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Fatigue in Multiple Sclerosis: Reducing the Impact Through Comprehensive Management

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R. Philip Kinkel, MD
Medical Director

Mellen Center for Multiple Sclerosis Research and Treatment
Cleveland Clinic
Cleveland, Ohio
Chair

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Kottil W. Rammohan, MD
Associate Professor
Department of Neurology
Ohio State University
Columbus, Ohio

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R. Philip Kinkel, MD, *Moderator*

Medical Director, Mellen Center for Multiple Sclerosis Research and Treatment
Cleveland Clinic, Cleveland, Ohio

Chair, Committee to Develop Clinical Practice Guidelines for the Management of Fatigue in MS

Kottil W. Rammohan, MD
Associate Professor
Department of Neurology, Ohio State University

Columbus, Ohio

Lauren B. Krupp, MD
Professor
Department of Neurology, State University of New York
Stony Brook, NY

Randall Schapiro, MD
Director
Fairview MS Comprehensive Care Center
Minneapolis, Minnesota

June Halper, MSN, ANP, FAAN
Executive Director
Bernard W. Gimbel MS Comprehensive Care Center
Holy Name Hospital
Teaneck, NJ

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Fatigue in Multiple Sclerosis

Reducing the Impact Through Comprehensive Management

R. Philip Kinkel, MD

R. Philip Kinkel is Medical Director of the Mellen Center for MS Research and Treatment, Cleveland Clinic, Cleveland, Ohio. He was also Chair of the Committee to Develop Clinical Practice Guidelines for the Management of Fatigue in MS.

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 very little idea of the underlying pathophysiologic mechanisms.

Table 1. Associations Between MS Characteristics and Fatigue

No Association
Age
Sex
Disease duration
MRI measures: <ul style="list-style-type: none">- 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.

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 alpha neurons,⁸ neuromuscular blockade, or excessive muscular fatigue 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 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.

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

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.



Figure 1. Fatigue algorithm.

NOTE: You can click on this image to see a larger version in a new browser window.

Source: 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

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

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.

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.

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 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 Sheean,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.

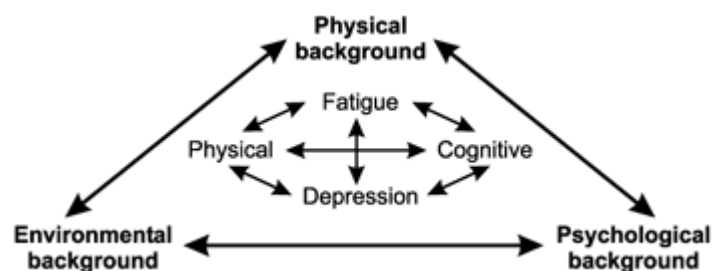


Figure 2. MS comprehensive care.

Physical background: Comorbidities, iatrogenic causes

Environmental background: Physical, social, institutional, cultural

Psychological background: Anxiety, stress, depression, other causes

Source: Multiple Sclerosis Council for Clinical Practice Guidelines.¹¹

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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Wake-Promoting Agent Shows Benefit in MS-Related Fatigue

Kottil W. Rammohan, MD

Abstract

While fatigue is a significant problem in multiple sclerosis patients—indeed, it has been reported to be the most disabling symptom of the disease—there are few pharmacologic agents that have shown any success in the long-term management of this symptom. Therefore, any study that demonstrates the efficacy of a drug therapy in MS-related fatigue is a welcome addition. At the CMSC meeting, a group of researchers led by Kottil W. Rammohan, MD, Associate Professor, Department of Neurology, Ohio State University, Columbus, reported successful results in MS fatigue with the wake-promoting agent modafinil. This novel drug, currently approved by the US Food and Drug Administration for the treatment of excessive daytime sleepiness associated with narcolepsy, showed benefit in several measures of fatigue, including the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS).

A recent study on the novel wake-promoting agent modafinil showed that this drug provides significant improvements on several fatigue measures in patients with primary MS-related fatigue. The drug, currently approved by the US Food and Drug Administration for treatment of excessive daytime sleepiness associated with narcolepsy, is a wake-promoting agent with effects specific to the hypothalamus and medial forebrain that offers an improved safety profile over traditional stimulants.

Kottil W. Rammohan, MD, Associate Professor of Neurology at Ohio State University, presented the results of this phase II, nine-week, single-blind, placebo-controlled trial. "The primary goals of this trial were to ensure the safety of the agent and test its efficacy in MS-related fatigue," he explained. Because this was the first time this agent had been tested in MS patients and the researchers wanted to ensure safety, a single-blind design was chosen in which the physician was not blinded. Nevertheless, as fatigue was self-rated in this study, the patient (who was also the rater) was effectively blinded, remarked Dr. Rammohan.

