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Fatigue in Multiple Sclerosis

Reducing the Impact Through Comprehensive Management

R. Philip Kinkel, MD

ABSTRACT

Fatigue is a common feature of multiple sclerosis (MS), affecting more than three fourths of patients, but it may also be one of the least understood. Multiple contributing factors, an insufficient understanding of the pathogenesis, and symptoms that mimic other disorders such as depression make the identification and management of fatigue in MS a difficult clinical challenge. A comprehensive management plan is necessary, however, because fatigue has been identified as the single most disabling symptom in the MS patient, with a severe impact on quality of life and the ability to perform activities of daily living. This supplement to the International Journal of MS Care addresses the overall management of fatigue in MS, identifying the potential causes and symptoms as well as the available treatment options.

Fatigue is the most common symptom in multiple sclerosis (MS). Overall, 75% to 90% of persons with MS report having fatigue, and 50% to 60% report it as the worst symptom of their disease.^{1,2} Fatigue can severely affect an individual's quality of life and functioning, even if the level of disability appears to be insignificant to the outside observer. Many MS care providers are unaware that fatigue is also a major reason for unemployment, especially for those individuals with otherwise minor disability. Moreover, fatigue in MS has a severe effect on patients' ability to feel as if they have control over their illness.

Uncertain Pathophysiology

Until 15 years ago, fatigue was a largely unrecognized symptom of MS; Freal et al² played an instrumental role in increasing awareness of this symptom. However, despite our increased awareness of MS fatigue as a primary symptom of the disease, MS researchers in particular still have

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very little idea of the underlying pathophysiologic mechanisms.

Since the 1980s, several studies have attempted to develop a better understanding of MS-related fatigue. Most have been cross-sectional investigations examining the characteristics of fatigue and the relationship of fatigue to other MS symptoms. Much like other MS impairments, such as cognitive dysfunction, no real association has emerged between MS-related fatigue and age, sex, or disease duration (see Table 1). There is also very little association between MS fatigue and typical magnetic resonance imaging (MRI) markers of the disease, such as regional or global T2 lesion burden or gadolinium-enhancing lesion activity.³⁻⁵ Only a weak association between fatigue and disability (as measured with the Expanded Disability Status Scale [EDSS]) has been observed after adjusting for depression (see Table 1).^{4,6,7}

Researchers have also found only a weak correlation between fatigue and MS progressive course after adjusting for EDSS score.⁷

The insufficient understanding of the pathophysiologic basis of MS fatigue has made the search for pharmacologic strategies especially difficult. Of the various ways that fatigue can be assessed, the most important and most widely used means has been through the use of patients' subjective reports. However, there is very little association between these subjective experiences and pathophysiologic measures of fatigue such as frequency-dependent conduction blocks, decreased central motor drive to α neurons,⁸ neuromuscular blockade, or excessive muscular fatigue

Table 1
Associations Between MS Characteristics and Fatigue

No Association

- Age
- Sex
- Disease duration
- MRI measures:
 - Regional/global T2 burden
 - Gd-enhancing activity

Weak Association

- EDSS (after adjusting for depression)
- Disease type (progressive>relapsing)
- Depression (after adjusting for EDSS)

MRI, magnetic resonance imaging; Gd, gadolinium; EDSS, Expanded Disability Severity Scale.

from either changes in muscles or simple deconditioning.

Fatigue does appear to be related to disruption of intracortical circuits, as has been made evident in recent studies using event-related potentials and positron-emission tomography (PET) scanning.^{3,9} In 1997, Roelcke et al³ published an important study that was the first to localize a potential association between focal brain dysfunction and fatigue in MS. This investigation, which used PET scanning to examine the brains of MS patients with and without fatigue, found decreased glucose utilization in the frontal lobes and basal ganglia in the individuals with fatigue. While

promising, the cross-sectional, noninterventional nature of this study limits our ability to draw firm conclusions regarding cause and effect. Prospective studies in this area are needed, especially those that examine the effects of various interventions on these types of functional parameters.

