

Potential Uses of Modafinil in Psychiatric Disorders

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ABSTRACT

Modafinil was administered as part of a treatment regimen in patients (N = 237) with a broad spectrum of treatment-resistant psychiatric, neurological and general medical disorders accompanied by some combination of excessive sleepiness, fatigue, executive dysfunction, and apathy. In a retrospective chart review of these patients, Clinical Global Impression of Severity (CGI-S) scores were evaluated. Most patients (84.4%) showed improvement in overall clinical condition with modafinil. Most patients tolerated this agent well; the most frequently reported adverse events were overstimulation, insomnia, headaches, and gastrointestinal distress. Modafinil may offer clinical benefit for treatment-resistant hypoarousal symptoms in a number of psychiatric, neurological and general medical conditions.

INTRODUCTION

Research appears to demonstrate that modafinil influences anatomical substrates that regulate wakefulness, higher cognitive processes, and executive functioning.^{1,2} Preclinical data indicate that modafinil selectively increases neuronal activation in discrete areas of the brain involved in the regulation of normal wakefulness and arousal, including the tuberomammillary nucleus (TMN) of

the posterior hypothalamus and orexinergic neurons within the lateral hypothalamus.^{1,3} In a clinical model of acute sleep deprivation, functional magnetic resonance imaging demonstrated that modafinil maintained activity in the cortex, including lateral and medial prefrontal cortices, producing patterns of neuronal activation similar to those observed when patients were alert and well rested.⁴

Large-scale, controlled clinical trials have shown that modafinil significantly improves wakefulness versus placebo in patients with excessive sleepiness associated with various clinical disorders including narcolepsy.⁵⁻⁸ Clinical trials have demonstrated that long-term treatment with modafinil provides continued safety and efficacy for up to 136 weeks,⁹⁻¹¹ with no evidence for development of tolerance.^{5,12} In recent 4- and 12-week, randomized, double-blind, placebo-controlled trials, modafinil significantly improved wakefulness in patients with obstructive sleep apnea (OSA) who experienced excessive sleepiness despite regular use of effective nasal continuous positive airway pressure.^{13,14} Findings from additional studies indicate that modafinil may be an effective treatment in other clinical disorders associated with symptoms of sleepiness and fatigue, including idiopathic hypersomnia,¹⁵ multiple sclerosis (MS),¹⁶ and Parkinson's disease.¹⁷⁻²⁰ Clinical studies indicate that modafinil also exerts beneficial effects on mental parameters, such

as psychomotor functioning, attention, and working memory in individuals experiencing sleepiness and/or fatigue. In sleep-deprived, normal human volunteers, modafinil improved objective measures of cognitive functioning, such as logical reasoning, short-term and working memory, and visual search processing.^{21,22} In narcolepsy patients, modafinil has improved executive function, productivity, and attention/concentration.^{5,6,8,23} Results of preliminary studies of modafinil therapy in patients with attention-deficit/hyperactivity disorder (ADHD),²⁴ treatment-resistant depression,²⁵ schizophrenia,²⁶ and alcoholic organic brain syndrome²⁷ have also been encouraging, suggesting a possible role for modafinil in improving executive function in psychiatric patient populations.

This article reports the findings of a retrospective chart review of patients with a broad spectrum of psychiatric, neurological, and general medical conditions in a private psychiatric practice who shared several treatment-resistant symptoms, including excessive sleepiness, fatigue, cognitive impairments, and poor motivation.

METHODS

Charts were reviewed of patients treated at a private psychiatric practice from February 2000 to March 2002. The review included children, adolescents, and adults who were identified as having received modafinil at some point in their treatment and for whom some follow-up chart information was available. The study group was drawn from patients who exhibited primarily psychiatric rather than sleep disorder symptoms.

The data extracted from the charts included Clinical Global Impression of Severity (CGI-S) scores, a measure of overall clinical condition (scored on a scale ranging from 1 = "normal, not at all ill" to 7 = "among the most extremely

ill patients"), before and after treatment; types of symptoms responding to modafinil; and adverse events and safety issues. The symptoms responding to modafinil were determined by structured initial clinical interviews and follow-up assessments, which included questioning, observing, voluntary reporting, and collateral information, that specifically focused on the status of residual symptoms. Overall results are reported for those patients included in the chart review; selected cases representative of the clinical experience with modafinil in this patient population are also described.

