

Pharmacologic Therapy for Multiple Sclerosis–Related Fatigue

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Fatigue is the most common symptom of multiple sclerosis and is perhaps the symptom with the most devastating impact on patient well-being. It is reported by 75% to 95% of individuals, and more than half describe it as the worst symptom of the disease. The mechanisms underlying the development of fatigue remain unclear; although fatigue is believed to be a primary symptom of MS (ie, related to the demyelinating processes of the disease), fatigue may also occur secondarily to factors such as sleep disturbances, depression, or the effects of medications. The highly variable presentation of MS and the number of agents used for disease modification and symptom management make it important for potential contributors to MS-related fatigue to be identified and managed appropriately. If fatigue continues despite elimination or adequate management of secondary causes, pharmacologic therapy may be required. Several agents have been reported to improve MS-related fatigue; however, only three have been investigated in controlled trials. Amantadine has been studied in several small controlled trials, and appears to be effective in one quarter to one third of those with mild-to-moderate fatigue. It has shown efficacy on a number of scales, including the Visual Analog Scale for Fatigue (VAS-F) and the MS-Specific Fatigue Scale (MS-FS). The central nervous system (CNS) stimulant pemoline has demonstrated limited benefit in clinical trials and is often poorly tolerated, especially in higher doses. Recently, the wake-promoting agent modafinil has been shown to significantly improve MS-related fatigue on a number of commonly used fatigue assessment scales, including the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS).

Fatigue is the most common symptom of multiple sclerosis (MS). It is reported by 75% to 95% of individuals with this disease, and is considered a major symptom in more than half of patients.¹⁻⁵ More than 55% of patients report it as the worst symptom of their disease.⁶ Primary MS-related fatigue is a centrally mediated symptom that can affect aspects of cognitive and mental functioning, such as concentration, memory, verbal learning, and executive functioning.⁷ Emotionally, it can contribute to irritability, anxiety, and depression, which in turn can worsen fatigue. It frequently requires patients to sharply curtail their activities, significantly affecting daily performance and activities of daily living, including work and self care. MS-related fatigue is debilitating, contributing significantly to unemployment and decreased quality of life.^{2,3,8}

Pharmacologic therapy is a central component of the management of MS-related fatigue. Currently, no drug is approved by the US Food and Drug Administration (FDA) for the treatment of this symptom in MS, and only a few have been evaluated for efficacy and safety in controlled trials, leaving clinicians with limited options in outlining a pharmacologic management strategy. Of the agents that have been used to treat MS-related fatigue, amantadine has demonstrated success in about one

quarter to one third of patients with mild-to-moderate fatigue in smaller controlled clinical trials.^{4,9-11} It is an inexpensive agent, with a generally positive safety profile. Only one trial of the central nervous system (CNS) stimulant pemoline has shown even moderate efficacy for this agent, and only at very high doses.¹² Its use is also associated with significant adverse effects, including irritability and liver failure.¹²

Recent published clinical data support the efficacy of the novel wake-promoting agent modafinil for MS-related fatigue.¹³ This drug has been shown to reduce MS-related fatigue, as shown by improved scores on several of the commonly used scales for assessing MS-related fatigue severity, including the Fatigue Severity Scale (FSS), the Modified Fatigue Impact Scale (MFIS), and the Visual Analog Scale for Fatigue (VAS-F).¹³ Many clinicians now consider modafinil a first-line choice for this symptom. This article reviews the published studies on agents that have been used for the pharmacologic management of fatigue, including their use of the most commonly employed assessment scales used to measure MS-related fatigue severity.

Assessing MS-Related Fatigue

Despite the high prevalence of fatigue among MS patients and its severe impact, the mechanisms of MS-related fatigue remain unclear. Much of the difficulty in identifying a pathophysiolog-

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ic cause lies in the exceedingly heterogeneous presentation of MS, the number of symptoms that can contribute to the presentation of fatigue in the MS patient, and the variety of terms, at times inconsistently used, that describe MS-related fatigue, including depression-related fatigue, central fatigue, nerve-impulse fatigue, and lassitude.⁶

The MS Council for Clinical Practice Guidelines published management strategies for fatigue to attempt to lend guidance to clinicians. In these guidelines, fatigue is described as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities.”¹⁴ Two types of fatigue have been categorized based on duration: acute (a new or significant increase in fatigue in the past 6 weeks that can be tied to specific factors such as infection or heat) and chronic (fatigue that is present on at least half of days for more than 6 weeks and that limits functional activities or quality of life).¹⁴

