, but also recognizes that the resources available to patients will vary from one area to the next.

The panel incorporated into the algorithm various self-report measures, which can be used to assess clients, evaluate outcomes at critical nodes, and evaluate the effectiveness of the algorithm for future modification. Some outcome measures are left to the discretion of the clinician or investigator without comment. For instance, if one were to test whether treatment of depression or spasticity improved fatigue, the outcome measure used to assess depression or spasticity must be selected from other sources.

Algorithm Instructions

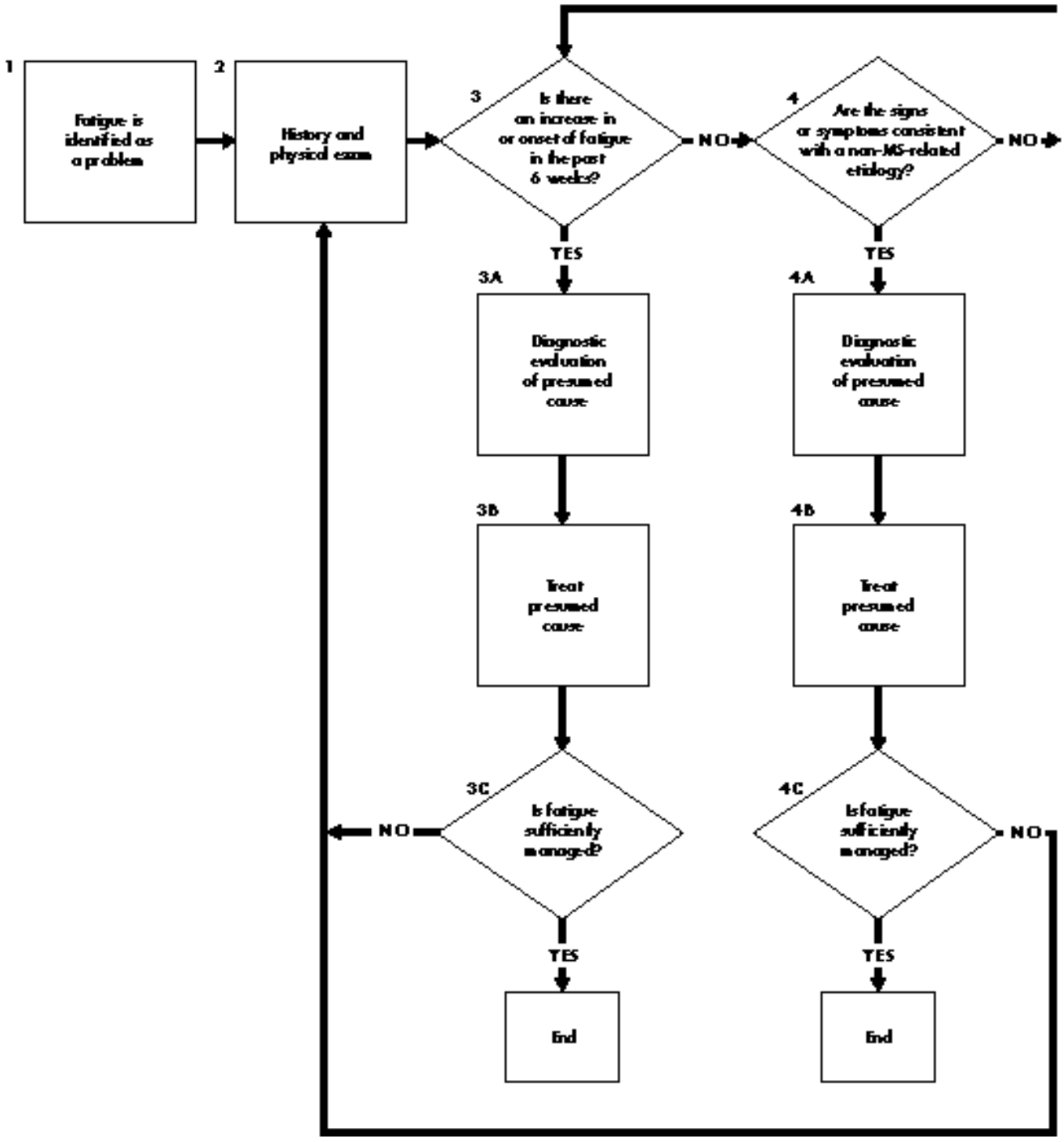
The algorithm is a flow chart intended to guide clinicians in the evaluation and treatment of MS-related fatigue. Decision nodes are indicated by diamond shaped boxes, whereas evaluation and treatment nodes are indicated by rectangular or square boxes. The section entitled Algorithm Treatment Recommendations categorizes the class of recommendation and provides a summary of the goals, procedures, personnel, and timeline for each node of the algorithm. For those interested in a more detailed summary of the scientific evidence supporting the algorithm, please refer to the section entitled Literature Review in the appendix.

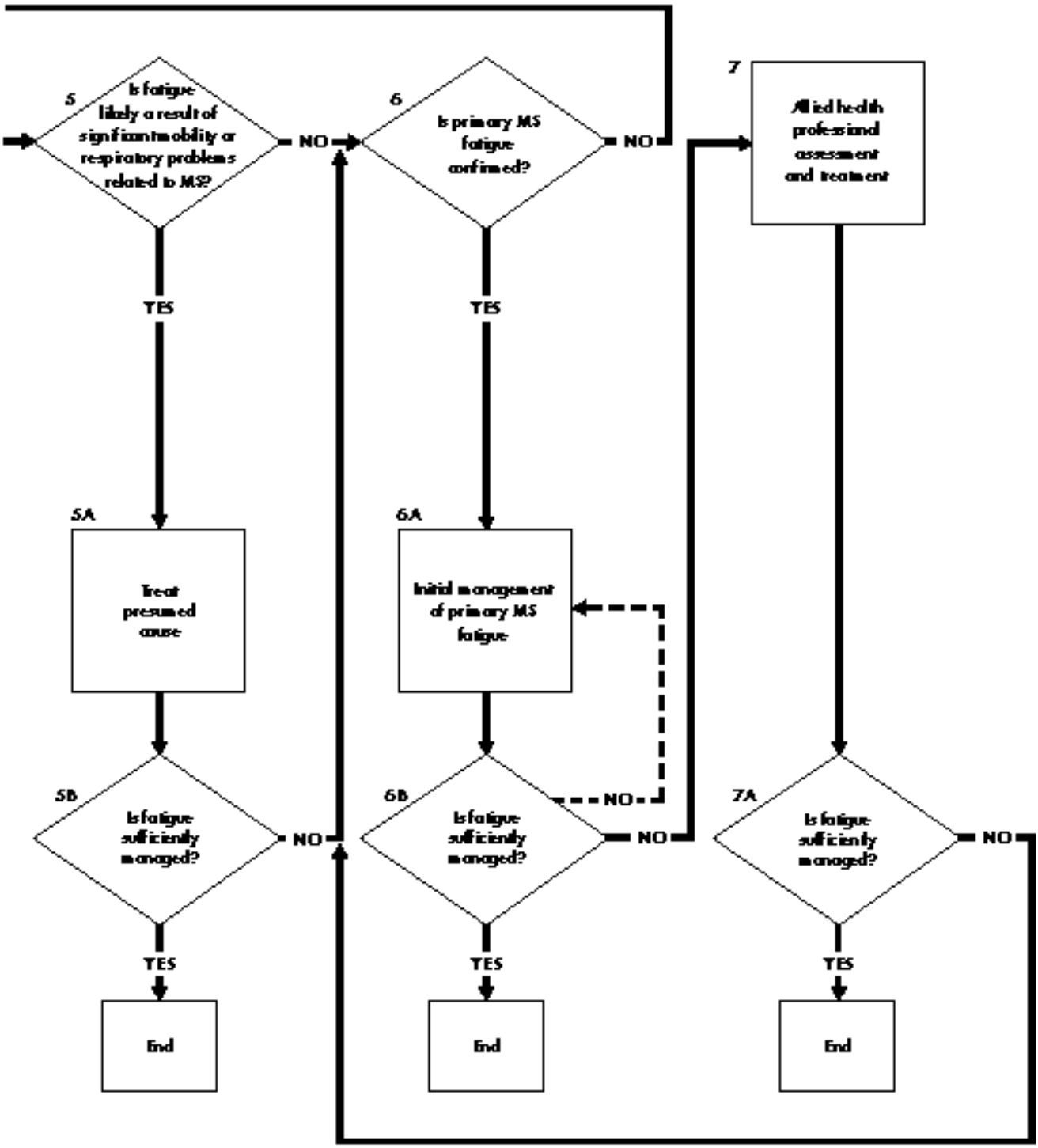
The outcome measure recommended to assess treatment response is the Modified Fatigue Impact Scale (MFIS: see discussion on page 2). This self-report measure with established validity and reliability is provided along with scoring instructions as a supplement to the document. Currently, there are no studies available to help clinicians determine clinically relevant changes, for better or worse, either in the total MFIS score or in any of the 3 subscale scores. It is anticipated that this information will become available once well-designed studies are initiated to evaluate the utility of these guidelines. In the interim, the Fatigue Guidelines Development Panel recommends that clinicians become familiar with the administration of the MFIS and use the derived scores as part of their assessment strategy when managing MS-related fatigue.