Perhaps the most dramatic evidence that fatigue is a distinct symptom of MS comes from the clinical characteristics that have been recognized by clinicians for years. These include the sensitivity of MS fatigue to heat,^{3,10} as well as the fact that in about 30% of MS patients, fatigue predates other symptoms of MS. In addition, clinical observation has shown that MS fatigue exhibits relapsing-remitting characteristics. Many individuals, in fact, appear to have "fatigue relapses," which often can be traced to an obvious source such as infection. At other times, however, individuals can suffer from weeks of extraordinary fatigue for no apparent reason; these

Table 2
Definitions of Fatigue

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

Chronic Fatigue

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

Acute Fatigue

- A new or significant increase in feelings of fatigue in the previous six weeks
- Fatigue that limits activities or quality of life

Primary Fatigue

- Significant fatigue that persists despite adjustment of medications and management of mobility issues as well as of confounding medical problems such as depression and sleep disruptions

Source: Multiple Sclerosis Council for Clinical Practice Guidelines.¹¹

episodes may or may not be associated with the typical symptoms of a relapse. All of these characteristics suggest that fatigue is not a secondary effect of MS but part of the disease itself.

Developing Management Guidelines

This was the state of understanding of MS fatigue at the time the MS Council for Clinical Practice Guidelines in Fatigue Management was assembled in 1996 to attempt to develop some form of evaluation and management consensus.¹¹ At that time, the council recognized that there would be relatively little scientific literature to support the forthcoming recommendations. Nevertheless, it was important to use the available published studies and combine them with some form of expert consensus to develop a set of guidelines that could serve as the groundwork for management in this area.

Fortunately, in the few years since the guidelines were first published, an increasing number of studies have addressed specific issues in areas where good clinical research has been lacking. These areas include energy effectiveness strategies and training measures, as well as the important role of exercise in the management plan.¹² Only a few years ago, many providers argued against any form of exercise for MS patients; it has only recently become accepted that exercise can be of substantial benefit.

A diverse, multidisciplinary group of MS clinicians formed a work group to compose the first set of fatigue guidelines and to lay the groundwork for similar sets of guidelines in other areas of MS management. The council's specific goals were to examine the dimensions of MS-related fatigue; to be able to assist patients and clinicians in identifying appropriate care and coping mechanisms; to develop an effective resource for all clinicians (not only those in multidisciplinary clinics); to document the types of resources that are available for patient care; and to serve as a framework for clinical research.

The first step was to attempt to classify various types of fatigue. Many clinicians have made similar attempts, categorizing fatigue in terms including normal fatigue, MS fatigue, nerve fiber fatigue, fatigue of depression, deconditioning, excessive daytime sleepiness, and others. Unfortunately, there is little evidence to support ways to classify fatigue reliably in clinical practice. Although some council members supported attempts to classify patients' fatigue, others remained unconvinced that this could be done in clinical practice.

Further, the council recognized that the pathophysiologic bases for fatigue in individual patients are most likely complex and interrelated; thus, to focus on specific types of fatigue would probably not result in optimal management. Lastly, the council recognized that different types of fatigue might benefit from identical management strategies. Therefore, the group initially decided on a single encompassing definition of fatigue: "A subjective lack of physical or mental energy perceived by the individual or caregiver to interfere with usual or desired activities" (see Table 2). From there, the council divided this definition into chronic (lasting at least six weeks) and acute (lasting up to six weeks) fatigue. Acute fatigue is likely to be related to some type of new event or precipitant that might be modified more readily than the mechanisms responsible for chronic fatigue.