The published guidelines also distinguish between secondary fatigue (related to factors such as comorbid medical conditions, medications, sleep disorders resulting in excessive daytime sleepiness, and psychological disorders such as depression) and primary fatigue (ie, related to the underlying disease process itself).¹⁴ It is important to be aware that both forms of fatigue may be present in any individual patient. The two types of fatigue are not mutually exclusive; in addition to causing new-onset fatigue, secondary causes of fatigue can exacerbate existing primary MS-related fatigue. For example, patients with existing centrally mediated fatigue may experience an increase in fatigue severity after injection of interferon betas, which are known to cause a “flu-like” response that includes fatigue.

Regardless of the cause, the severe impact that MS-related fatigue has on everyday functioning and quality of life often requires that it be treated aggressively. Managing fatigue first requires determining the duration (acute or chronic), then evaluating the presumed cause, which is likely to differ depending on duration. If MS-related fatigue can be traced to a specific cause (eg, depression, physical deconditioning resulting in limitations in mobility, or an underlying sleep disorder), addressing the cause can alleviate this symptom partially or completely.¹⁴ As is generally the case with management of any chronic symptom, therapy requires an individualized approach, with non-pharmacologic measures (eg, energy-effectiveness strategies coordinated by an occupational therapist) as the first step.

Because MS-related fatigue is assessed primarily by patient self-report, the patient’s perception of fatigue is critical to assessing the outcome of any intervention. A number of self-assessment tools have been developed to evaluate MS-related fatigue, including the Fatigue Severity Scale (FSS),¹⁵ the MS-Specific Fatigue Scale (MS-FS),⁹ the Modified Fatigue Impact Scale (MFIS),¹⁴ and the Visual Analog Scale for Fatigue (VAS-F).^{10,13} (Additional scales developed for specific studies have

also been used.^{11,16})

The FSS is a validated tool developed by Krupp, et al, that has demonstrated a high degree of reliability and internal consistency.¹⁵ The scale, which assumes that fatigue is a single construct, has been shown to distinguish features of fatigue in the medically ill (eg, those with MS or systemic lupus erythematosus) from controls without medical illness, and to distinguish between symptoms of fatigue and depression.¹⁵ The nine statements on the FSS are designed to assess how easily the patient becomes fatigued, the effect of fatigue on motivation, and the impact of fatigue on daily activities. Patient responses to each statement are rated on a scale from 1 (strong disagreement) to 7 (strong agreement).¹⁵ The calculated score is the numerical mean of the nine responses. The FSS is resistant to “impulse answering;” therefore, it is a difficult scale on which to show a positive response.

In contrast to the single-construct FSS, the 21-item MFIS assesses fatigue across multiple domains, including physical, cognitive, and psychosocial functioning (as well as an aggregate measure).¹⁴ This scale was developed by a National Multiple Sclerosis Society–funded panel and was recommended for use in the MS Council for Clinical Practice Guidelines.¹⁴ It is a shortened version of the 40-item Fatigue Impact Scale, with apparent redundancies eliminated and fewer questions in the subset of psychosocial functioning.

The MS-FS is a useful tool that uses six questions to assess items that are relatively specific to MS-related fatigue (heat, long periods of inactivity, stress, and depression).¹⁵ Its use was first reported in 1993 by Schwartz, et al.¹⁷ The VAS-F, another single-construct scale, does not focus on the impact of fatigue on specific activities; rather, it is a global assessment of fatigue whose use in MS has been validated in a trial of amantadine by the Canadian MS Research Group.¹⁰ The VAS-F has been criticized because of its arbitrary nature.

Pharmacologic Management

Three agents have been evaluated in clinical trials of MS-related fatigue: the antiviral agent amantadine, the CNS stimulant pemoline, and the wake-promoting agent modafinil.^{4,9-13} Use of a number of other agents, including methylphenidate, baclofen, antidepressants, 3,4-diaminopyridine, and pyridostigmine, has also been reported in MS-related fatigue. However, little or no empirical evidence for their efficacy has been generated; therefore, they will not be included in this discussion.

