Off-Label Drug Uses

Amantadine: Multiple Sclerosis–Related Fatigue

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Fatigue, a common and disabling symptom experienced by patients with multiple sclerosis (MS), may encompass both physical and cognitive characteristics.¹ Although an exact mechanism is unknown, fatigue associated with MS may be related to central nervous system (CNS) impairment. Unfortunately, effective rational therapy for MS-related fatigue is hampered by the lack of understanding regarding its pathophysiology and difficulties in measuring fatigue via objective methods.

Amantadine is an antiviral agent, specifically active against influenza A viruses. The mechanism of action for treating MS-associated fatigue is unclear, but it may be related to antiviral activity, immune-mediated activity, or an amphetamine-like action. Current recommendations for the treatment of MS-associated fatigue focus on nonpharmacologic therapies.² Although the use of routine medications is not recommended, there may be a limited clinical benefit from the use of amantadine. Other factors potentially contributing to fatigue should be identified and treated when possible.

PATIENT POPULATION

Adults with MS-associated fatigue.

DOSAGE AND DURATION

100 mg orally twice daily.^{3,4}

RESULTS

Amantadine in the management of MS-related fatigue has been studied in controlled trials, demonstrating improvements in subjective and objective ratings of fatigue in some patients. Benefits in patients with advanced illness require further study. Consensus guidelines from the German Multiple Sclerosis Society (GMSS) state that amantadine produces moderate improvement in subjective fatigue, concentration, memory, and problem solving compared with placebo based on strong evidence.

Guidelines

German Multiple Sclerosis Society

Consensus group guidelines from GMSS recommend the exclusion of other causes (eg, depression, hypothyroidism) in the management of MS-related fatigue. A strong recommendation for cooling the body and extremities is stated. These guidelines also state that amantadine produces moderate improvement in subjective fatigue, concentration, memory, and problem solving compared with placebo and is well tolerated. A strong recommendation is stated for the use of amantadine. If insufficient, 4-aminopyridine (strong evidence), L-acetylcarnitine (moderate evidence), or modafinil (expert opinion) should be considered.²

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Literature Review

In a Cochrane literature review performed to determine the safety and efficacy of using amantadine in treating fatigue in patients with MS, 5 randomized controlled trials published from 1987 to 2004 were included. Two of the studies assessed amantadine versus other medications, and 3 of the trials assessed amantadine compared with placebo. Treatment durations ranged from 1 week to 3 months. Various primary outcomes were used to measure fatigue in the trials. Reviewers indicated that the overall methodological quality of the studies was considered poor, based on concerns with inadequate data collection and reporting, high attrition rates, inconsistent results, and questionable clinical and quality of life-related outcomes. Because of these findings, clear recommendations for the use of amantadine in MS-associated fatigue could not be made. In addition, tolerability of amantadine in this population was not well documented. The reviewers stated that there was no overall evidence supporting this use and further quality research was needed to identify the role of amantadine for this indication.⁵ A follow-up Cochrane review regarding interventions for fatigue and weight loss in adults with advanced progressive illness noted the earlier Cochrane review and stated that amantadine may provide improvement in fatigue for some people with MS, although beneficial effects in advanced stages of illness are yet to be proven.⁶

Controlled Trials

Two controlled trials have been published after the guidelines and systematic review were created.

In a double-blinded, crossover trial, 52 adult patients with MS-related fatigue (mean duration, 3 years) were randomized to receive either aspirin (500 mg once daily) or amantadine (100 mg twice daily) for 4-week treatment periods separated by a 2-week washout period. All patients had been receiving interferon-beta therapy for at least 1 year prior to enrollment. The mean age was 35.6 and 35.0 years in the amantadine and aspirin groups, respectively. The mean Fatigue Severity Scores (FSS) prior to the initiation of the study were 4.8 and 4.6 in the amantadine and aspirin groups, respectively, and 5.1 and 4.4 prior to the second round of treatment. Both groups demonstrated significant decreases in FSS after both treatment periods. Mean FSS reductions in the amantadine group were 0.8 (4.8 vs 4.0; 95% CI, 0.46-1.15; $P < .001$) after the first round of treatment and 1.6 (5.1 vs 3.5; 95% CI, 1.04-2.27; $P < .001$) after the second round of treatment. In the aspirin

group, mean FSS reductions were 1.1 (4.6 vs 3.5; 95% CI, 0.67-1.49; $P < .001$) and 0.7 (4.4 vs 3.7; 95% CI, 0.46-1.15; $P < .001$), respectively. Overall analysis revealed no differences between the 2 groups in FSS values. There were also no significant differences between the 2 groups for the incidence of side effects (eg, nausea and epigastric pain), which were mild and did not require treatment.⁴

In a blinded, placebo-controlled trial, 60 adult patients (mean age, 38.6 years) with relapsing remitting MS (mean duration, 6.6 years) were randomized to receive 1 month's treatment with amantadine (200 mg daily), acetyl-L-carnitine (2 g daily), modafinil (200 mg daily), or placebo. Medication doses were taken in the morning and afternoon. Primary outcome measurement was the Modified Fatigue Impact Scale (MFIS; range, 0 to 84). At 1 month, the mean MFIS score was significantly reduced from baseline in those treated with amantadine (48.3 vs 31.2; mean difference = 14.5; 95% CI, 5.2-23.8; $P = .005$) and acetyl-L-carnitine (53.6 vs 36.1; mean difference = 13.2; 95% CI, 6.4-20; $P = .001$). In contrast, mean MFIS scores were increased in the placebo group (33.8 to 48.5; mean difference = 11.1; 95% CI, 0.6-22.9; $P = .062$) or unchanged in the modafinil group (49 vs 49.4; mean difference = 0; $P = 1$). Contrast analysis showed significant differences in the 1 month MFIS scores when amantadine was compared to placebo but no differences between the acetyl-L-carnitine and placebo. There were no differences between the mean MFIS between amantadine and acetyl-L-carnitine. No patient relapsed during the study.³

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

The most commonly cited reactions in reviewed trials have included nausea and dizziness, which were mild and did not require treatment.³⁻⁵

THERAPY CONSIDERATIONS

Amantadine in the management of MS-related fatigue has been studied in controlled trials, demonstrating improvements in subjective and objective ratings of fatigue in some patients. Benefits in patients with advanced illness require further study. Consensus guidelines from the GMSS state that amantadine produces moderate improvement in subjective fatigue, concentration, memory, and problem solving compared with placebo based on strong evidence.

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