The fatigue algorithm has three outcomes in mind: 1) to reduce fatigue severity, if possible; 2) to reduce the impact of fatigue, even if the severity cannot be reduced; and 3) to improve quality of life. The algorithm was an evidence-based approach, although in many instances, this evidence was limited to clinical trials such as the amantadine and pemoline treatment trials. The council emphasized the multidimensional nature of fatigue and the need for fatigue management to be an iterative process (ie, a comprehensive process in which providers are constantly reevaluating individuals and reassessing the need for further interventions). Finally, the council wanted to make sure to incorporate many of the health care disciplines that can have a beneficial impact on fatigue.

Table 3
Medication Classes That May Cause Fatigue in MS Patients

Analgesics
Anticonvulsants
Antidepressants
Antihistamines
Antihypertensive agents
Anti-inflammatories
Antipsychotics
Asthma drugs
Carbonic anhydrase inhibitors
Cardiac agents
Diabetic agents
Gastrointestinal agents
Hormone replacement therapies
Immune modulators
Muscle relaxants
Nicotinic agents
Sedative hypnotics

Source: Multiple Sclerosis Council for Clinical Practice Guidelines.¹¹

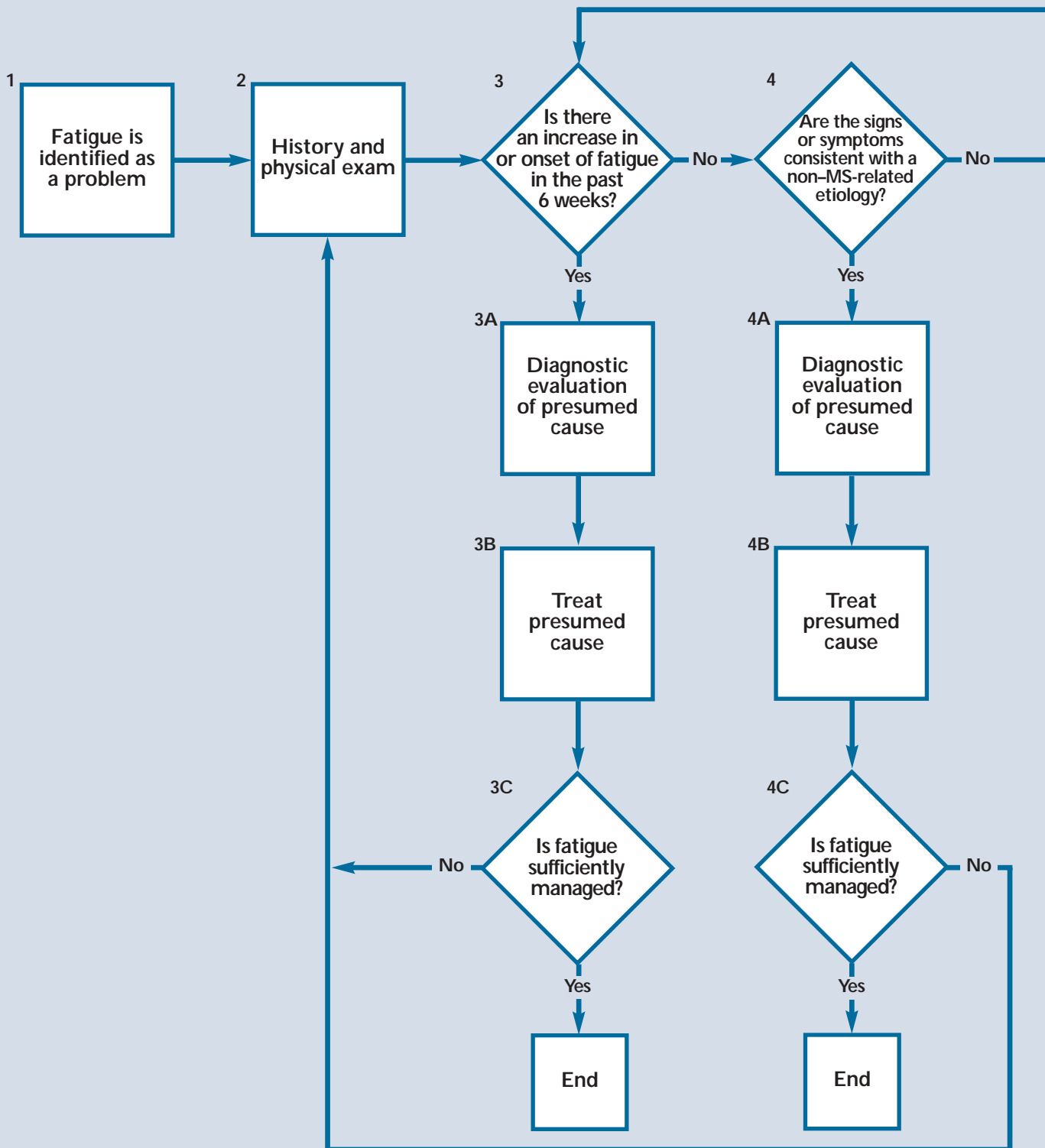
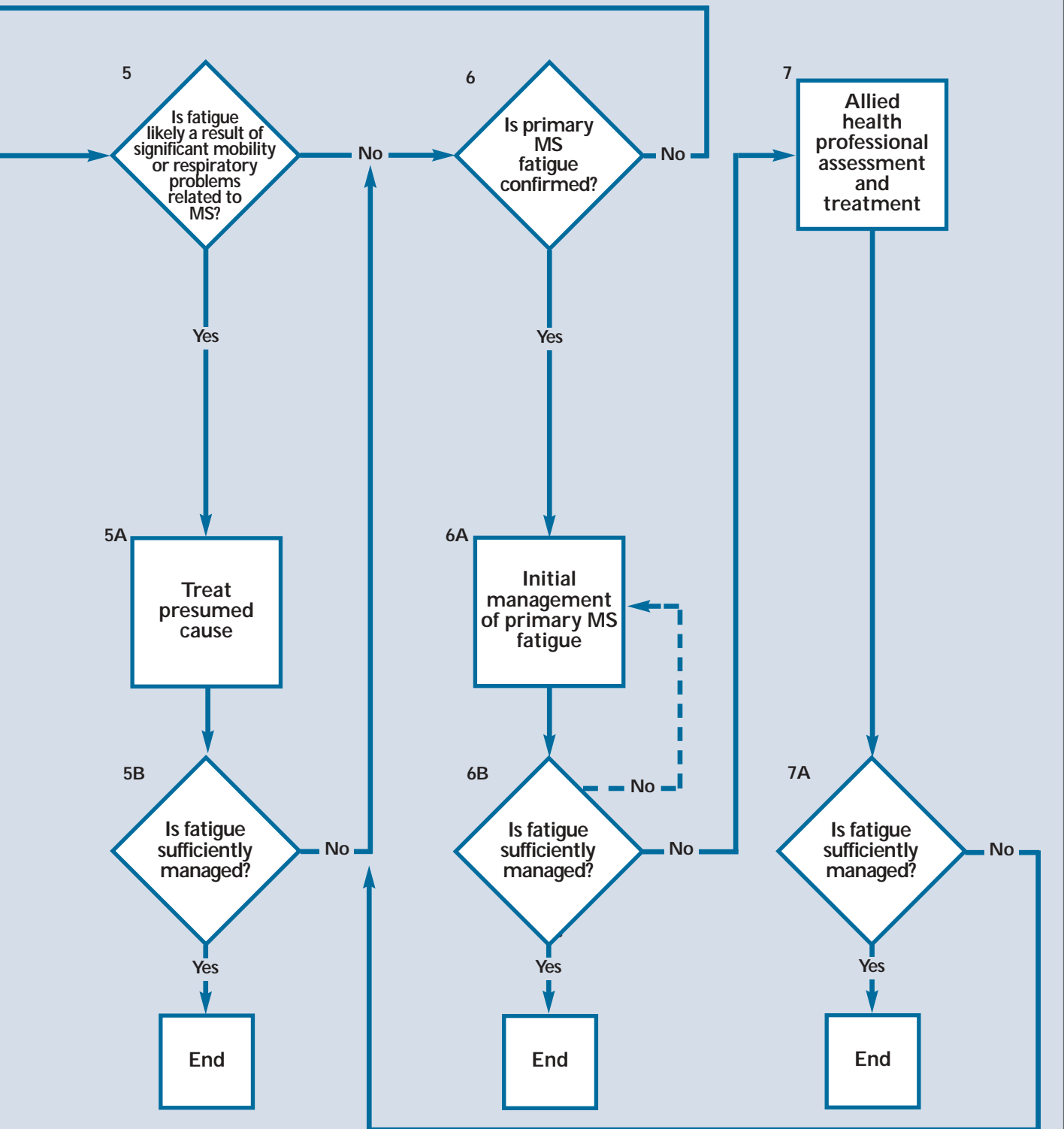