Amantadine

The first randomized trial of amantadine for the treatment of MS-related fatigue was conducted in the early 1980s.⁴ Amantadine is approved by the FDA for the prevention and treatment of influenza type A infection and for management of parkinsonian and drug-related extrapyramidal reactions.¹⁸ Its

antiparkinsonian activity relates to its ability to block presynaptic dopamine reuptake and to directly stimulate postsynaptic receptors.¹⁹ Its effect on MS-related fatigue is likely related to its dopaminergic mechanisms.

Amantadine has been evaluated for the treatment of MS fatigue in at least four controlled trials, all of which administered the agent in a dose of 100 mg bid to the active treatment groups.^{4,9-11} Three of these were randomized, controlled trials conducted in the 1980s that compared amantadine with placebo,^{4,10,11} with each trial using a different evaluation scale to assess the effects on fatigue symptoms.

The first trial, published in 1985 by Murray et al, was undertaken following the observation that an MS patient taking amantadine for influenza showed improvement in MS-related symptoms.⁴ Following an open-label investigation of amantadine, in which 14 of 18 treated patients achieved a positive response, the investigators enrolled 32 patients in a double-blind, crossover comparison of amantadine and placebo. A simple four-point scale (marked, moderate, mild, or no improvement) was used to evaluate response to treatment after three months of therapy. Amantadine treatment improved fatigue, as evidenced by a significant difference in the number of patients reporting any degree of improvement (62.5% vs 21.8% for placebo; $P = .0005$). At the end of the trial, no patient expressed a preference for placebo over amantadine.

Cohen et al compared amantadine with placebo in 29 MS patients who had symptomatic fatigue for at least 3 months prior to study entry.¹¹ This randomized, crossover trial consisted of two two-week treatment periods, with a 2-week washout between treatments. Fatigue was measured by patient self rating on seven indices, each with a five-point scale ranging from 1 (poor) to 5 (excellent). Amantadine treatment did not significantly improve the overall fatigue score compared with placebo (3.18 vs 2.96; $P = .058$). However, in a separate analysis of each of the indices used in the study, significant differences were seen in general energy level, concentration and memory, well-being, and the ability to solve problems. No significant improvement was seen in muscle strength, motivation level, or the ability to finish a task. Eight of the 22 patients reported that they felt less fatigued while taking amantadine.

The largest of these three studies was the 10-week, multicenter trial by the Canadian MS Research Group, which included 115 patients with a three-month history of "chronic persistent fatigue."¹⁰ The 50-mm VAS-F was used to assess daily fatigue. This tool asks patients to indicate their perceived fatigue severity on a line ranging from "no fatigue" to fatigue "as bad as could be." Activities (selected by each patient) most affected by fatigue and 13 activities of daily living were also evaluated weekly by a VAS. The study consisted of a two-week placebo run-in period, with two three-week treatment periods separated by a two-week washout.

A cross-over analysis of variance detected a significant period effect, with fatigue significantly greater in the two-week baseline period (31.6 mm) compared with the two-week washout period (27 mm). This effect was seen regardless of the treatment (placebo or amantadine) during the first period. To accommodate this period effect, an analysis of covariance model was fitted for each of the three treatment weeks using the mean of the two baseline fatigue scores as a covariant.

Amantadine decreased fatigue in this study; however, the improvement was only statistically significant at week one ($P = .01$). Amantadine use resulted in a significant mean decrease in the effect of fatigue on selected activities compared with placebo at each of the three weeks ($P < .05$), and when the overall treatment effect was analyzed ($P < 0.01$). The percentage of patients reporting adverse effects was 57% with amantadine and 54% with placebo. Of 13 adverse effects specifically monitored in the study, only insomnia was reported significantly more often with amantadine (13 patients) than with placebo (four patients; $P = .029$).

In the most recent study, Krupp and coworkers evaluated the efficacy of amantadine in 39 patients with clinically definite MS, using the FSS and MS-FS as the outcome measures. This was a multicenter, parallel-group trial that also included pemoline ($n = 37$) and placebo ($n = 43$) treatment arms.⁹ Patients had clinically significant fatigue (scores of ≥ 4 on the FSS) and were ambulatory. Exclusion criteria included recent use of fatigue-promoting medications and severe depression. Treatment effect was assessed before, during, and at the end of treatment using the FSS and MS-FS. Patients were also asked to give verbal self reports at the end of 8 weeks of treatment and 2 weeks after treatment ended.