RESULTS

Patients

A total of 341 patients who were prescribed modafinil were identified. Of these patients, follow-up information was available for 237 (116 men and 121 women). The age range of these patients was 7 to 92 years (average 39). The ethnic distribution was 224 white, 4 Hispanic, 3 African-American, and 2 Middle Eastern. The 3 most common psychiatric diagnoses were depression with apathy and/or fatigue (29%); Lyme encephalopathy with multiple cognitive impairments (29%); and ADHD with a predominance of concentration impairments rather than distractibility (26%). Only 3 patients had a primary diagnosis of a sleep disorder, one of whom met the full diagnostic criteria for narcolepsy and was prescribed modafinil for the treatment of excessive daytime sleepiness. The other 2 sleep-related diagnoses were sleep apnea and idiopathic hypersomnia. Table 1 contains a comprehensive list of diagnoses presented by the patients included in this chart review. Agents that these patients were receiving during the period of modafinil treatment are shown in Table 2. The 3 most common medications were antidepressants (60%), anticonvulsants (15%), and

antipsychotics (10%).

Modafinil Treatment

The patients included in the review were treated with modafinil for a period ranging from 1 day to 2 years. Among the patients who responded, most were treated for several months. The starting dose was most commonly 100 mg/day in the morning. In children and drug-sensitive individuals, the starting dose was more commonly 50 mg/day in the morning. The dosage range was 12.5 to 800 mg/day. However, most patients were maintained in the dosage range of 100 to 400 mg/day; the most common dose was 200 mg/day.

Overall Clinical Condition

Seventy (29.5%) patients were rated as severely ill at baseline; 145 (61.2%) were rated as moderately ill; and 22 (9.3%) were rated as mildly ill. None of the patients had CGI-S scores of 1 or 2 at baseline. Modafinil treatment improved overall clinical condition in 84.4% of these patients (Figure), with most responders exhibiting a 2-point reduction in CGI-S scores relative to baseline. Of patients reviewed, 15.6% were non-responders or patients who worsened with modafinil treatment. Patient response or inability to tolerate treatment was often evident within a few days.

Modafinil-Responsive Symptoms

Modafinil was associated with improvement in 4 distinct groupings of symptoms: excessive sleepiness, fatigue, executive dysfunction, and apathy/poor motivation. Marked improvement in excessive sleepiness was reliably observed with modafinil. This improvement was not limited to the patients with primary sleep disorders, but extended to patients with other types of problems marked by sleepiness, including those with somnolence or sedation relat-

ed to medication use and those undergoing chemotherapy for cancer. Many patients also reported improvement in symptoms of fatigue, with increased feelings of energy and an improved ability to engage in daily activities. With respect to executive functioning, cognitive components in which patients noted improvement included sustained attention, reading comprehension, working memory, concentration, organizing, prioritizing, planning, complex problem solving, mental flexibility, and a complaint of "mental fog." Among patients with treatment-resistant symptoms of low initiative, apathy, pervasive boredom, emotional numbness and poor motivation, many reported more normal levels of both positive and negative emotion and an improved ability to "get going in the morning" and engage in normal daily activities. Some patients reported an improvement in mood with modafinil; however, it was unclear if this was a direct effect of modafinil upon affect or a secondary improvement as a result of improved functioning in other areas. Importantly, many patients at baseline exhibited a constellation of more than one of these types of symptoms and, with the addition of modafinil to the treatment regimen, improvements were often seen in multiple symptom categories.

Adverse Events and Safety

Modafinil was well tolerated. The most common side effects included overstimulation, insomnia, headaches, and gastrointestinal distress. Adverse events that led to discontinuation of modafinil administered in doses of either 100 or 200 mg every morning included auditory hallucinations ($n = 2$) and exacerbation of depression when modafinil was given in combination with citalopram ($n = 1$). One of the patients who discontinued because of auditory hallucinations had a primary diagnosis of major depression

Table 1. Summary of Diagnoses of Patients Included in Chart Review (N = 237)