The first two weeks served as a placebo run-in in this forced-titration trial. In weeks 3 and 4, the patients received 200 mg/d of modafinil, which was increased to 400 mg/d in weeks 5 and 6. The final three weeks were a washout period. Men and women aged 18 to 65 with a diagnosis of MS and relatively mild disability (an average Expanded Disability Status Scale score of 3.3) were included in the trial. Exclusion criteria included use of any medication that would affect fatigue, including caffeine, antidepressants, central nervous system stimulants, and sedating antihistamines.

Several measures of fatigue were used, including the Fatigue Severity Scale (FSS), which was chosen as the primary instrument because "it is a tried and tested instrument," said Dr. Rammohan. Also used were the Modified Fatigue Impact Scale (MFIS), the Visual Analog Scale for Fatigue (VAS-F), and the Epworth Sleepiness Scale (ESS). The ESS was used to attempt to determine whether the effects of the drug were related to its effect on sleepiness

or some other mechanism. Safety was assessed through adverse event reporting, as well as the number of patients who discontinued treatment.

Results

The patients had a mean baseline FSS of 5.9. This score decreased significantly ($P < .05$) during the run-in phase, which Dr. Rammohan noted was most likely due to a placebo effect. Therefore, during the active treatment phase, the drug had to overcome this effect, which the 200-mg dose did ($P = .001$; see Figure 1). The 400-mg dose did not have a statistically significant effect; however, it did have a significant effect compared with the baseline FSS scores. About 17% of patients actually had an FSS change of greater than two points.

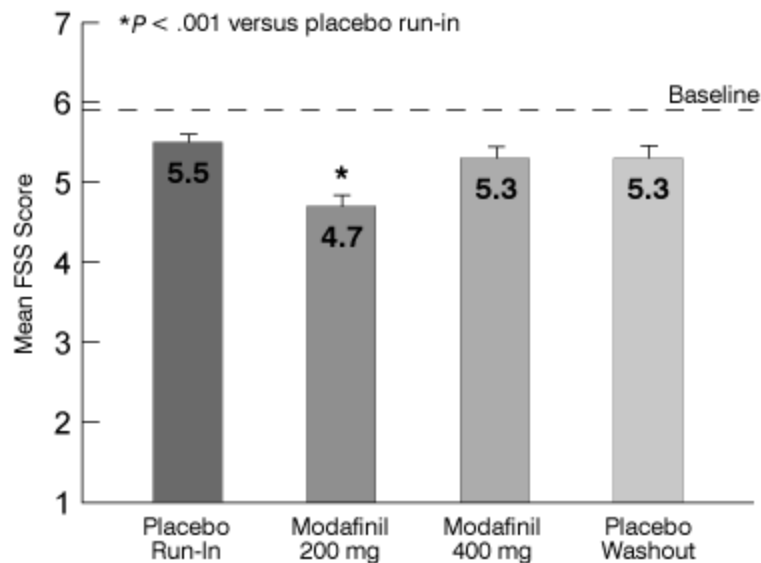


Figure 1. Fatigue Severity Scale (FSS) scores with modafinil.

Similar results were seen on the MFIS; compared with the run-in phase, those taking the 200-mg dose achieved significant improvement in fatigue scores ($P = .001$; see Figure 2). Subanalyses of the three subscales of the MFIS—physical, cognitive, and psychosocial functioning—all demonstrated improvement on the 200-mg dose. As seen with the FSS, a significant number of patients (about 18%) saw a large reduction (more than 20 points) in total MFIS scores. Results between the FSS and MFIS scales were largely consistent; 69% of patients reported improvement on each scale (see Figures 3A and 3B).

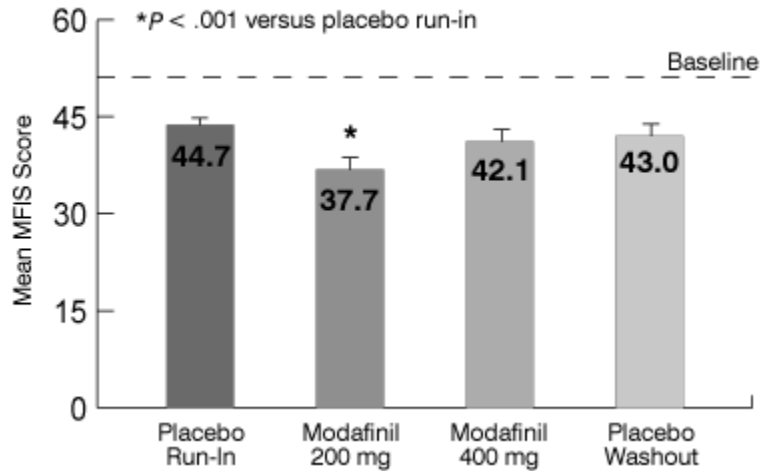


Figure 2. Modified Fatigue Impact Scale (MFIS) scores with modafinil.