In addition to the MFIS, a number of self-report questionnaires have been included in the appendix. Although none are required to use the algorithm, these questionnaires were included to help clinicians more easily gather information to guide assessment and treatment strategies. These questionnaires include the following:

- **Fatigue Questionnaire:** This self-report measure categorizes the quality and severity of fatigue, determines whether there has been a recent worsening of fatigue, and helps summarize previous therapeutic strategies used to lessen the impact of fatigue. This questionnaire is best used at the beginning of the algorithm (box 1).
- **Sleep Questionnaire:** This self-report questionnaire documents usual sleep habits. It is useful in gathering the initial history in box 2 to determine the presence or absence of primary and secondary sleep disorders.
- **MS Daily Activity Diary:** This diary is intended for use by clinicians involved in assessing and teaching energy effectiveness strategies (see box 7).

Fatigue Algorithm




5
Is fatigue likely a result of significant mobility or respiratory problems related to MS?
NO
6
Is primary MS fatigue confirmed?
NO
7
Allied health professional assessment and treatment
YES
YES
5A
Treat presumed cause
6A
Initial management of primary MS fatigue
5B
Is fatigue sufficiently managed?
NO
6B
Is fatigue sufficiently managed?
NO
NO
7A
Is fatigue sufficiently managed?
NO
YES
YES
YES
End
End
End

ALGORITHM TREATMENT RECOMMENDATIONS

1. **Fatigue is identified as a problem.**
(Class of recommendation–B)

   Goal: To identify the characteristics of fatigue that will determine the need for treatment and guide further evaluations.

   Procedure: Determine if fatigue has been present on more than 50 percent of the days for more than 6 weeks or if there has been a significant development or increase of fatigue in the past 6 weeks, **and** if fatigue is reported to limit functional activities or interfere with quality of life. (See appendix for optional fatigue questionnaire.)

   Personnel: Any clinician involved in the care of the patient.

   Timeline: Initial visit.

2. **Obtain personal history and conduct a physical examination. Evaluate for the following:**
   - **Comorbid medical conditions**
   (Class of recommendation–A)
   - **Iatrogenic contributions**
   (Class of recommendation–A)
   - **Depression or psychologic distress**
   (Class of recommendation–B)
   - **Sleep disturbances**
   (Class of recommendation–C)
   (Expert consensus regarding the importance of evaluating all four dimensions initially)

   Goal: To characterize the dimensions of fatigue and identify alternative, treatable causes that may not be directly related to the MS disease process.

   Procedure:
   - Complete medical history, review medications (see Table 2 in appendix for a list of medications associated with fatigue, asthenia, somnolence, and lethargy), and review systems, with particular attention to iatrogenic (medication) causes or comorbid medical conditions associated with fatigue.
   - Obtain sleep history to help identify primary or secondary sleep disorders (see optional self-report sleep questionnaire in the appendix).
   - Evaluate for depression (that is, loss of interest in activities; feelings of sadness, worthlessness, or guilt; changes in appetite or sleep; or suicidal ideation), anxiety, stress, or other psychological distress.
   - Conduct a general medical examination and a focused neurologic exam.
   - Have the client complete the Modified Fatigue Impact Scale (see supplement).

   Personnel: Physicians, nurses.
   Timeline: One visit.

3. **Is there an increase in or an onset of fatigue in the past 6 weeks?**
(Expert consensus)

   Goal: A recent increase in or an onset of fatigue within the past 6 weeks is highly suggestive of certain comorbid medical conditions (such as infections), iatrogenic causes (such as new medications), environmental changes (such as hot or humid weather or major changes in level of activity), or recent psychological stressors. Sometimes a recent increase in or an onset of fatigue may represent a prodrome to an MS exacerbation (prior to any changes in a neurologic exam). These precipitants require focused intervention and more frequent reevaluation than cases involving chronic fatigue.

   Procedure: Determine likely etiology based on evaluation in box 2 and proceed to box 3A and 3B.

   Personnel: Physicians, nurses.

   Timeline: Same visit as box 2.

   A. Diagnostic evaluation of presumed cause, if required.
   (Expert consensus)

   Goal: To clarify the likely etiology of the acute increase in or onset of fatigue, if not clear after evaluation in 2.

   Procedure: If medical comorbidity is suspected, further diagnostic laboratory tests or referral to a medical specialist may be required. Psychological stressors may require professional psychological evaluation.

   Personnel: Physicians, nurses, psychologists.

   Timeline: Same visit as 2 or separate visit if a referral is required.

   B. Treat presumed cause. (Expert consensus)

   Goal: Treatment will focus on the likely etiology of the acute increase in or onset of fatigue.

   Procedure: Treatment may entail:
   - Management of comorbid medical conditions
   - Adjustment or cessation of medications
   - Psychotherapy or pharmacologic management of depression or acute anxiety
   - Acute environmental changes — such as a heat wave — may require education regarding cooling, referral for a cooling vest, or a medical leave of absence from work.
   - If no obvious etiology is determined based on evaluations in boxes 2 and 3A, a short trial of amantadine 100 mg q morning and afternoon is warranted.

   All patients should be instructed to return for repeat evaluation if the signs and symptoms of an MS exacerbation occur following a recent increase in or onset of fatigue.

Personnel: Physicians, nurses, psychologists, or allied health professionals for cooling vest.

Timeline: Treatment of an acute increase in or onset of fatigue should be reevaluated after 4 weeks.

C. Is fatigue sufficiently managed?
(Expert consensus)

Goal: To determine if further evaluations or management strategies are required for fatigue.

Procedure: The evaluation should focus on the progress of treatment and on the current impact of fatigue. MFIS may be used pre- and posttreatment to monitor progress.

- If the individual is improving but the fatigue is still significant, reevaluate in another 2 to 4 weeks.
- If the precipitant has resolved or is maximally managed and the fatigue is still significant, go back to box 2. (This is likely to occur if multiple potential etiologies were initially identified.)
- If fatigue is no longer identified as a problem, exit algorithm.

Personnel: Physicians, nurses, or other personnel involved in treatment initiated in box 3B.

Timeline: One visit.

4. Are the signs or symptoms consistent with a non-MS-related etiology?

(Expert consensus)

Goal: To decide if the signs or symptoms of chronic fatigue elicited in box 2 are consistent with comorbid medical conditions, medications, significant depression or psychological distress, or a primary or secondary sleep disorder, which could be a cause of chronic persistent fatigue.

Procedure: Analysis of information obtained after evaluation in box 2.

Personnel: Physicians, nurses.

Timeline: Same visit as box 2.

A. Diagnostic evaluation of presumed cause, if required.

(Expert consensus)

Goal: To clarify the etiology of chronic fatigue, if required.

Procedure: Initiate appropriate diagnostic studies or referrals, including the following:

- Diagnostic testing for suspected comorbid medical conditions
- Psychological evaluations for depression or psychological distress
- Sleep studies — polysomnogram (PSG) and multiple sleep latency test (MSLT) — to determine the cause of primary or secondary sleep disorders if initial empiric management of the sleep disorder is unsuccessful.

Personnel: Physicians, nurses, psychologists, sleep specialists.

Timeline: Initiate at time of box 2 visit or later if empiric management is tried and fails.

B. Treat presumed cause.
(Expert consensus)

Goal: To focus treatment on potential non-MS related etiologies of chronic fatigue.

Procedure: Determined by evaluations in boxes 2 and 4A. If more than one potential etiology is determined, then treatments should be initiated sequentially, beginning with the most likely cause of the patient's fatigue. For example, if medication side effects are suspected as a significant cause of fatigue, then medications should be adjusted before initiating new medications to treat suspected depression, which may or may not be contributing to fatigue. Special attention should be given to avoid treatments that may worsen fatigue.

Personnel: Physicians, nurses, psychologists, sleep specialists (if required).

Timeline: Initiate treatment after evaluations in boxes 2 and 4A are complete. Reevaluate in 1 to 3 months.

C. Is fatigue sufficiently managed?
(Expert consensus)

Goal: To determine if further evaluations or management strategies are required for fatigue.

Procedure: Repeat administration of the MFIS to assess current impact of fatigue. If fatigue is still inadequately managed, perform focused reevaluation of potential causes of chronic fatigue identified in boxes 2, 4, and 4A and determine if further management strategies of potential non-MS related causes of fatigue are required before moving to box 5 in the algorithm.

Personnel: Physicians, nurses.

Timeline: One visit after initiating treatment in box 4B.

5. Is fatigue likely a result of significant mobility or respiratory problems related to MS?

(Expert consensus)

Goal: To decide if fatigue is a result of mobility or respiratory impairments that significantly increase the energy cost of usual activities of daily living and to determine the likelihood that the rehabilitation measures listed below will improve the fatigue. (Note: Box 5 of the algorithm applies primarily to those people with MS who are severely disabled — that is, those who at a minimum require ambulatory aids for limited ambulation or who are wheelchair dependent.)

Procedure: Neurologic exam performed in box 2. This must include an evaluation of strength, spasticity, gait, transfer, and wheelchair mobility. May refer to occupational therapist or physical therapist to determine the need for therapies listed below, depending upon the impairment and disability issues identified.

Personnel: Physicians, nurses, occupational therapists (OTs), physical therapists (PTs).

Timeline: Same visit as box 2 or later if other treatments for potential non-MS related causes of fatigue are initiated prior to moving into this section of the algorithm.

A. Treat presumed cause.
(Expert consensus)

Goal: To provide severely disabled MS patients with focused rehabilitation designed to decrease the energy costs and increase the ease of performing daily activities.

Procedure: Treat as follows:

Mobility dysfunction

- Treat weakness or ataxia by introducing a strengthening program, gait assist devices, transfer devices, or wheelchairs or scooters.
- Treat spasticity through stretching exercises or pharmacotherapy. Avoid sedation when using pharmacotherapy.

MS-related respiratory dysfunction

- Provide expiratory muscle training and pulmonary evaluation if needed.