Figure 1. Fatigue algorithm.

Source: The Multiple Sclerosis Council for Clinical Practice Guidelines. Reprinted with permission.¹¹



Using the Algorithm

At first look, the fatigue algorithm (see Figure 1) appears to be quite complex—and indeed, diagnosis and management of fatigue must be a logical and considered process. Nevertheless, many of the steps in the algorithm are common-sense approaches, such as assessing patients for other modifiable factors that may be contributing to their experience of fatigue. These include medical comorbidities such as depression and sleep disorders, the side effects of certain medications (Table 3¹¹), and those factors that are considered secondary complications of MS (eg, mobility and respiratory disturbances).¹¹

Exclusion of these potential causes points to a diagnosis of primary MS-related fatigue. The council defined primary MS fatigue as significant fatigue that persists despite adjustment of medications and management of mobility issues as well as confounding medical problems such as depression and sleep disruptions (Table 2). For patients with primary MS-related fatigue, the algorithm combines in a logical order a number of important interventions, including self-help education, pharmacologic management, and energy-effectiveness strategies. (The term “energy effectiveness” was favored over “energy conservation” because the latter implies not engaging in certain activities,

rather than teaching patients to use their resources more effectively in their normal activities.) Other interventions include aerobic exercise, as well as environmental and equipment modifications that will help patients achieve their goals.

The Role of Pharmacologic Agents in MS Fatigue Management

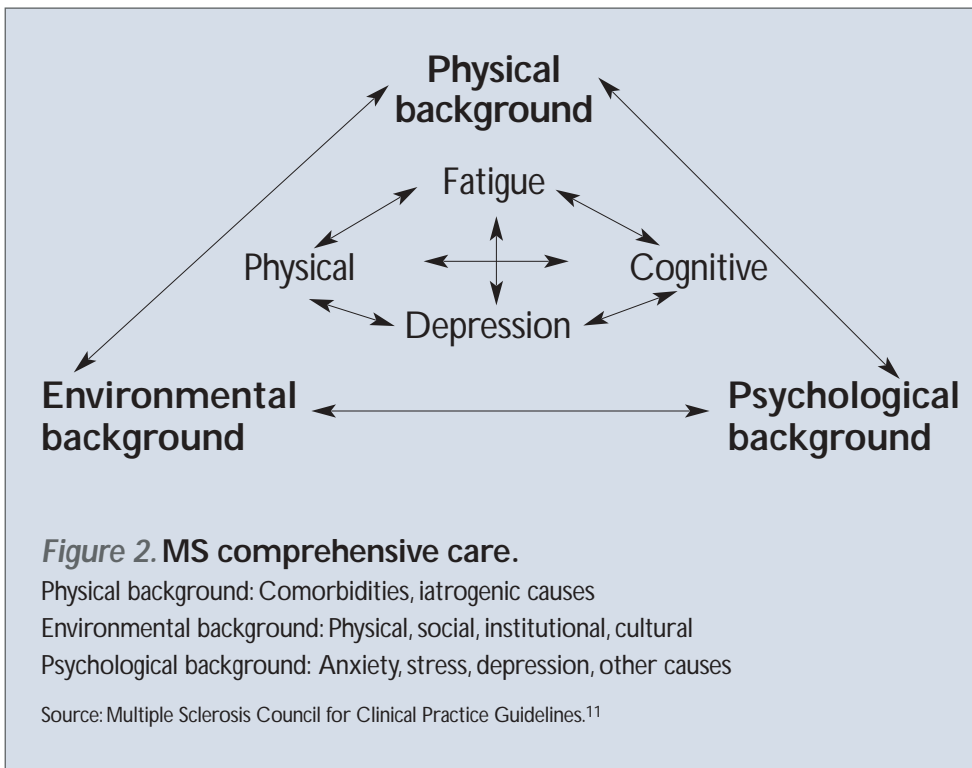
Pharmacologic therapy by itself cannot solve the problem of fatigue in MS, but pharmacologic agents can play a significant role in the overall management plan. The guidelines identify two potential pharmacologic options for primary MS fatigue: amantadine as a first-line therapy and pemoline as a second-line therapy.¹¹ These designations were made because there is more evidence that amantadine is beneficial, and better tolerated.