Amantadine significantly decreased fatigue on the MS-FS compared with placebo ($P = .037$). In addition, following the two-week washout period at the end of the study, 79% of amantadine patients vs 52% of placebo patients stated that they felt better on study medication compared with no treatment ($P = .03$). However, FSS scores were not significantly different for amantadine compared with placebo.

Pemoline

Pemoline, which is indicated for the treatment of attention deficit hyperactivity disorder, is a central nervous system (CNS) stimulant that causes widespread cortical activation.²⁰ Its effects usually peak about four hours postdose and last up to eight hours.

Two randomized, controlled clinical trials have evaluated the use of pemoline for MS-related fatigue.^{9,12} In the study by Krupp discussed above, pemoline was started at a dose of 18.75 mg at week one and titrated to 56.25 mg by week three. No significant difference between pemoline and placebo was seen on the MS-FS or FSS in this study. In addition, significantly more patients in this study showed a preference for amantadine than

for pemoline (79% vs 32%, $P = .035$). More patients also expressed a preference for placebo than for pemoline (52% vs 32%), although this difference did not reach statistical significance.⁹

Weinshenker et al compared pemoline with placebo in a two-center, crossover trial of 46 patients with severe fatigue.¹² Compared with the Krupp study, a higher dose of pemoline (75 mg/day) was used in this four-week dose-escalation study, and a 50-mm VAS was used as the assessment tool. Again, pemoline failed to significantly reduce fatigue in this study; 19 patients (46.3%) experienced excellent or good relief of fatigue with pemoline, compared with eight patients (19.5%) with placebo ($P = .06$). In addition, a significantly greater number of adverse effects was seen with patients receiving pemoline compared with placebo, including irritability, insomnia, nausea, and anorexia. One quarter of the participants did not tolerate pemoline well, and 7% discontinued the drug due to intolerable adverse effects.

Pemoline has been associated with life-threatening liver failure, and the drug's product labeling was updated in June 1999 to include a boxed warning of this association.²¹ For these reasons and the lack of good efficacy data, pemoline use is minimal and the drug has been removed from many formularies.

Modafinil

Modafinil is a novel wake-promoting agent that is chemically and pharmacologically distinct from CNS stimulants, and is believed to work selectively in areas of the brain involved in the regulation of normal wakefulness.^{22,23} This agent increases cortical activity by activation of histaminergic pathways from the tuberomammillary nucleus.²³ Modafinil facilitates wakefulness in a number of clinical models, including narcolepsy, obstructive sleep apnea, Parkinson's disease, and idiopathic hypersomnia.²⁴⁻²⁷ Recent research specifically examining improvements in fatigue and sleepiness has also shown that modafinil can be used as an adjunct treatment to antidepressants in depressed patients with significant residual fatigue despite treatment with antidepressant therapy.²⁸ Modafinil appears to be well tolerated; the most common adverse effects are headache, nausea, and nervousness. Modafinil has a low potential for abuse,^{29,30} and was not associated with tolerance with long-term use (over 136 weeks in narcolepsy populations).³¹

The efficacy of modafinil for MS-related fatigue was evaluated in a nine-week, single-blind (to patients), forced titration trial of 72 patients with a mean FSS ≥ 4 .¹³ The first two weeks of study served as a placebo run-in phase, followed by two weeks of modafinil 200 mg/day, two weeks of modafinil 400 mg/day, and a three-week washout period. A number of scales commonly used to evaluate MS-related fatigue were employed, including the FSS, the MFIS, and the VAS-F.

The 200-mg dose of modafinil significantly improved fatigue compared with placebo at endpoint on all of these scales. Specifically, reduction of fatigue for modafinil was seen on the

FSS (mean score, 4.7 vs 5.5 for placebo, $P < .001$), the MFIS (mean score, 37.7 vs 44.7, $P < .001$), and the VAS-F (mean score, 5.4 vs 4.5, $P = .003$). Overall, 69% of patients experienced improvement with this dose on each of these scales.

Modafinil was well tolerated in this study. The most common adverse effects with the 200-mg dose were headache (17% vs 15% for placebo run-in), nausea (11% vs 6%), and anxiety (9% vs 1%). The most common adverse effects with the 400-mg dose were asthenia (14% vs 8%), headache (10% vs 15%), nausea (6% vs 6%), and nervousness (6% vs 3%). Six patients withdrew from the study due to adverse effects: four during the higher-dose treatment, one during the run-in phase, and one during the washout period.

