Modafinil for the Treatment of Pain-Associated Fatigue: Review and Case Report

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ABSTRACT. Fatigue is a symptom that is frequently found in chronic pain patients with low back pain and/or neck pain. At the present time, no specific psychopharmacological treatment for this problem has been identified. Modafinil is a wakefulness-promoting agent that the FDA has approved for the treatment of excessive daytime sleepiness associated with narcolepsy. There have been reports on the use of modafinil for the treatment of fatigue in various neurological syndromes. This literature is reviewed. As such, modafinil treatment was initiated for a patient with severe fatigue associated with chronic low back pain and neck pain. There was dramatic improvement in fatigue and associated function. This case is described. It is the first such case report in the literature. The significance of this finding to the treatment of pain-associated fatigue is discussed. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <http://www.HaworthPress.com> © 2004 by The Haworth Press, Inc. All rights reserved.]

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INTRODUCTION

Fatigue has been defined as a subjective feeling of tiredness that may/may not be related to activity. A more complex definition encompassed within diagnostic criteria for fatigue developed by Portenoy and Miaskowski is as follows: sensations described as fatigue, diminished energy, or an increased need to rest that is disproportionate to any recent change in activity and sensations described as distressing or associated with diminished capacity to perform usual physical or intellectual activities. Perception of fatigue is frequently found in patient diagnostic groups where one of the symptoms of the disease is pain. These diagnostic groups are the following: fibromyalgia, headache, rheumatoid arthritis, and chronic low back pain. Recently, Fishbain et al. reviewed this literature in an evidence-based structured review manner. The results of this review indicated that there is an association between fatigue and pain and that there may be an etiological relationship between pain and fatigue.

As indicated above, the potential relationship between pain and fatigue has been definitively established. Unfortunately, there is presently only one study that has reported on treatment outcome for low back pain or neck pain associated fatigue. This treatment was nonspecific to
fatigue and improvement in fatigue appeared to be a function of multi-disciplinary pain treatment.15 No specific psychopharmacological treatments for chronic low back pain-associated fatigue have been reported in the literature. As such, we would like to report on a patient whose fatigue and functional status appear to respond dramatically to a psychopharmacological treatment regimen with modafinil. We chose to treat this patient with modafinil because of the body of literature relating to modafinil reviewed below. Some of this literature indicates that modafinil may be useful in the treatment of fatigue.

Modafinil (Provigil®) is marketed as a wakefulness-promoting agent and is FDA approved for the treatment of excessive daytime sleepiness associated with narcolepsy.16,17 It is chemically unrelated to the central nervous system stimulant drugs, such as amphetamines and methylphenidate, and has a pharmacological profile different than that of sympathomimetic amines.18,19 It is neither a direct nor an indirect acting dopamine receptor agonist and is inactive in several preclinical models capable of detecting enhanced dopaminergic activity.20,21 Modafinil has a differential pattern of regional C-FOS induction in the rat brain versus amphetamines22 and is believed to work selectively in the areas of the brain involved in the regulation of normal wakefulness.23,24 This agent does not cause the global activation seen with stimulants.25 It appears to increase cortical activity via activation of the histaminergic pathways from the tuberomammillary nucleus; the putative-wake generator.23

Modafinil has been classified as a Schedule IV controlled substance by the Drug Abuse Administration (DEA) because there is evidence that it has a low abuse potential20,26 compared to other wakefulness-promoting drugs which are Schedule II, i.e., amphetamines, methylphenidate. Modafinil also seems not to produce tolerance in long-term use (greater than 136 weeks).20,27 Gold and Belster28 found this medication was 250 times less potent thanamphetamine and 50 times less potent that ephedrine in producing cocaine-like discriminative stimulus effects in rats.28 Single oral dose of modafinil did not cause elevation or euphoria in health volunteers or those with substance abuse disorders.29,30 Compared with amphetamines, modafinil has a limited side effect profile with weak peripheral sympathomimetic activity and minimal effects on hemodynamics.31

Modafinil has been used off-label and has been reported to be useful for a number of other disorders besides narcolepsy. It has been reported to be useful in six patients with obstructive sleep apnea, hypopnea syndrome.32 There has also been a case series (three cases)1 demonstrating its usefulness in reversing sedation induced by antipsychotic medica-
tions. Another interesting off label use was reported by Elovic (case reports). Another interesting off label use was reported by Elovic (case reports). Here patients suffering from under-arousal secondary to traumatic brain injury appeared to improve. There has also been one case report on the use of modafinil for augmentation of schizophrenia treatment. Modafinil has also been utilized as a depression augmenting agent for those patients who only had a partial response in their depression to antidepressants. In the first report, exploring this use, Menza et al. reported on seven patients who with placement on modafinil achieved full or partial remission. The other report on this use was a placebo controlled trial. Here Sherman utilized patients with major depression who only had a partial response to an adequate doses of a selective serotonin uptake inhibitor or nefazodone, and had residual symptoms such as fatigue or daytime sleepiness. Sixty-nine patients were placed on modafinil and 67 received placebo in a six-week trial. There was significant decline in sleepiness in the active drug at the first week versus placebo and in fatigue at week two. Modafinil has also been utilized in two neurological condition: myotonic dystrophy (MD) and multiple sclerosis. Forty patients with MD were randomized to receive modafinil and placebo for 14 days, each using a double-blind crossover design. Modafinil was found to decrease sleepiness and fatigue in MD. Interestingly, modafinil treatment did not increase maximal grip strength. The efficacy of modafinil for the treatment of multiple sclerosis (MS) associated fatigue was evaluated in two studies. The first study was a 50-patient prospective three-month open-label study. Here modafinil treatment significantly improved sleepiness and fatigue. The second study was a double-blind placebo-controlled crossover study of 72 patients who had MS associated fatigue. Here fatigue scores were significantly improved versus placebo at 200 mg modafinil per day.