A third agent, modafinil, has shown efficacy in a recent placebo-controlled study¹³ and will be discussed at length later in this supplement. Because of this new evidence, the MS community may consider adding modafinil to future MS fatigue guidelines. Additional agents, such as the aminopyridines and selective serotonin reuptake inhibitors (SSRIs), require further study (see Table 4).¹¹

Although amantadine is often used for MS-related fatigue, its mechanism of action remains unclear.¹⁴

Amantadine is a dopaminergic agent, with some evidence that at therapeutic doses it inhibits *N*-methyl-D-aspartate-mediated release of choline from the striatum. Its benefit may be related to its effects on the circuits between the striatum and frontal cortex; however, the supporting evidence in this regard is quite limited. It is well tolerated, with fewer than 10% of patients experiencing adverse effects related to the drug. The most common adverse effects include nausea, lightheadedness, insomnia, irritability, and depression.^{14–17}

Pemoline is a central nervous system stimulant



(chemically unrelated to amphetamines or methylphenidate¹⁴) that has far more side effects than amantadine. These include anorexia, irritability, insomnia, weight loss, and gastrointestinal side effects, in addition to hepatic dysfunction (13 cases of liver failure have been reported) and aplastic anemia. As a result, use of pemoline results in a greater need for liver function monitoring. Overall, 25% of individuals on pemoline experience some type of adverse event.¹⁴

Four clinical trials, each using different outcome measures, support the use of amantadine for primary MS-related fatigue. The first, published by Murray in 1985,¹⁵ was conducted primarily in low-disability patients. Like many of these trials, this was a crossover placebo design of short duration. The researchers measured fatigue on a four-point scale and noted moderate to marked improvement in about 37% of patients. Of the participants, 60% blindly elected to remain on therapy—a promising result.

The Canadian MS Research Group conducted a larger study in 1987¹⁶ in a sample of somewhat more

disabled patients. This three-week, placebo, crossover study used a Visual Analog Scale of fatigue severity, as well as 13 activities of daily living. Significant improvements were seen in the Visual Analog Scale scores; overall, 41% of the patients preferred amantadine, compared with 21% for placebo.

A third study of similar design, conducted by Cohen and Fisher in 1989,¹⁷ measured outcomes using seven dimensions of fatigue, each with a five-point scale. More than two thirds of the participants had higher ratings on self-report scales while taking amantadine; 36% preferred the agent and stayed on it.