Personnel: Physicians, nurses, occupational therapists, physical therapists, physical medicine and rehabilitation specialists, pulmonary specialists.

Timeline: Evaluate treatment response after 1 to 3 months.

B. Is fatigue sufficiently managed?
(Expert consensus)

Goal: To determine the need for further assessments and treatments.

Procedure: Treat as follows:

- Focused examination including strength, spasticity, gait, transfers, and wheelchair mobility.
- Repeat MFIS to assess current impact of fatigue. If mobility is not optimized, pursue further treatment options. If mobility optimized and fatigue is still significant, go to box 6.

Personnel: Physicians, nurses, occupational therapists, physical therapists, physical medicine and rehabilitation specialists, pulmonary specialists.

Timeline: One visit.

6. Is primary MS fatigue confirmed?
(Expert consensus)

Goal: To serve as a checklist for the diagnosis of primary MS fatigue.

Procedure: Primary MS fatigue is a diagnosis of exclusion that requires the following:

- Management of all confounding medical comorbidity.
- Adjustment of medications as permitted.
- Management of depression as much as possible.
- Management of sleep disruption as well as possible.
- Treatment of mobility issues.

Personnel: Physicians, nurses.

Timeline: One visit.

6A. Initial management of primary MS fatigue.
(Class of recommendation–A; Expert consensus)

Goal: To educate the patient and initiate treatment for chronic primary MS fatigue.

Procedure:

Education and counseling. Sessions for consumers and caregivers should focus on the nature of MS fatigue and on common self-management strategies.
(Expert consensus)

Self-management strategies: Many individuals with MS are able to modify their lifestyles and environments with minimal help from allied health professionals. For example, some people stop smoking, modify their diets, manage their time differently, adjust their activity levels, take naps, drink cool beverages, take cool showers and baths for heat intolerance, begin an exercise program, or engage in relaxation exercises. For those who are disappointed with the results of self-management strategies or who require more structure and supervision, see box 7. (Expert consensus)

Pharmacotherapy

a) *Amantadine (100mg po q morning and afternoon).* (Class of recommendation–A)

b) *Pemoline (37.5mg po qd to 37.5 po q morning and q afternoon).* Pemoline may be considered in cases refractory to amantadine therapy, despite the generally negative results of two level II clinical trials. (Expert consensus) (See Pharmacologic Management (page 25) for a discussion of other potential drug therapies not currently supported by clinical research.)

Personnel: Physicians, nurses.

Timeline: Same visit as box 6. Initial management strategies should be given a 1- to 3-month trial before reevaluation.

6B Is fatigue sufficiently managed?
(Class of recommendation–A; Expert consensus)

Goal: To determine if further education or management strategies outlined in box 6A should be initiated or if individuals should be referred for assessment and intervention by an allied health professional.

Procedure: Repeat Modified Fatigue Impact Scale and assess response to treatment. If the response to initial management is inadequate, consider amantadine trial if the person elected not to try this initially; consider pemoline if the amantadine trial was inadequate; and/or refer for consultation with an allied health professional (see box 7).

Personnel: Physicians, nurses.

Timeline: One visit.

7. Allied health professional assessment and treatment.
(Expert consensus)

Assessment

Goal

- To determine current activity configurations and strategies to conserve energy and reduce fatigue at home, at work, and in the community.
- To determine current level of aerobic fitness and identify barriers to improvement in aerobic fitness.
- To determine physical, behavioral, social, cultural, and institutional environmental barriers in all relevant settings that increase fatigue and interfere with the accomplishment of desired goals.
- To determine current use and acceptance of adaptive equipment to improve mobility and decrease energy demands.

Procedure:

- Baseline completion of the MFIS if not recently completed.
- General occupational and physical therapy assessments, with emphasis on the history of fatigue; on the aggravating or ameliorating features of fatigue (for example, the effect of heat and exertion on various activities); and on the MS impairments associated with fatigue (for example, weakness, altered ambulation or mobility, spasticity, and ataxia).
- Evaluation by the caregiver; description by the individual; or onsite observation of the home, work, and community environments.
- Training in appropriate completion of an activity diary (see page 16).
- Aerobic fitness evaluation, including a determination of strength, identification of risk factors for exercise (using the American College of Sports Medicine guidelines for exercise testing and prescription in normal populations), and clinical evaluation of exercise tolerance.
- Evaluation of current adaptive mobility devices, such as standard or powered wheelchairs, scooters, walkers, or ankle foot orthotic (AFO), and acceptance as well as financial practicality of further modifications.

Treatment:

Goal: To systematically apply a rational combination of the four interventions listed below in a manner that is acceptable to the patient and that reduces the impact of fatigue. Choosing when and if an intervention is required depends on the individualized assessments performed by expert therapists and on the desired goals. (Note: Energy effectiveness strategies (EES) and aerobic exercise are usually central components of any strategy to lessen fatigue. Equipment and environmental modifications are required in some cases to enable people with MS to apply EES and perform exercise.)

Procedure:

Energy effectiveness strategies (See appendix entitled Teaching Energy Effectiveness Strategies)

- Review the completed activity diary with analysis of the energy cost of activities and the aggravating factors associated with worsening fatigue, including heat, stress, and sleep disruption.
- Review goals, prioritize activities, and determine strategies.
- Prepare a written plan for the following week's activities and determine the need for further interventions. Plan to meet weekly for 2 to 4 weeks.

Aerobic exercise

- Determine mode of aerobic exercise based on individual interest, ability, and availability.
- Recommend an individualized home exercise program consisting of 3 to 5 sessions per week at a mild to moderate level of perceived exertion for 3 to 30 minutes; increase by approximately 10 percent per week to maximum tolerance. [Note: Group exercise sessions may increase adherence. (Expert consensus)]
- Remember that heart rate via pulse monitoring may not be a good way to monitor exercise intensity in persons with MS due to sensory loss in the fingers and dysautonomia. Instead, perceived level of exertion may be a more accurate means of monitoring exercise intensity in dysautonomic individuals. (Note: No consensus was reached regarding reduction or discontinuation of an exercise program during an MS exacerbation.)
- Evaluate individuals who are weak to determine if certain muscle groups need to be strengthened so that aerobic exercise for cardiovascular training can be performed.

Equipment modifications

- Identify potential modifications, arrange trial, evaluate effectiveness, and obtain equipment required to decrease fatigue. Possible types include mobility equipment, self-care equipment, and ergonomic equipment.

Environmental modifications

- Identify potential modifications, arrange trial, evaluate effectiveness, and obtain, if necessary, appropriate environmental adaptations. This intervention will frequently require direct environmental assessment (such as job site evaluation, a home OT/PT evaluation, or a driving evaluation). Adaptations may include air-conditioning, modifications to the home or work site, ergonomic equipment, or modification to methods of transportation.
- Educate family members, employers, and other people in the home and work environments regarding the importance of suggested modifications.

Personnel:

- Therapists with experience in prescribing adaptive equipment and in teaching energy effectiveness strategies.
- Therapists with experience in aerobic fitness evaluation and training.

Timeline: Generally two assessments by each therapist, separated by 1 to 2 weeks. Training in Energy Effectiveness Strategies may require weekly sessions for 2 to 4 weeks.

7A. Is fatigue sufficiently managed?

Goal: To perform brief assessments to evaluate progress and assess the need for further supervision or additional interventions.

Procedure:

- Administer MFIS to assess fatigue status.
- Review activity configuration following modifications.
- Review cardiovascular fitness and progress with aerobic exercise.
- Review equipment and environmental adaptations and benefits.
- Assess the need for behavioral modification or vocational rehabilitation.

Personnel: Therapists involved in allied health interventions.

Timeline: Reassessments should be performed every 3 months during allied health professional intervention period.

SUPPLEMENT: Modified Fatigue Impact Scale (MFIS)

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following is a list of statements that describe the effects of fatigue. Please read each statement carefully, then *circle the one number* that best indicates how often fatigue has affected you in this way during the *past 4 weeks*. (If you need help in marking your responses, *tell the interviewer the number* of the best response.) *Please answer every question*. If you are not sure which answer to select, choose the one answer that comes closest to describing you. Ask the interviewer to explain any words or phrases that you do not understand.

Name:_____ Date: _____/_____/_____

ID#: _____ Test: 1 2 3 4

Because of my fatigue during the past 4 weeks...

		Never	Rarely	Sometimes	Often	Almost always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motivated to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13.	My muscles have felt weak.	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4

	Never	Rarely	Sometimes	Often	Almost always
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21.

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19.

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9.

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales.

APPENDIX: Fatigue Questionnaire

Fatigue is a feeling of physical tiredness or lack of energy that many people experience from time to time. Please read the following questions concerning your experience with fatigue and indicate the best response by checking the appropriate box. Some questions request written clarification of your response. If you have trouble answering any of the questions, please ask for assistance.

Name:_____ Date: _____/_____/_____

ID#: _____ Test: 1 2 3 4

1. How long have you experienced problems with fatigue?
   - ☐ Less than 6 weeks
   - ☐ Between 6 weeks and 3 months
   - ☐ Between 3 and 6 months
   - ☐ Greater than 6 months

2. How often have you experienced fatigue during the past month?
   - ☐ Daily
   - ☐ Most
   - ☐ Occasionally (fewer than half of the days)
   - ☐ Rarely

3. Is fatigue one of your top three problems with multiple sclerosis?
   - ☐ Yes
   - ☐ No

   If yes, list your top three problems with multiple sclerosis, beginning with the worst problem (possible answers include fatigue, weakness, imbalance, pain, numbness, memory loss, spasms, and inability to control urination).