There has also been limited use of modafinil in one clinical syndrome, which is associated with pain: fibromyalgia (FM). Here, however, there have only been case reports or case series. In the first case report an FM patient who had narcolepsy responded to modafinil with a marked decrease in daytime sleepiness, cataplexy, and fatigue, but no decrease in pain. In the second report, Schaller and Behar reported on four FM patients whose fatigue improved with modafinil. Finally, Pachas reported on a series of 15 FM patients, all of whom reported some improvement in their fatigue with modafinil.
Ms. X was a 35-year-old White female who was admitted to the Rosomoff Pain Center for complaints of neck and low back pain, weakness and fatigue. Ms. X had originally injured her back in a lifting injury at the age of 17. Diagnosis was a bulging disk. The low back pain waned over the years, but was significantly exacerbated at the age of 29 through another lifting injury. Diagnosis was again a bulging disk. No surgery was recommended. One year later at the age of 30, Ms. X received a whiplash injury to the neck and developed neck pain. Diagnosis was a bulging disk and no surgery was recommended. However, Ms. X then began using a reclining chair for part of the day. Complaints at that time were neck pain, LBP, muscle weakness and fatigue. Neurological workup, including EMG, revealed no evidence of radiculopathy, neuropathy or myopathy. In addition, extensive medical workup did not reveal any endocrinological problems. A diagnosis of chronic fatigue syndrome was never assigned/reached.

Through the years Ms. X was intermittently thought to be depressed. However, attempts to place Ms. X on various antidepressants all met with failure secondary to alleged hypersensitivity to the medications. However, preadmission Ms. X had been in psychotherapy for depression and anxiety with no positive outcome in terms of increased function. At the time of admission, Ms. X was entirely disabled, being in a reclining wheelchair with full-time attendants. Functional tolerances for that time are presented in Table 1 in addition to the Oswestry Disability Index and Fatigue Severity Scale scores. Neurosurgical and physical medicine diagnoses were the following: (1) cervical and lumbar myofascial syndromes; and (2) generalized weakness and deconditioning. Psychiatric evaluation revealed mild depression and anxiety only. Beck Depression Inventory scores were 12, supporting the above clinical opinion. However, Ms. X complained of significant fatigue, which was related to/associated with any elevation in pain. Pain in turn was brought on by increase in activity, such as sitting, standing, and walking. Fatigue Severity Scale Score was 63 (the maximum possible score). DSM-IV diagnosis was adjustment disorder with depressed mood.

Because of the significant fatigue perception, previous hypersensitivity to antidepressants and the above reviewed literature on modafinil and FM, Ms. X was offered a trial of modafinil as part of the center treatment. Treatment with modafinil was started one day after admission as well as physical therapy, occupational therapy, massage, reha-
bilitation groups, and individual counseling. Two days after starting modafinil treatment, Ms. X was noted to be more energetic, responsive, and more motivated. Her functional status after six days of treatment is presented in Table 1. As can be seen in Table 1 after six days of modafinil treatment, there is a dramatic increase in functional scores and a dramatic decrease in fatigue scores.

**DISCUSSION**

This is the first case report on the treatment of LBP and neck pain-associated fatigue with modafinil. According to clinical observation, patient self report and various rating scales, the patient’s fatigue and function dramatically improved with placement on modafinil. As noted in the case description, clinical improvement in fatigue was observed and reported after two days of starting modafinil treatment. This speed of response therefore cannot be attributed to other aspects of the treatment program, which typically would be expected to be effective within a longer period of time. However, a placebo response cannot be ruled out. Because of this and because case reports are subject to sample bias and over-inference as sources of error, conclusions about the efficacy of modafinil for low back pain and neck pain-associated fatigue await placebo controlled studies. However, modafinil could offer a possible

**TABLE 1. Functional Tolerances, Oswestry Disability Index Scores and Fatigue Severity Scale Scores of Ms. X at Beginning of Treatment and After Initiation of Modafinil**

<table>
<thead>
<tr>
<th></th>
<th>At Admission (Day 1)</th>
<th>After 6 Days of Treatment (Day 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VaS (Intensity average over 24 hours)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Oswestry (best scale is zero)</td>
<td>30/50 = 66%</td>
<td>10/50 = 20%</td>
</tr>
<tr>
<td>Fatigue Severity Scale (FSS) (Best scale score is 9–Worst possible score is 63)</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>Sitting</td>
<td>12 min</td>
<td>40 min</td>
</tr>
<tr>
<td>Standing</td>
<td>&lt;&lt; 2 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Walking</td>
<td>&lt;&lt; 20 feet with cane.</td>
<td>212 feet without a cane.</td>
</tr>
<tr>
<td>Modafinil Dose</td>
<td>0</td>
<td>100 mg</td>
</tr>
</tbody>
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alternate treatment approach to a problem frequently encountered in the chronic pain setting: low back pain and/or neck pain-associated fatigue.

REFERENCES


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