A more recent study by Krupp et al¹⁴ was the only parallel-group design, involving amantadine, pemoline, and placebo. In that study, conducted in predominantly low-disability patients, amantadine showed a significant reduction in fatigue on the MS-Specific Fatigue Severity Scale but not the Fatigue Severity Scale. Seventy-nine percent of the patients on amantadine, versus 52% on placebo and only 32% on pemoline, preferred treatment with these respective agents

Table 4
Evidence for Pharmacotherapeutic Efficacy in MS Fatigue

Trial	Measure	Result
Amantadine		
Murray ¹⁵	Four-pt fatigue assessment scale (no change–marked improvement)	Moderate to marked improvement in 46.6%
Canadian MS Research Group ¹⁶	VAS, ADLs	Small but significant decrease in fatigue
Cohen ¹⁷	Seven 5-point fatigue scales (incl. energy, muscle strength, well-being)	68% showed higher self-report ratings
Krupp ¹⁴	MS-specific FSS; FSS	Significant improvement in MS-specific FSS, but not FSS scores
Pemoline		
Krupp ¹⁴	MS-specific FSS; FSS	No significant benefit in doses of 56.25 mg/d
Weinshenker ¹⁸	VAS	Good to excellent results for 46.3% in high doses (up to 75 mg/d)
DAP		
Sheean ¹⁹	Self-reported fatigue	Significant improvement in 6 of 8 patients
Modafinil		
Rammohan ¹³	FSS, MFIS, VAS-F	Significant reduction in fatigue scores on FSS, MFIS, VAS-F

VAS, Visual Analog Scale; ADLs, activities of daily living; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; VAS-F, Visual Analog Scale for Fatigue; DAP, 3,4-diaminopyridine.

over no treatment; the fact that more individuals preferred placebo over pemoline suggested that this agent was ineffective.

Two studies have evaluated the use of pemoline. In addition to the study by Krupp et al, a 1992 study by Weinshenker et al¹⁸ showed good to excellent results in 46% of patients on pemoline versus 20% on placebo. However, the dose used in the Weinshenker study was higher than that in the Krupp study (a maximum of 75 mg/d versus 56.25 mg/d). Pemoline was poorly tolerated in the 1992 study, and subsequent clinical experience has shown that few patients can tolerate the drug in the doses that are necessary to achieve significant benefits.

In summary, the four clinical trials of amantadine show that about 40% of MS patients demonstrate significant short-term reductions in self-reported fatigue. Although amantadine is well tolerated, the council's consensus was that it appears to have a limited long-term usefulness and that many individuals become refractory to treatment. In addition, the council concluded from the evidence cited that pemoline not be used as a first-line therapy for MS-related fatigue.

Of the other potential agents, 4-aminopyridine and 3,4-diaminopyridine are potassium channel blockers that have demonstrated some benefits in temperature-sensitive patients and improvement in some neurologic functions. In a three-week, open-label study by Sheehan,¹⁹ six of eight patients showed significant improvements in self-reported fatigue. The SSRIs may also be of some benefit, but there are currently no studies nor is there expert consensus to support use of these agents for MS-related fatigue.

Conclusions

Fatigue is one of the four major symptom groups (in addition to physical, cognitive, and depression symptoms) that appear to be directly related to the disease process in MS (see Figure 2). All four of these symptom groups appear to be interrelated. In addition, all occur in the context of the individual's physical, environmental, and psychological background. Therefore, it is important to evaluate and treat individuals in a comprehensive manner. As the fatigue guidelines demonstrate, the long-term management of MS-related fatigue requires individualized combinations of education, pharmacologic therapies, energy effectiveness strategies, aerobic exercise programs, and environmental modification.

Finally, it will be important to determine the potential effects of disease-modifying therapies on fatigue studies. While clinical trials of MS agents have incorporated measures of cognition, physical functioning, and even depression, fatigue is rarely monitored in clinical trials. If fatigue is truly a symptom of MS, and pharmacologic therapies are having a significant effect, it is hoped that these drugs may also modify or lessen the development of fatigue over time.

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