   1._____

   2._____

   3._____

4. When does your fatigue typically begin during the day? (choose only one answer)
   - ☐ I awaken fatigued.
   - ☐ Fatigue begins later in the morning.
   - ☐ Fatigue begins in the early afternoon.
   - ☐ Fatigue begins in the late afternoon.
   - ☐ Fatigue begins in the evening.

5. How long do you typically feel fatigued during a usual day? (choose only one answer)
   - ☐ Less than 3 hours
   - ☐ 3 to 6 hours
   - ☐ 6 to 12 hours
   - ☐ 12 to 24 hours

6. Has fatigue significantly limited your activities at work or at home?
   - ☐ Yes
   - ☐ No

7. Have you been unable to fulfill any of your responsibilities at home or at work in the past month because of fatigue?
   - ☐ Yes
   - ☐ No
   - ☐ Not applicable (I do not have a job or I am disabled)

8. Does heat—in the form of a hot day, a hot bath or shower, or a fever—make your fatigue worse?
   - ☐ Yes
   - ☐ No
   - ☐ Not sure

9. Does cooling—in the form of a cool bath or shower, an air-conditioned room, or a cool drink—make your fatigue better?
   - ☐ Yes
   - ☐ No
   - ☐ Not sure

10. Have you exercised in the past month?
    - ☐ Yes
    - ☐ No

    If yes, how often did you exercise?
    - ☐ Less than once a week
    - ☐ Once or twice a week
    - ☐ Three times a week
    - ☐ More than three times a week

    If yes, what type of exercise did you do? _____

11. Has your fatigue significantly increased during the past month?
    - ☐ Yes
    - ☐ No

    If yes, what do you think is the reason(s) for this recent increase in fatigue? (check all that apply)
    - ☐ A relapse or attack of multiple sclerosis
    - ☐ A recent or current infection (for example, a urinary tract infection, bronchitis, sinusitis, or a cold)
    - ☐ Hot or humid weather
    - ☐ An increase in physical activity at home or at work
    - ☐ An increase in problems or stress at home or at work
    - ☐ Depression
    - ☐ Difficulty sleeping or frequent awakening
    - ☐ Medication (please list) _____
    - ☐ Other reason(s) not listed above (please describe)_____

12. Have you tried any of the treatments listed below for your fatigue? (check all that apply)
    - ☐ Napping or resting during the day
    - ☐ Taking cool showers or baths or drinking a cold beverage
    - ☐ Exercising
    - ☐ Changing your diet
    - ☐ Taking vitamins (please list)_____
    - ☐ Using a scooter or other device to conserve energy
    - ☐ Getting a handicap parking sticker to decrease walking distance
    - ☐ Changing your level of activity at home or at work or changing jobs
    - ☐ Taking amantadine (also called Symmetrel)
    - ☐ Taking pemoline (also called Cylert)
    - ☐ Drinking caffeinated beverages or taking caffeine pills
    - ☐ Taking fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), or another type of antidepressant medication
    - ☐ Taking 4-aminopyridine
    - ☐ Other treatments or medications not listed above _____

13. What fatigue medication are you taking now? _____

14. If you are currently taking a medication for fatigue, do you think it helps?
    - ☐ Not at all
    - ☐ A little, but it's hard to tell
    - ☐ I experience much less fatigue while taking this medication, but fatigue still limits my activities
    - ☐ I'm much better taking this medication, and I can do activities that were very difficult before starting the medication

APPENDIX: Sleep Questionnaire

Problems with sleep are very common and can contribute to your daytime fatigue. Please answer the following questions about your sleep.

Name:_____ Date: _____/_____/_____

ID#: _____ Test: 1 2 3 4

Sleep Habits

How much sleep do you usually get each night?_____

What time do you usually go to bed?_____

What time do you usually wake up?

How long does it usually take you to fall asleep? _____

How often do you usually wake up at night?_____

Why do you awaken at night? (choose all that apply)

- ☐ I don't know.
- ☐ I'm worried about something.
- ☐ Children or other family members awaken me.
- ☐ I need to urinate.
- ☐ I have muscle spasms.
- ☐ I experience pain (other than spasms).
- ☐ Other (please describe) _____

_____

_____

Have you ever had severe inability to sleep (insomnia)?	☐ Yes	☐ No	☐ Don't know
Do you feel excessively sleepy during the day?	☐ Yes	☐ No	☐ Don't know
Do you fall asleep even though you're trying not to?	☐ Yes	☐ No	☐ Don't know
Do you usually feel refreshed after a typical night of sleep?	☐ Yes	☐ No	☐ Don't know
Do you have headaches when you awaken in the morning?	☐ Yes	☐ No	☐ Don't know
Do you snore?	☐ Yes	☐ No	☐ Don't know
Do you thrash about in your sleep?	☐ Yes	☐ No	☐ Don't know
Do you frequently drink alcohol in the evening?	☐ Yes	☐ No	
Do you drink any caffeinated beverages in the evening?	☐ Yes	☐ No	
Do you nap during the day?	☐ Yes	☐ No	☐ Unable

How many naps do you usually take during the day? _____

How long do you usually nap? _____

Do you feel rested after daytime naps? ☐ Yes ☐ No ☐ Sometimes

APPENDIX: MS Daily Activity Diary

Instructions

1. At the top of the day's diary, describe how you slept the night before.
2. Assign a number value from **1 to 10** (1 being very low and 10 being very high) for:
   - Your level of fatigue **(F)**
   - The value or importance of the activity you are doing **(V)**
   - The satisfaction you feel with your performance of the activity **(S)**

   You can compute the "value" of an activity by comparing it to other activities you would like to do during the course of the day.

   For example:

   1 pm: F=7 V=3 S=2 Activity: Fixing lunch standing 15 minutes (hot); Comment: Blurred vision
3. Always describe the physical work done in the **Activity** section (e.g., stood to shower 10 minutes, went up 20 stairs, walked 200 feet).
4. Note the **external temperature** of the environment under Activity.
5. List under **Comments** all MS symptoms as they appear or worsen during the day, including cognitive problems, visual problems, weakness, dizziness, dragging foot, pain, numbness, burning, and so forth.
6. Make notes **every hour.**

Name: _____ Date: _____

Describe sleep last night: _____

Time	F	V	S	Activity	Comment
6:00 AM					
7:00					
8:00					
9:00					
10:00					
11:00					
12:00 PM					
1:00					
2:00					
3:00					
4:00					
5:00					
6:00					
7:00					
8:00					
9:00					
10:00					
11:00					

APPENDIX: Teaching Energy Effectiveness Strategies

Energy effectiveness strategies can be defined as the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home, and leisure activities in all relevant environments. Sessions on EES should be conducted by a trained professional, such as an occupational therapist. Although pharmacotherapy to maximize energy is usually initiated before attempts are made to modify activity levels, other therapies designed to maximize energy require the simultaneous teaching of EES if they are to have any chance of success. For example, aerobic exercise programs to maximize energy availability have little chance of success if they are not combined with training in cooling techniques and activity adjustments. For this reason, therapies such as aerobic exercise are frequently combined with an EES program.

The process of developing individualized strategies must be based on knowledge of the disease in combination with expertise in the following:

- Energy expenditures of daily activities
- Activity analysis
- Rest-activity ratios
- Adaptive equipment
- Community resources
- Applicable employment regulations
- Ability to educate and motivate others

Although the process is usually performed by an occupational therapist, simultaneous services rendered by physical therapists, social workers, psychologists, nurses, and vocational rehabilitation counselors are frequently required to assist with goal setting, behavior modifications, gait and mobility modifications, aerobic exercise programs, and work-related issues. By the end of the treatment period, which usually involves two to four 1-hour sessions, the average person should be able to use the process independently to develop additional activity strategies.

EES interventions are generally designed to enable individuals with MS to use their limited energy on useful, meaningful activities that they have chosen to do and that they can perform and organize in a different manner. The approach is based on the knowledge that quality of life and health are enhanced by exercising choice and control in everyday occupations.

The process of developing an EES program involves three steps:

Step 1

1. An initial assessment of the individual's fatigue using both qualitative and quantitative methods, such as the MFIS.
2. A detailed prospective activity diary that the individual can complete over the course of one week and can repeat at selected intervals.
3. Written short- and long-term goals.

Step 2

1. Expert diary analysis in conjunction with the individual.
2. Development of rest-activity ratios.
3. Identification of modifications in behavior combined with environmental and equipment changes.
4. A written summary of the energy-activity analysis and of general EES principles for the individual to take home.

Step 3

1. A final followup visit, several weeks later, in which the effectiveness of the modifications is assessed, further modifications are developed, and reiteration of the activity analysis process is presented.
2. Incorporation of other services, such as psychological counseling, vocational rehabilitation, and social work consultation to reach desired goals.