The lower dose of modafinil, but not the higher dose, also demonstrated statistically significant efficacy on the VAS-F. On the ESS, however, Dr. Rammohan noted that both the 200- and 400-mg doses were capable of improving alertness. This finding, he stated, "suggested that the mechanism of improvement for fatigue is independent of the mechanism involved in improvement of sleep."

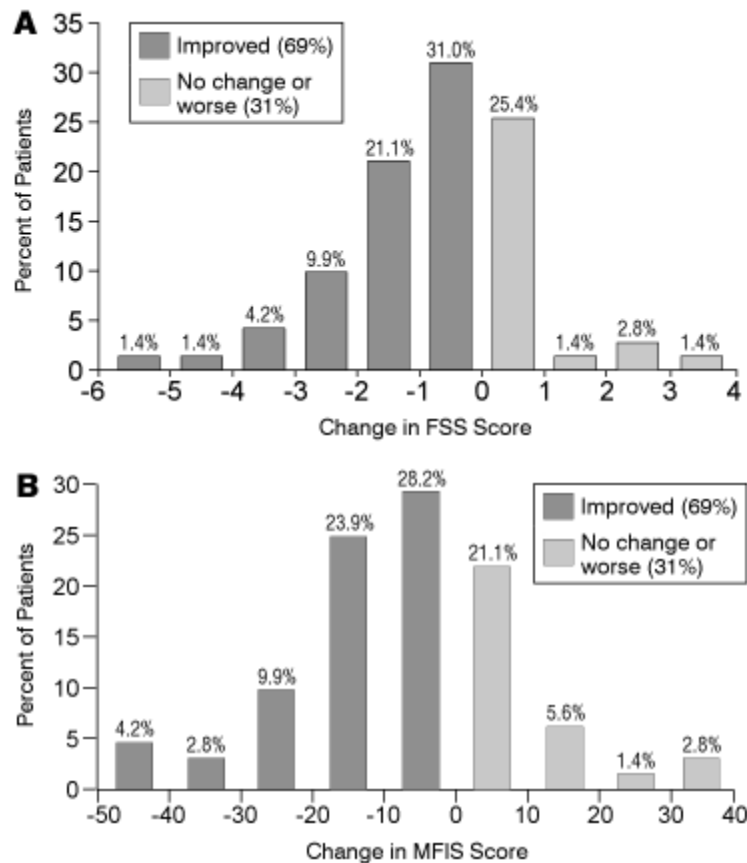


Figure 3. Change from placebo run-in in mean A) FSS score and B) MFIS score with modafinil 200 mg.

Finally, at the end of the study, patients were asked which of the four phases they preferred, if they did have a preference. Five percent chose the run-in phase, 53% chose the 200-mg phase, 28% the 400-mg phase, and the remaining 14% chose the final wash-out phase, meaning that, in total, 81% of the patients chose one of the active drug phases.

Overall, adverse events "were not a major factor," said Dr. Rammohan. They were more prevalent in the higher dose phase than with any of the other three phases, with more patients (four) discontinuing treatment in this phase due to adverse events. The only drop-out in the 200-mg phase was a patient who was lost to follow-up. The most prevalent adverse effects in the 200-mg group were headache (15%), nausea (11%), anxiety (9%), and dry mouth and nervousness (7% each). In the 400-mg group, 14% of patients experienced asthenia, while 10% had headache.

Putting the Results in Perspective

Based on these data, Dr. Rammohan and colleagues concluded that the 200-mg daily dose of modafinil significantly improved MS fatigue on each of several subscales. Perhaps most important, "the patients' perceptions of accomplishment during the day were significantly improved on modafinil treatment." Because therapy for this patient group must be highly individualized, he emphasized, the findings do not mean that the 200-mg dose "should be the limit that you use in a given patient. There will be patients who will respond better to the higher dose." He speculated that adverse effects may have limited some of the beneficial results with the higher dose.

Modafinil has several advantages that make it a favorable agent for use in MS fatigue. It has a relatively long half-life of 15 hours that lends itself to once-daily administration (if a second dose is given, said Dr. Rammohan, it should be given before 1 pm to avoid interfering with nighttime sleep). The agent does not appear to have a direct effect on chronobiology; ie, it does not affect the circadian rhythm and normal sleep architecture—a distinct advantage over conventional stimulants such as the amphetamines and methylphenidate. These traditional agents carry a significant risk for anxiety and hypertension, and are labeled by the FDA as class II drugs because of their significant abuse potential. Modafinil is a class IV agent, with a relatively small potential for abuse.