<p>Psychiatric Diagnoses</p> <p>Adjustment reaction</p> <p>Affective disorders</p> <p> Bipolar illness</p> <p> Dysthymia</p> <p> Major depression*</p> <p>Alcoholism/substance abuse</p> <p>Alzheimer's disease</p> <p>Anxiety disorders</p> <p> GAD</p> <p> OCD</p> <p> Panic disorder</p> <p> PTSD</p> <p> Simple phobia</p> <p>ADHD*</p> <p>Body dysmorphic disorder</p> <p>Borderline personality disorder</p> <p>Depersonalization disorder</p> <p>Eating disorders</p> <p>Intermittent explosive disorder</p> <p>Multiple personality disorder</p> <p>Schizophrenia</p> <p>Selective mutism</p> <p>Sex addiction</p> <p>Sleep disorders</p> <p>Trichotillomania</p> <p>Genetic and Developmental Disorders</p> <p>Asperger's syndrome</p> <p>Autism</p> <p>Cerebral palsy</p> <p>Fetal alcohol syndrome</p> <p>Huntington's disease (early)</p> <p>Marfan's syndrome</p> <p>Endocrine/Metabolic Disorders</p> <p>Acromegaly</p> <p>Hypoglycemia</p> <p>Hypothyroidism</p>	<p>Neurological Disease/Disorders</p> <p>Aplastic oligodendroglioma</p> <p>Cognitive impairments associated with cerebral radiation treatment</p> <p>Compressed skull injury</p> <p>Encephalopathy (injury- and illness-related)</p> <p>Essential tremor</p> <p>Mild cognitive impairments</p> <p>Multiple sclerosis</p> <p>Narcolepsy</p> <p>Parkinson's syndrome disease</p> <p>Post-CVA cognitive impairment</p> <p>Seizure disorder</p> <p>Tourette's syndrome</p> <p>Miscellaneous Conditions (Infectious, Malignant, Rheumatological, etc)</p> <p>Babesiosis</p> <p>Bartonella infection</p> <p>Cancer (breast, prostate, brain, Hodgkin's lymphoma)</p> <p>Chemotherapy-related fatigue</p> <p>Chronic fatigue syndrome, fibromyalgia</p> <p>Encephalopathy associated with HHV1, 2 & 6-A infections</p> <p>Encephalopathy associated with meningococcal meningitis</p> <p>Epstein-Barr infection</p> <p>Hepatitis C</p> <p>Irritable bowel syndrome</p> <p>Lyme and associated diseases*</p> <p>Mitral valve prolapse</p> <p>Morbid obesity</p> <p>Raynaud's syndrome</p> <p>Shingles</p> <p>Sjögren's syndrome</p>
<p>* Depression, ADHD, and Lyme and associated diseases were the 3 most commonly observed diagnoses among the patient charts reviewed. ADHD indicates attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; CVA, cerebrovascular accident; and HHV, human herpes virus.</p>	

without psychosis, and the other patient had a primary diagnosis of Lyme disease. All adverse events resolved when modafinil was discontinued in these patients. One 41-year-old severely debili-

tated male patient with MS and possible Lyme disease died while being treated with modafinil; however, there was no indication of any causal relationship between the death and modafinil treatment.

Table 2. Medications Given Concomitantly With Modafinil in This Series

Benzodiazepines	Cholinergic Agents
Alprazolam	Donepezil
Clonazepam	Galantamine
Diazepam	Rivastigmine
Lorazepam	Antiepileptic Medications*
Antidepressants*	Diphenylhydantoin
Bupropion sustained release	Gabapentin
Citalopram	Lamotrigine
Desipramine	Oxcarbazepine
Fluoxetine	Tiagabine
Fluvoxamine	Valproate
Mirtazapine	Psychostimulants
Paroxetine	Dextroamphetamine
Sertraline	Methylphenidate
Tranlycypromine	Hypnotics
Trazodone	Zaleplon
Trimipramine	Zolpidem
Venlafaxine	Miscellaneous
Atypical Antipsychotics*	Amantadine
Olanzapine	Atenolol
Quetiapine	Benzotropine
Risperidone	Bromocriptine
Ziprasidone	Cyproheptadine
Anxiolytics	Lithium
Buspirone	Pindolol
Hydroxyzine	Propranolol
	Ropinirole
	Sildenafil
	Testosterone

* Antidepressants, antiepileptic agents, and atypical antipsychotics were the most commonly prescribed medications within the group of patients whose charts were included in the present review.

None of the patients exhibited signs of addiction, craving, or drug-seeking behavior with modafinil treatment, even among patients with substance abuse disorders. Moreover, a number of the late-stage Lyme disease patients who had mild mitral valve prolapse tolerated modafinil without difficulties.

CASE HISTORIES

Case 1

Mr A is a 49-year-old white male with a 29-year history of treatment-resistant depression. Symptoms included episodes of derealization, leaden paralysis in the morning, social anxiety, anhedonia, suicidal preoccupations, anxiety, panic, apathy, and poor concentration. He had