APPENDIX: Literature Review

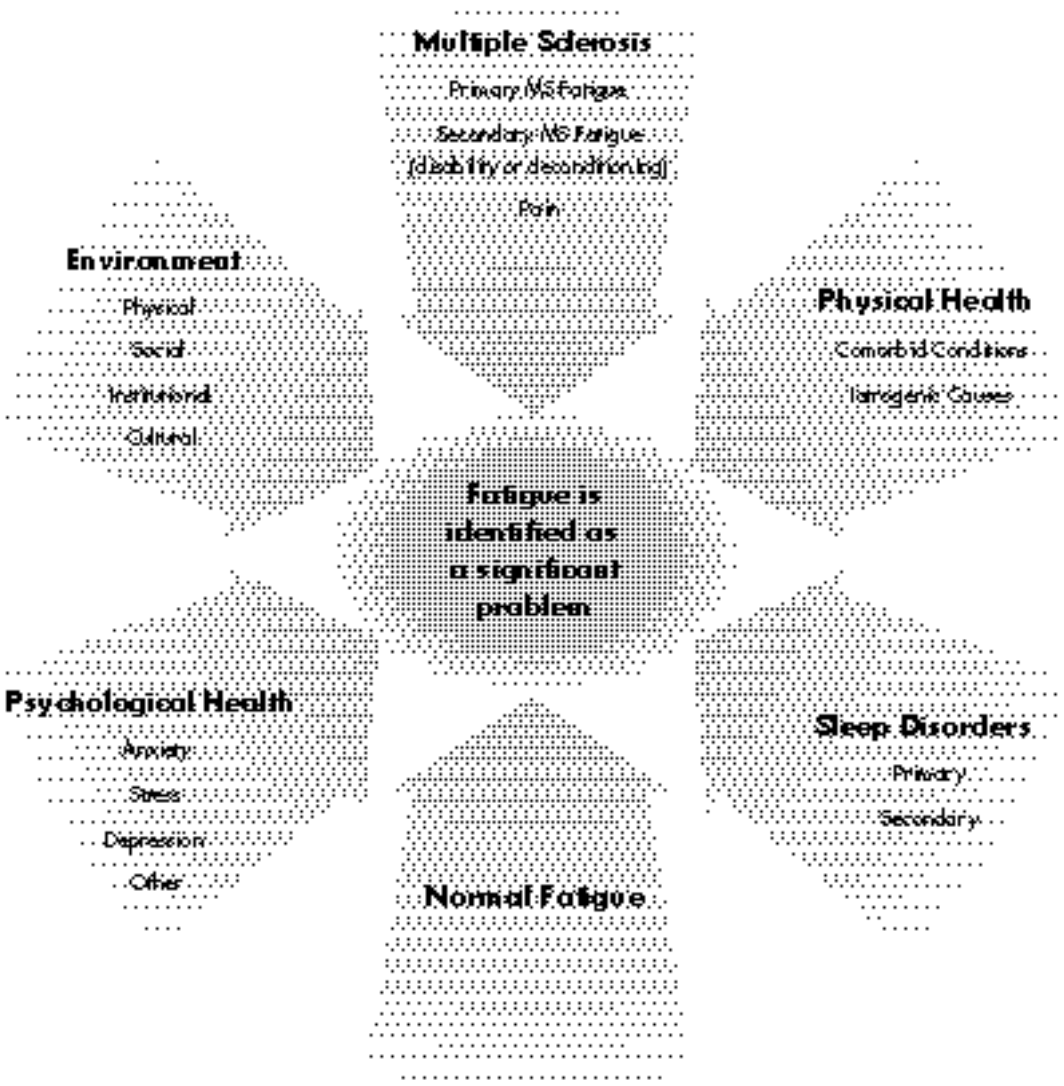
Methodology

A literature review was conducted by a professional librarian specializing in electronic databases, based on the dimensions of fatigue identified in Figure 1. The diagram outlines those dimensions, intrinsic and extrinsic to the disease process, that are likely to contribute to the development of fatigue. Under each dimension, factors were identified for which the following simple questions could be asked in the literature search:

- What is the evidence, direct or indirect, that a given factor contributes to fatigue in MS?
- What is the evidence, direct or indirect, that effective management of this factor modifies fatigue?

The literature review included Medline from 1986 to present (all languages), CINALH from 1982 to present, the Nursing and Allied Health Literature Index, and ClinPSYC from 1987 to present. The search identified

Figure 1. Potential Causes and Effects of MS Fatigue



700 potentially relevant abstracts for review by the entire Guidelines Development Panel. Complete articles of original research were selected for review if 70 percent of the panel voted that the abstract was relevant. Although the selection process was liberal, only 86 original research articles were identified for review. These articles were then assigned for review to particular panel members based on area of expertise. All articles were reviewed by at least two panel members, including the panel chair.

In the process of reviewing an article, panel members could select a citation for review if it was missed by the original search or was published prior to 1985 and looked to be relevant. The citation process identified approximately 50 original research articles for further review.

Each panel member completed a standardized form to score every article reviewed, which assessed the type of study, inclusion and exclusion criteria, outcome measures, conduct of study, results, statistical methods, and relevance. These forms were reviewed by the panel chair for completeness and accuracy prior to scoring. Only studies of sufficient merit based on pre-established criteria were included in the recommendations. A few of the articles that did not satisfy this requirement but did influence the expert consensus were noted as such and cited. Articles cited in the recommendations were categorized according to level of evidence.

Although the level of evidence provided by a study was an important determinant in development of the algorithm, only pharmacologic intervention studies using amantadine or pemoline reached level II significance (a class A recommendation). Therefore, most of the evaluations and all but the pharmacologic interventions recommended in the algorithm were based on the process of expert consensus discussed earlier (see page xi).

Overview of Fatigue in MS

Fatigue is a common symptom in both health and disease. Surveys and cross-sectional studies reveal that the major feature differentiating fatigue in MS from fatigue in normal health is the persistent incapacity associated with MS fatigue. Some 40 to 70 percent of individuals with MS who experience fatigue do so on a daily basis, typically up to 6 hours, usually in the afternoon (Freal et al., 1984; Fisk et al., 1994). Recent longitudinal studies suggest that people with MS who have severe fatigue do not experience significant spontaneous improvement of fatigue over intervals as long as 2 years (Cookfair et al., 1997). This is in stark contrast to individuals who do not have MS, whose fatigue fluctuates significantly over intervals as short as 2 weeks (Vercoulen et al., 1996a). Krupp et al. (1988) systematically defined the following characteristics that distinguished fatigue in MS from normal fatigue:

- It comes on easily.
- It prevents sustained physical functioning.
- It is worsened by heat.
- It interferes with responsibilities.
- It interferes with physical functioning.
- It causes frequent problems.

Features that did not distinguish fatigue in individuals with MS from those without MS included worsening of fatigue associated with exercise, stress, depression, prolonged physical activity, and time of day (afternoons), and improvement of fatigue with rest, sleep, positive experiences, and sex.

In most studies attempting to characterize fatigue in MS, it was assumed that study participants and clinicians were referring to the same phenomena. Krupp et al. (1988) attempted to define MS fatigue as follows: a sense of physical tiredness and lack of energy distinct from sadness or weakness. Implicit in this definition is a separation of fatigue from depression and MS-related weakness. Other clinicians have empirically categorized types of fatigue such as MS-specific fatigue (or lassitude), nerve fiber fatigue, the fatigue of depression, the fatigue of deconditioning, and normal fatigue (Schapiro et al., 1987). The splitting of the fatigue experience into discrete categories assumes the following:

- Different types of fatigue are defined by discrete pathophysiologic mechanisms.
- Categorizing fatigue types is required for appropriate management.

Although the Guidelines Development Panel recognized the need to categorize fatigue, it also recognized the problems inherent in most classification schemes.

- Evidence in support of different pathophysiologic mechanisms for different types of fatigue is often lacking or insufficient.

- The pathophysiologic substrate of fatigue in any given patient is complex and interrelated, usually resulting in the coexistence of multiple types of fatigue.
- Different types of fatigue can have the same management strategies.

The panel elected to categorize fatigue by defining the dimensions associated with fatigue in individuals with MS (see Figure 1). These include the dimensions of physical health, psychological health, sleep, MS, and the environment. These features can be subjected to scientific inquiry and utilized in the categorization of fatigue for appropriate management.

Dimensions of MS-Related Fatigue

Physical Health Dimension

Medical Comorbidity

Many medical specialties are called upon to evaluate the complaint of fatigue in the context of normal health and disease. At any point in time, the percentage of people with chronic fatigue in primary care practices ranges from 24 to 37 percent; some two-thirds of these cases presumably are due to identifiable medical and psychiatric conditions (Bates et al., 1993; Kroenke et al., 1988; Buchwald et al., 1987). Although the prevalence of comorbid medical conditions associated with fatigue has not been formally evaluated in MS populations, it is clear that individuals with MS are subject to all the common conditions associated with fatigue and require thorough evaluation before clinicians assume that fatigue is caused solely by MS. Although this statement may appear self-evident to experienced clinicians, all too often it is forgotten in the evaluation of individuals with MS. Common comorbid medical conditions associated with fatigue include infectious diseases, anemia, hypo- or hyperthyroidism, cardiovascular disease, pulmonary disease, renal disease, and hepatic disease. A thorough history, a review of systems, a medical examination, and, when appropriate, laboratory studies are clearly required when a person presents with a new or unusual complaint of fatigue.

Iatrogenic Causes

Of particular note is the necessity to identify iatrogenic contributions to fatigue. Table 2 lists level I evidence linking medications commonly prescribed for individuals with MS patients who have symptoms of fatigue, lethargy, asthenia, or sedation. It is incumbent upon the clinician to reevaluate the need for these medications if they may be contributing to fatigue. This is especially true if fatigue is the major complaint.

Summary

1. Thorough evaluation for alternative comorbid medical conditions as a cause of fatigue should be undertaken before assuming that fatigue is related to MS.
2. Medications that commonly contribute to fatigue should be adjusted whenever possible if the fatigue significantly interferes with quality of life.

Psychological Health Dimension

Empirical literature on the relationship between stress, coping, and anxiety and fatigue is virtually nonexistent. A few studies address the relationship between depression and fatigue. Point-prevalence estimates of the rate of depression among persons with MS range from 14 to 57 percent (Joffe et al., 1987; Whitlock and Siskind, 1980), while estimates of lifetime prevalence range from 37 to 54 percent (Minden et al., 1987; Schiffer et al., 1983). There are four basic issues in examining the relationship between fatigue and depression.