A number of issues, however, will require further research. For example, the efficacy of modafinil is less clear in patients with progressive forms of the disease. "Because the majority of patients in this study had relapsing-remitting disease, and some data suggest that progressive MS may have a greater fatigue burden, this is an important question to address in the future," Dr. Rammohan concluded.

Clinical Practice Issues in MS-Related Fatigue

A Roundtable Discussion

The faculty at the CMSC symposium organized a roundtable discussion to comment on the current state of treatment in MS-related fatigue and use of fatigue interventions in clinical practice. The panel included noted experts who reflected the multidisciplinary fields of nursing and medicine.

Participants

R. Philip Kinkel, MD (Moderator)
Kottil W. Rammohan, MD
Lauren B. Krupp, MD
Randall Schapiro, MD
June Halper, MSN, ANP, FAAN

R. Philip Kinkel, MD:

Dr. Rammohan, it is interesting in your modafinil study that the most prominent adverse effect was asthenia, which occurred in approximately 15% of patients on the 400-mg dose, compared with 3% on the 200-mg dose. Does this suggest a paradoxical effect at the higher doses?

Kottil W. Rammohan, MD:

We are still trying to figure out why the higher dose did not achieve a statistically significant benefit. I would consider it a paradoxical effect if the drug actually made fatigue worse, but there were very few persons who actually had an increase in fatigue. My own opinion is that the 400-mg dose is less tolerated in the MS population, compared with the narcolepsy population, in which this dose is commonly used. Of course, not every MS patient falls into this category.

Dr. Kinkel:

Dr. Krupp, you are one of the leaders in this area of MS. Can you put the modafinil results into perspective? We really have not seen these changes using these scales with other therapies for fatigue.

Lauren B. Krupp, MD:

All of the scales used share the feature of self-reporting. In these scales, regardless of whether they are broken down into subscales such as physical, social, cognitive, etc, the most important outcome is based on what people perceive. And people's perceptions are very different from objective measures of cognitive and motor testing.

With regard to the effect seen here on these fatigue scales versus what we have seen in other studies, I interpret this study to mean that the drug is effective, because this is a hard scale to budge. The questions on the FSS reflect almost trait-like characteristics; therefore, how fatigue is incorporated into the individual's sense of self gets reflected in how the individual answers these questions. The scale is hard to move because individuals tend to talk about "the part of me that is fatigue," instead of "how I am feeling at this moment."

The fact that use of modafinil appeared to be able to improve on that sense of self is fairly dramatic.

Dr. Kinkel:

What has your clinical experience been with modafinil?

Dr. Krupp:

I believe that the drug works. Even though the study was not double-blinded, I believe the results are telling us something very real. Obviously, for some persons, a pharmacologic approach is not appropriate. However, there are others for whom fatigue is their major issue. If their fatigue does not stem primarily from behavioral or psychological issues, and they are fairly mobile and have low disability, I think this is the drug to go with. Such persons tend to have relapsing-remitting disease, and they tend to tolerate medication well. If the problem of fatigue is sufficiently overwhelming, you want to intervene quickly.

Randall Schapiro, MD:

I think it is important for physicians to realize, however, that the medication is not inexpensive. Many of us in managed care environments have difficulty in writing prescriptions because the agent is not on formulary. I have always said, however, that once a drug is available for use by physicians, the physicians will figure out a way to use that medication better than the studies show. In order to do so, I need clinical experience.

Dr. Kinkel:

Do you feel we need more study on this agent?

Dr. Krupp:

I do believe that more studies are needed. For example, studies should be designed to assess efficacy in patients with high versus low EDSS and those with different types of MS fatigue, as well as long-term efficacy.

June Halper, MSN, ANP, FAAN:

As Dr. Schapiro said, we need more experience with this agent, and we also need some support for a new indication. Many of us have been using this agent for months, and are having to write letters of medical necessity to insurance plans. It is very disappointing when you give a patient samples and you have great response, but the insurance company will not pay for the prescription.

I believe that we also need more than just drugs, however. Everything in MS follows a symptom chain. Managing fatigue has to be a comprehensive approach in which we examine factors such as sleep disorders, energy expenditures, and bowel and bladder management. At our center, we have found that a number of our patients have respiratory or pulmonary problems that may go unrecognized and that result in a lot of sleep disruption.

Dr. Kinkel:

Do you think there is a place for developing specific programs for patients directed at fatigue, such as through an occupational, physical, or psychological therapy program?

Dr. Schapiro:

Fatigue is the single most common symptom in MS. I believe that there are many varieties

of fatigue in MS. With these varieties, I think we need to develop appropriate therapies, and this is where a specific fatigue program would be valuable.



Consortium of MS Centers
718 Teaneck Road
Teaneck, NJ 07666
www.msca.org