A second, open-label study by Zifko et al evaluated the use of modafinil in 50 patients with relapsing-remitting or secondary progressive MS.³² The mean FSS score in this study was 30.3 at baseline (scores were calculated as the sum of the nine individual item scores, and not as the numerical mean of the responses). Treatment was started with a single daily modafinil dose of 100 mg, which was titrated in 100-mg increments based on efficacy and tolerability to a maximum daily dose of 400 mg.

Modafinil significantly improved fatigue, with the mean FSS score decreasing to 25.4 after 3 months ($P < .0001$). On self-appraisal measures, 45 patients reported either clear improvement or some improvement in their fatigue. Only two patients reported no change. Half of the patients remained on the 100-mg dose, with 42% increasing to 200 mg and 4% to 300 mg; no patient required 400 mg. Three patients discontinued modafinil use because of adverse events (nervousness and dizziness).³²

Discussion

Despite its high prevalence and significant impact on functioning,¹⁻⁴ MS-related fatigue remains a symptom with limited pharmacologic options for treatment. The reasons for this are likely varied, and include a lack of understanding of the mechanisms of fatigue in MS and a failure to recognize the prevalence and impact of fatigue in the MS population. Both of these may help to discourage intensive study into this symptom.

The difficulty in defining and diagnosing MS-related fatigue has led to the development of multiple tools to attempt to diagnose MS-related fatigue, which the pharmacologic studies above illustrate well. Common scales are used by studies only twice (the VAS-F by Rammohan¹⁵ and the Canadian MS Research Group,¹⁰ and the FSS by Krupp,⁹ Rammohan,¹⁵ and Zifko³²). In each case, the study design is different, making between-study comparisons problematic at best. The Canadian Study¹⁰ used a crossover design, the Rammohan study¹³ was a single-blind, forced titration trial with no crossover element, the Zifko study was open-label,³² and the Krupp study⁹ was a double-blind design with a parallel-group format. Of the other studies, those by Murray⁴ and Cohen¹¹ used simple four-item and seven-item

scales. The only scales that had been validated at the time of the study by Rammohan¹³ were the VAS-F and the FSS; both were incorporated into the trial design, along with the MFIS (the scale included in the published MS fatigue guidelines).¹⁴

The tremendous shift in management strategies since the advent of partially effective therapies to prevent MS exacerbations may also play a significant role in the failure to place proper focus on the pharmacologic management of MS-related fatigue. The approval of the first immunomodulator, interferon [beta]1b,³³ in 1993, marked a fundamental change in perception of the disease for many physicians and patients alike. Whereas the goal for decades in MS therapy had been solely one of symptom management, the development of immunomodulators dramatically shifted focus toward agents that reduce exacerbations and potentially prevent disease progression.

The findings in the studies of MS-related fatigue are encouraging for a number of reasons. First, they show that pharmacologic therapies can be effectively and safely used for MS-related fatigue. Amantadine and modafinil showed significant efficacy in moving the more well-accepted scales such as the VAS-F and MFIS. Modafinil at a dose of 100 to 200 mg also significantly improved fatigue scores compared with placebo on the FSS—making it the only agent to date to significantly improve scores compared with placebo on this scale.^{13,32}

The safety of any agent that will potentially be used for chronic therapy is of significant importance. Amantadine has a favorable safety profile. Modafinil has been shown to be well tolerated, with a low incidence of adverse events, which were largely limited to transient headache and nausea in the Rammohan study.¹³ The incidence of anxiety, agitation, and nervousness (adverse effects common among CNS stimulants such as pemoline) was generally low.¹³ Future research in this area should employ larger cohorts (including a large, placebo-controlled trial), and expand testing of agents to different MS subtypes other than relapsing-remitting MS, because fatigue is present in all MS clinical subtypes. It would be interesting to determine whether different results can be achieved in fatigue that is of shorter duration (acute fatigue) versus fatigue that is long-standing (chronic fatigue), as several agents, such as interferon therapy, can cause short-term fatigue. Consistent use of fatigue scales across studies and use of similar study designs will also help to clarify findings in this area.

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