Do cross-sectional or prospective studies find a relationship between depression and fatigue?

One level I, one level III, and two level IV studies failed to demonstrate a relationship between fatigue and self-reported depression in MS (Cookfair et al., 1997; Vercoulen et al., 1996a; Fisk et al., 1994; Krupp et al., 1988). One level IV study reported low but statistically significant correlations between fatigue severity and depression (0.17), anxiety (0.21), social activity (0.22), and well-being (0.21-0.23) (Schwartz et al., 1996). Importantly, a low sense of environmental mastery was the best predictor of self-reported fatigue (0.31-0.36). One level IV study examined the relationship of depression and fatigue to adherence to medication regimens. It was found that both depression and fatigue were noted in individuals discontinuing interferon beta-1b. However, the results suggest that depression was the cause of both fatigue and treatment discontinuation (Mohr et al., 1996).

Does the treatment of depression have an effect on fatigue?

A level II study of group therapy for depression found that compared to controls, whose level of

(continued on page 22)

Table 2. Medications Prescribed to MS Patients that Cause Fatigue*

This information was derived from the 1998 *Physicians' Desk Reference* (Medical Economics, Inc.), unless otherwise stated. Agents are cited that cause symptoms in >5% of patients. The rate is indicated by the "+" sign (+ = 5-10%, ++ = 10-25%, +++ = 25-50%, ++++ = >50%). When a range was given "e.g., 5-11%," the number of "+s" corresponds to the highest number.

Analgesics
butalbital "among most frequent", butorphanol (Stadol NS) +++, dihydrocodeine "among the most frequent", fentanyl (Duragesic transdermal)++, hydrocodone (Vicoprofen)+, morphine "among frequent", oxycodone (Oxycontin) ++,
tramadol (Ultram) ++

Anticonvulsants
carbamazepine (Tegretol) "among most common", chlorazepate (Tranxene) "most frequent", divalproex (Depakote) +++, felbamate (Felbatol) +++, gabapentin (Neurontin) ++, lamotrigine (Lamictal)++, phenobarbital "can develop during therapy"[1], primidone (Mysoline) "occasional"

Antidepressants
buspirone (Buspar) ++, clomipramine (Anafranil) ++++, doxepin (Sinequan) "most common",
fluoxetine (Prozac) ++, fluvoxamine (Luvox) ++, mirtazapine (Remeron) ++++, nephazodone (Serzone) +++, paroxetine (Paxil) ++, sertraline (Zoloft)++, trazodone (Desyrel) +++, tricyclic agents "most frequent"[1], venlafaxine (Effexor) +++

Antihistamines
astemizole (Hismanal)+, azatedine (Trinalin) "among most frequent", azelastine (Astelin)++, cetirizine (Zyrtec)++, chlorpheniramine "among most common", diphenhydramine "among most frequent", loratadine (Claritin)+, phenylephrine "among most common", terphenadine (Seldane)+

Antihypertensive
acebutolol (Sectral) ++, amiloride (Moduretic) +, atenolol (Tenoretic, Tenormin)+++, benzapril (Lotensin)+, betaxolol (Kerlone)+, carteolol (Cartrol)+, clonidine (Catapres, Combipress)+++, diltiazem (Tiazac)+, doxazocin (Cardura)++,
guanadrel (Hylorel) ++++, guanfacine (Tenex) ++, labatelol (Normodyne, Trandate)+, metroprolol (Lopressor, Toprol)+, nifedipine (Adalat)++, perindopril (Aceon)+, prazosin (Minipress, Minizide)+

Anti-inflammatory
fenoprofen (Nalfon)+, ketorolac (Toradol)+, naproxen (Anaprox, Naprelan, Naprosyn), tolmetin (Tolectin)+

Antipsychotic
clozapine (Clozaril)+++, mesoridazine (Serentil) "one of the 2 most prevalent," molindone (Moban) "most frequent", olanzapine (Zyprexa)++, risperidone (Risperdal)+++

Asthma drugs
fluticasone (Flovent) +++, terbutaline ++

Carbonic anhydrase inhibitors
dichlorphenamide (Daranide) "among the most common"

Cardiac
bepridil (Vascor)++, amiodurone (Cordarone)+, disopyramide (Norpace)+, flecainide (Tambocor) +, nifedipine (Procardia)++, quinine (Cardioquin, Quinidex)+, satolol (Betapace) ++

Diabetic agents
glipizide (Glucotrol)++, troglitazone (Rezulin)+

Gastrointestinal
Bentyl +, granisetron (Kytril)++, metoclopramide (Reglan)+

Genitourinary
terazocin (Hytrin ++)

Hormone replacement
Depo-Provera (medroxyprogresterone)+, progesterone cream (Crinone)+++, leuprolide (Lupron)+ (Lupron depot preparation)++

Immune modulators
interferon beta-1a (Avonex) ++, interferon beta-1b (Betaseron)+++

Muscle relaxants
carisoprodal (Soma) "most frequent", cyclobenzaprine (Flexeril) +++, dantrolene (Dantrium) "among the most frequent", diazepam (Valium) "among the most common", tizanidine (Zanaflex)++++

Nicotine agents
Habitrol +, Nicotrol Nasal Spray +, Prostep+

Sedative hypnotics
alprazolam (Xanax) ++++, clonazepam (Klonopin)+++, diazepam (Valium) "among the most common," estazolam (ProSom)+++, quazapam (Doral)++, secobarbital "most common", temazepam (Restoril) ++ , triazolam (Halcion) ++, zoloprim (Ambiens)+

Other
dexfenfluramine (Redux)++, fenfluramine (Pondimin) "among most common", scopolamine (Transderm Scop)++

* "Fatigue," "weakness" ("asthenia"), "somnolence," and "lethargy."

[1] 1994-1997 Gold Standard Multimedia, Inc.

fatigue increased during the trial, fatigue in individuals treated for depression declined slightly (Crawford and McIvor, 1987).

Does the treatment of fatigue have an effect on depression?

A level II study examining the potential benefits of amantadine as a treatment of MS-related fatigue concluded that amantadine benefited fatigue but had no effect on depression (Krupp et al., 1995). This conclusion is difficult to substantiate because severely depressed people were excluded from the study. Another level II study of 3 months duration examining the effects of exercise found statistically significant but short-lived improvements for both fatigue, as measured by the Sickness Impact Profile, and depression (Petajan et al., 1996). However, although exercise is often recommended for people with MS, treatment of fatigue was not the goal of the intervention in the study.

The measurement of fatigue and depression may be confounded in measures of depression.

Because fatigue is a symptom used in the diagnosis of depression (American Psychiatric Association, 1994), most methods of assessing depression are confounded by fatigue. For example, in an analysis of the Beck Depression Inventory (BDI) (Beck et al., 1961), Mohr et al. (1997b) found that the item assessing fatigue accounted for 15 percent of the total depression score among individuals with MS, as opposed to 6 percent in people who did not have MS but were diagnosed with major depression and 11 percent in normal controls. If items from the BDI identifying work difficulty or concerns about health — both common in MS and not necessarily related to depression — were added to the item concerning fatigue, then the total contribution to the total BDI score increased to 34 percent in the MS group but only 17 percent in the major depression group and 19 percent in the healthy control group. Thus, much of the literature identifying a relationship between fatigue and depression using self-report measures may be affected by problems of validity.

Summary

1. Studies examining individuals with MS generally find little or no relationship between depression and fatigue. There is, however, some evidence that within depressed MS samples fatigue and depression are related. Depressed individuals with MS treated with psychotherapy show lower levels of posttreatment fatigue as compared to untreated depressed individuals with MS.
2. Although stress, coping, anxiety, and other forms of psychological distress are suspected to contribute to fatigue in MS, this has not been examined empirically.

Sleep Dimension

Recent studies report disrupted sleep in 25 to 35 percent of individuals with MS (Clark et al., 1992; Ferini-Strambi et al., 1994; Vercoulen et al., 1996a). Common causes include neurogenic bladder dysfunction, spasticity or spasms, anxiety, depression, and pain (Leo et al., 1991; Saunders et al., 1991; Clark et al., 1992). Less commonly, the etiology is a primary sleep disorder such as sleep apnea or periodic leg movements, but limited evidence suggests that the frequency of these disorders in MS is still much greater than in control populations (Ferini-Strambi et al., 1994).

Although it is reasonable to expect a relationship between disrupted sleep and daytime fatigue, studies addressing this issue have had mixed results. Two level IV studies reported a relationship between nocturnal awakening and daytime fatigue (Leo et al., 1991; Saunders et al., 1991). Both studies reported an association of depression with nocturnal awakening, but the variance contributed by depression to daytime sleepiness was not assessed. One level III study (Vercoulen et al., 1996a) and one level II study (Krupp et al., 1995) reported no relationship between disrupted sleep or depression and daytime fatigue severity. Both studies assessed sleep, depression, and fatigue prospectively over 2 to 6 weeks using validated, reliable, self-report measures. Despite the quality of these later studies, the low proportion of depressed patients (17 percent) in the first study and the exclusion of significantly depressed individuals from the second study confounds any conclusions regarding this association.

More problematic is distinguishing daytime complaints of fatigue from excessive daytime sleepiness related to primary or secondary sleep disorders. Tiredness, fatigue, and sleepiness are considered similar symptoms by many people. To distinguish the nature of a person's complaint, it is crucial to take a structured approach that includes

a general medical and psychological assessment, a sleep history from both the patient and the bed partner (if one), and an assessment of daytime sleepiness. Features suggestive of a primary sleep disorder may require assessment through polysomnography and, at times, a multiple sleep latency test.

In the assessment of symptoms suggestive of upper airway sleep disordered breathing, it is important to remember that women frequently do not fit the clinical picture that is well-described in men. Women are more likely to report morning fatigue and morning headache and are less likely to report restless sleep or to have been informed of apnea during sleep (Ambrogetti et al., 1991). Not infrequently, these women are not obese and have normal neck circumferences. A distinguishing feature in younger, thinner women is the presence of overbite and high ogival hard palates (Guilleminault et al., 1995). These features must be appreciated to assess sleep disorders in MS, since the majority of patients are young women.

Despite the theoretical link between disrupted sleep and daytime fatigue in people with MS, no study has directly evaluated the benefits of improved sleep on daytime fatigue. Interestingly, studies of aerobic exercise document improved sleep and quality of life with no detrimental effect on daytime fatigue (Petajan et al., 1996).

Summary

1. Primary and secondary sleep disorders occur in MS and may contribute significantly to daytime fatigue.

The Multiple Sclerosis Dimension

Primary MS Fatigue

Studies seeking to identify the component of fatigue directly attributable to the MS disease process (primary fatigue) have investigated characteristics of MS associated with fatigue severity. An early level IV study involving a small cohort of people with MS failed to show a relationship between Fatigue Severity Scale (FSS) scores and neurologic disability, as measured by the Expanded Disability Status Score (EDSS) (Krupp et al., 1988).

However, a recent level I, phase III clinical trial of interferon-beta 1a in mild relapsing remitting MS showed a correlation between FSS scores and EDSS scores at baseline and at week 104 (Cookfair et al., 1997). Correlations between EDSS and FSS remained after adjusting for Beck Depression Inventory scores. Importantly, within-patient worsening in FSS scores over 2 years was significantly greater for individuals whose MS disease progressed by EDSS during the trial and only weakly correlated with the number of exacerbations in the previous 2 years. The majority of these low disability people with MS (EDSS range of 1–3.5) reported severe fatigue; almost 60 percent had FSS scores of 5.0 at baseline (FSS range of 1–7). On average, only persons with baseline FSS scores < 5.0 showed a worsening in FSS score by week 104 (37 percent of study participants). The majority of participants showed remarkably stable and persistent levels of fatigue over the 104 weeks of the study.

This ceiling effect of self-reported fatigue severity in individuals even mildly affected may be responsible for the observation in previous small cross-sectional studies reporting little or no correlation between fatigue severity and disability.

The results of the Cookfair study (1997) confirm the high prevalence of severe fatigue in even mildly disabled individuals with MS. This finding is consistent with previous surveys in which one-third to one-half of persons with MS reported fatigue predating the onset of other symptoms of MS, sometimes by years (Krupp et al., 1988; Fisk et al, 1994). It is tempting to speculate that this appearance of fatigue prior to other symptoms of MS is directly related to the MS disease process, since approximately one-third to one-half of patients presenting with their first identifiable symptoms of MS (i.e., optic neuritis, transverse myelitis, or a brainstem syndrome) have disseminated white matter lesions by magnetic resonance imaging that must have been present for some time prior to diagnosis (Morissey et al., 1993; Beck et al., 1993). The finding that FSS scores did not correlate with T2 lesion burden in the Cookfair et al. study does not detract from this hypothesis, because a recent study associating frontal lobe and basal ganglia hypometabolism with fatigue in MS also did not find any correlation between MRI abnormalities and fatigue (Roelcke et al., 1997).

Despite the known association between the MS disease process and fatigue, the specific pathophysiologic mechanisms resulting in the subjective sense of fatigue are still unclear. Current research indicates four

hypothetical sources of this fatigue. First, evidence from event-related potential recordings during auditory memory tasks suggests an impairment between stimulus evaluation and activation of motor programs (Sandroni et al., 1992). This is consistent with the observation of frontal lobe hypometabolism in fatigued individuals with MS (Roelcke et al., 1997) and could account for a cortical component to fatigue. The mechanism of this cortical impairment is unknown, but could involve conduction block involving intracortical circuits.

Second, fatigue could be a manifestation of intermittent conduction block in partially demyelinated central motor pathways. Either mechanism could presumably account for the heat sensitivity of individuals with MS and has specific therapeutic implications. Current evidence favors a cortical component to the subjective sense of fatigue, since a recent level IV study attempting to document conduction block in central motor axons of individuals with MS under fatiguing conditions was unable to substantiate this hypothesis (Sheean et al., 1997).

Third, recruitment of alpha motor neurons is impaired because of corticospinal tract involvement and could result in increased energy demands for muscle activation (Rice et al., 1992). Fourth, abnormal coactivation of agonists and antagonists associated with spasticity could increase energy demands (Olgiati et al., 1988). Lastly, there is no evidence at present linking mediators of inflammation (e.g., cytokines such as tumor necrosis factor) in people with MS and fatigue.

Secondary MS Fatigue

Deconditioning. Although MS is strictly a disease of the central nervous system, peripheral sources of fatigue could involve a number of mechanisms. A series of level IV observations suggest an intramuscular component to fatigue in MS (Miller et al., 1990; Kent-Braun et al., 1994; Sharma et al., 1995). Using intermittent isometric tetanic stimulation of dorsiflexor muscles in individuals with MS to isolate peripheral and central sources of fatigue, the researchers concluded that muscle fatigue in MS was, at least in part, a result of impaired excitation-contraction coupling and abnormal muscle metabolism. Furthermore, they found a relationship between the impaired muscle fatigue and the Ashworth score of spasticity and foot tapping rates, suggesting changes in muscle secondary to upper motor neuron impairment.

However, the researchers were not able to correlate muscle fatigue with an individual's subjective sense of fatigue. These results further suggest that aerobic exercise and strengthening may be important to prevent secondary changes in muscle due, in part, to deconditioning.

Respiratory Muscle Weakness. Another potential peripheral source of fatigue is respiratory muscle weakness. Even people who are ambulatory may demonstrate a reduced exercise capacity at least partially due to inspiratory or expiratory muscle fatigue (Foglio et al., 1994). As the disease progresses and people become wheelchair dependent, respiratory muscle weakness may become an important source of peripheral fatigue and may also result in significant sleep disruption (Smeltzer et al., 1996). The contribution of deconditioning to respiratory muscle weakness and the potential improvements in respiratory muscle function with exercise and expiratory training need to be confirmed in further studies. No studies have attempted to link subjective fatigue with respiratory muscle weakness in people with MS.

Pain. The relationship between pain and MS fatigue has not been clarified. Recent level IV studies involving outpatients representative of a geographic area suggest that 40 to 53 percent of people with MS experience chronic pain, often ill-defined in etiology (Moulin et al., 1988; Warnell, 1991; Archibald et al., 1994). Of interest is the common association of chronic widespread or regional pain, sleep disturbance, and fatigue in MS (Warnell, 1991; Archibald et al., 1994).

Summary

1. Fatigue can occur very early in the disease process and frequently occurs in the absence of neurologic impairment. One level I study suggests an association between disease progression and increasing fatigue severity. This requires further confirmation.
2. The specific contribution of central and peripheral mechanisms to MS fatigue is unclear and requires further study.
3. The association of chronic pain and fatigue in MS has not been clarified and requires further study. One level IV study suggests that fatigue aggravates pain in MS, but the association needs to be clarified (Warnell, 1991).

Environmental Dimension

It was the consensus of the panel that people's experience of fatigue is influenced by their physical, social, cultural, and institutional environments.

However, the evidence for these relationships is scant to nonexistent. One exception to this is the effect of elevations in core and ambient temperature on neurologic function and fatigue, a subject recently reviewed by Syndulko et al. (1996). Numerous published observations and controlled studies of heating reactions since Uhthoff's initial report in 1890 have estimated the incidence of heat sensitivity in individuals with MS to be between 60 percent and 80 percent. A similar incidence of heat-related worsening of MS fatigue was documented in two level IV studies (Freal et al., 1984; Krupp et al., 1988). More importantly, this phenomenon can be observed with core temperature elevations as little as 0.5°F (i.e., normal diurnal temperature fluctuations). Therefore, heat sensitivity must be considered as a dimension of fatigue during everyday activities of daily living as well as during the heat waves of summer.

The exact mechanisms by which heat may worsen neurologic signs and symptoms in MS remain unclear. Presumably, the enhanced susceptibility of demyelinated axons to conduction block with elevations in temperature plays an important role in this phenomenon (Davis and Jacobson, 1971; Rasminsky, 1973).

Summary

1. Heat sensitivity is associated with MS-related fatigue. However, the relative contribution of heat sensitivity to the increase in MS-related fatigue associated with everyday activities of daily living is unclear.

Treatment

Pharmacologic Management

Amantadine

Amantadine, an antiviral agent as well as a dopamine agonist, has been used for the treatment of fatigue in MS since the early 1980s. The mechanism of action of this drug is unknown. Four level II clinical trials assessed the benefit of amantadine for MS-related fatigue (Murray, 1985; Canadian MS Research Group, 1987; Cohen and Fisher, 1989; Krupp et al., 1995). All four trials were short (3 to 6 weeks), and all but one employed a randomized, crossover design with 2-week washout periods. The remaining trial was a randomized, parallel design, placebo-controlled trial of amantadine and pemoline (Krupp et al., 1995). All studies excluded people with severe depression and significant medical comorbidity. Two studies required a 2-week run-in phase to determine the stability of fatigue severity (Canadian MS Research Group, 1987; Krupp et al., 1995). All studies utilized different self-report measures of fatigue, making direct comparisons difficult.

Murray's study involved participants with the lowest disability and reported the most significant results: moderate to marked improvement on amantadine occurred in 37 percent of participants (total n = 32) with 60 percent blindly electing to remain on therapy (Murray, 1985).

The Canadian MS Research Group studied participants who were more disabled (mean EDSS 4.3); 50 percent of participants were characterized as having progressive MS. Significant improvement in fatigue visual analog scores and in physical activity visual analog scores was reported; 41 percent of patients preferred amantadine compared to 21 percent preferring placebo.

The study by Cohen and Fisher (1989) also involved people with moderate disabilities (mean EDSS 4.0), with 45 percent of them progressive; 68 percent of participants had higher overall ratings on amantadine using an outcome measure identifying 7 dimensions of fatigue, each scored on a 5-point scale. Approximately 36 percent of patients preferred amantadine to placebo. Importantly, this study reported significant improvements in energy, attention, concentration, problem solving, and well-being and in objective performance on a neuropsychological measure (the Stroop Test) for the amantadine group.

The final study involved predominately relapsing-remitting persons with low disability, randomized to treatment with amantadine (n = 31), pemoline (n = 27), or placebo (n = 35) (Krupp et al., 1995). The group treated with amantadine showed a significantly greater reduction in fatigue, as measured by the MS-Specific Fatigue Severity Scale (Krupp et al., 1995), compared to the placebo group. Some 79 percent of the participants treated with amantadine versus 52 percent treated with the placebo and 32 percent treated with pemoline reported a preference for drug therapy compared with no treatment.

Side effects reported with amantadine therapy for MS-related fatigue are generally mild, but can include hallucinations, vivid dreams, nausea, hyperactivity, anxiety, insomnia, constipation, and rash. Less than 10 percent of the people treated with amantadine discontinue therapy because of side effects.

Summary

1. Accounting for placebo effects, approximately 20 to 40 percent of mild to moderately disabled people with MS show significant short-term reductions in fatigue on amantadine.
2. Amantadine is generally well tolerated.
3. Some people become refractory to amantadine therapy over time. Long-term treatment with amantadine has not been studied.

Pemoline

Pemoline, a central nervous system stimulant, has been used for the treatment of fatigue. Two level II clinical trials assessed the benefits of pemoline in the treatment of MS-related fatigue (Weinshenker et al., 1992; Krupp et al., 1995).

As mentioned previously, the study by Krupp et al. reported no benefit, with fewer participants treated with pemoline preferring the drug compared to the placebo. Pemoline was initiated at a dose of 18.75 mg per day and gradually escalated to a maximal dose of 56.25 mg per day. Similarly, the study by Weinshenker et al. initiated treatment at a low dose but gradually escalated to a higher dose (75 mg per day). Forty-six percent of people treated with pemoline reported good or excellent results, compared to 20 percent on placebo during this randomized, crossover trial. Unfortunately, with the higher doses used in the Weinshenker et al. study, 25 percent of participants experienced side effects and 7 percent discontinued pemoline because of side effects. This compares to less than 5 percent of participants experiencing side effects with the smaller doses studied by Krupp et al. Common side effects associated with pemoline include anorexia, irritability, and insomnia.

Summary

1. Pemoline may be an effective short-term treatment of MS-related fatigue at a dose of 75 mg per day, but the side effects at this level are significant.
2. One small study suggested that lower doses of pemoline are not as beneficial as amantadine.
3. Long-term treatment with pemoline has not been investigated.
4. Pemoline may be effective therapy for MS-related fatigue in people who do not respond to amantadine.

Other Medications

The aminopyridines, 4-aminopyridine (AP) and 3,4-diaminopyridine (DAP), are potassium channel blockers shown to improve nerve conduction in experimentally demyelinated axons. Preliminary studies of AP and DAP demonstrated benefits in temperature-sensitive persons with MS and improvement in some neurologic function (reviewed in Bever, 1994). Neither drug has been approved for therapy in the United States, but further studies are planned.

Although the panel recognizes that selective serotonin reuptake inhibitor (SSRI) therapy is used to treat fatigue in MS, there is no evidence or expert consensus to support its use. Because no studies have been reported on SSRI therapy in the treatment of MS-related fatigue, no recommendations can be made at this time.

Summary

1. No expert consensus or scientific studies support the use of aminopyridine or SSRI therapy for MS-related fatigue at this time.

Aerobic Exercise

Historically, people with MS have been told to limit their physical activity in order to avoid elevations of body temperature and minimize fatigue. Furthermore, some people with MS report that initiation of an exercise program worsens fatigue and avoid all forms of exercise to prevent this from occurring (Freal et al., 1984; Krupp et al., 1988). This results in an increasingly deconditioned state with further increases in weakness and fatigue.

A recent level II randomized, controlled trial of an aerobic training program in mildly to moderately disabled people with MS demonstrated that people with MS can improve fitness (Petajan et al., 1996). Following 15 weeks of 3 40-minute training sessions per week, the exercise group demonstrated significant increases in maximum aerobic capacity (VO2 max increase of 22 percent versus 1 percent), physical work capacity (48 percent versus 12 percent), and maximum voluntary isometric muscle strength of most upper extremity muscle groups and the knee extensor group. Furthermore, improvements in VO2 max were highly correlated with decreases in fatigue ($r = -0.68$). Quality-of-life measures (Sickness Impact Profile) showed significant improvements in all physical

dimensions as well as in social interaction, emotional behavior, home management, and recreation and pastimes. Another health status measure (Profile of Mood States) showed depression and anger scores were significantly reduced at weeks 5 and 10, and fatigue was reduced at week 10.

Unlike the results of a previous pilot study of cardiovascular fitness in MS (Schapiro et al., 1987), the Petajan study found that training effects were not related to the level of neurological impairment as measured by the EDSS. This study suggests the need for an increasing role for exercise therapy in maintaining fitness and well-being in people with MS.

Summary

1. Aerobic exercise therapy improves cardiovascular fitness, strength, and health status in people with mild to moderate disability from MS.
2. Aerobic exercise therapy may help improve fatigue in mildly disabled people with MS.

Cooling Therapy

The adverse effects of heat on MS symptoms in general and fatigue in particular have already been mentioned.

Recent technology has led to the development and marketing of active and passive cooling garments to control body temperature in individuals with MS. However, studies to determine the efficacy of cooling therapy are limited. One level V study reported improvement in fatigue and strength for approximately 2 hours following 45 minutes of cooling with the Mark VII microclimate system (Capello et al., 1995). A pilot level II study comparing cooling versus sham cooling reported improvement in neurologic function in the cooling group, but fatigue was not assessed (Coyle et al., 1996). The clinical significance of the benefits observed is unclear.

Summary

1. Cooling is beneficial in reducing fatigue in heat-sensitive individuals with MS.

Energy Effectiveness Strategies

Although teaching energy effectiveness strategies to people with MS to decrease their fatigue is a well-established practice (Copperman et al., 1994; Welham, 1995), review of the MS literature did not find any scientifically based evidence to establish the efficacy of this practice. Recommendations are based on extensive experience and professional consensus. One survey of neurologists at MS centers found that 95 percent reported treatment by occupational therapy as somewhat, moderately, or very effective in treating fatigue (Copperman et al., 1994). A small British survey indicated that all hospitals and rehabilitation units sampled utilize occupational therapists to instruct individuals with MS in EES (Welham, 1995).

Summary

1. Teaching EES to individuals with MS to reduce fatigue is a well-established practice.

DIRECTIONS FOR FUTURE RESEARCH

The Guidelines Development Panel identified a broad range of topics needing further research. The panel recommended that researchers undertake studies to:

- Determine the clinical relevance and utility of self-report fatigue measures — such as the MFIS and FSS — in managing MS-related fatigue.
- Determine the cost-effectiveness of diagnostic tests to identify comorbid medical conditions associated with fatigue in people with MS.
- Identify screening measures for depression in people with MS that are not confounded by symptoms of fatigue or concerns related to work or health, items that may not be related to depression in this population.
- Determine if treatment of depression in people with MS improves fatigue.
- Determine the relationship of stress and anxiety to MS-related fatigue.
- Determine if standard sleep laboratory techniques such as polysomnograms are useful and cost-effective in the evaluation of primary and secondary sleep disorders in people with MS-related fatigue.
- Determine if treatment of primary or secondary sleep disorders improves daytime fatigue in people with MS.
- Determine the mechanisms of primary MS-related fatigue.
- Determine the relationship between specific MS-related impairments — such as cognitive or upper motor neuron dysfunction and respiratory muscle weakness — and MS–related fatigue.
- Determine the relationship between chronic pain and fatigue in MS.
- Determine if expiratory muscle training improves fatigue in severely impaired MS patients.
- Determine the effect of physical, social, cultural, and institutional environments on MS-related fatigue.
- Determine the appropriate use and benefits of cooling therapy for MS-related fatigue.
- Determine if aminopyridines are beneficial and safe in the treatment of MS-related fatigue.
- Determine if selective serotonin reuptake inhibitor therapy is beneficial in the treatment of MS-related fatigue in depressed and nondepressed MS patients.
- Determine optimal methods of teaching energy effectiveness strategies (formerly known as energy conservation) to allied health professionals and individuals with MS.
- Determine the effectiveness of EES in reducing the severity or impact of fatigue in individuals with MS.
- Determine the long-term benefits of amantadine in treating MS-related fatigue.
- Determine if aerobic exercise reduces fatigue in people with MS.
- Determine if moderate to severely disabled individuals with MS who also experience significant fatigue tolerate aerobic exercise.

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