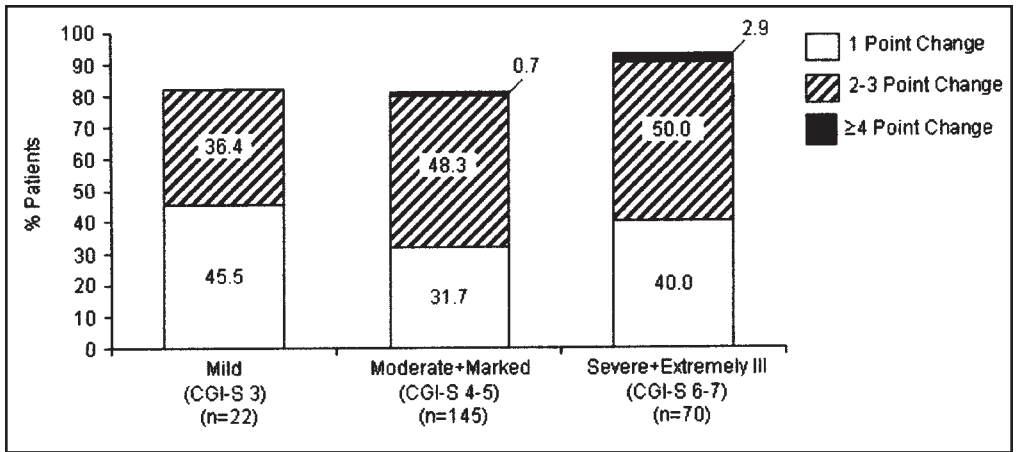


Figure. Proportion of patients exhibiting a therapeutic response to modafinil, by baseline illness severity and degree of improvement. (CGI-S indicates Clinical Global Impression of Severity.) Among patients who showed a therapeutic response to modafinil, most experienced a 2-point decrease in baseline CGI-S scores. With modafinil, the proportion of patients who showed a 2-, 3-, or ≥ 4 -point decrease in CGI-S scores was slightly larger among those who were moderately and severely ill at baseline (49.0% and 52.9%, respectively) than among patients who were mildly ill at baseline (36.4%).

failed to respond to a number of therapeutic strategies, which included psychotherapy, paroxetine, fluoxetine, venlafaxine, sertraline, bupropion sustained release (SR), mirtazapine, lithium, valproate, doxepin, trimipramine, trazodone, buspirone, nortriptyline, citalopram, olanzapine, alprazolam, and temazepam, as well as electroconvulsive therapy. The patient had a partial response to lamotrigine and bupropion SR 200 mg every morning, which was subsequently changed to lamotrigine 125 mg twice daily and tranylcypromine 30 mg/day. Modafinil was added to this regimen. Initially, the patient responded to modafinil 200 mg/day; this dose was gradually increased to 400 mg every morning and 200 mg at noon to sustain improvement. At one point, the patient experienced excessive emotional intensity, which appeared to be unrelated to modafinil treatment and responded to an increase of lamotrigine to the current dose. Patient interviews indicated that addition of modafinil to his treatment regimen resulted in increased initiative, greater feeling of being connected to something, and improved ability to get

out of bed in the morning and start the activities of the day. Additionally, he began exercising and lost 15 pounds. He stated that he was “multitudes better from modafinil, and I would be dead without it.” The patient also reported an improvement in his functioning and financial productivity. Mr A has been on modafinil for the past 3 years and has remained stable and functional for the past 2 years on the current treatment. Before this treatment, the patient was judged to be severely ill; with modafinil, the patient has exhibited only mild impairment. Mr A has not reported side effects from modafinil treatment.

Case 2

Ms B is a 21-year-old white female with a long history (6 years) of psychiatric illness, including anorexia nervosa, suicide attempts, psychiatric hospitalizations, school failures, poor treatment compliance, and multiple substance abuse. She initially presented with numerous psychiatric and neuropsychological symptoms typical of substance abuse (heroin was the most commonly abused drug; cigarette addiction was also present) and

depression, including impulsivity, poor concentration, anhedonia, lack of motivation, fatigue, anxiety, low libido, and suicidal ideation. History obtained from previous care providers indicated that several antidepressants had been tried. The patient demonstrated a partial response to a combination of fluoxetine, valproate, and bupropion SR, but she continued to suffer from heroin addiction and abuse. In the initial interview with Ms B, she stated her “whole life was being run by drugs.” The patient was started on bupropion SR 200 mg and modafinil 200 mg every morning. The patient reported improvements in motivation, fatigue, mood, and daily productivity. She stated her mood improved because she was “happy about getting things done.” Additionally, the patient indicated that modafinil reduced her craving for heroin. Although compliance with treatment and abstinence were erratic for the first few months, she has sustained a period of abstinence, even from cigarettes, to the present time. She is currently gainfully employed in a responsible position and has been relatively stable for the past 2 years. She is currently receiving modafinil 200 mg every morning with bupropion SR 200 mg every morning and afternoon. The patient’s overall clinical condition has improved from severely ill at baseline to mildly ill after modafinil treatment. Ms B has experienced no side effects from modafinil.

Case 3

Ms G is a 48-year-old white female with a history of ADHD, posttraumatic stress disorder, and sensitivity/poor tolerance to many medications. She presented with mixed symptoms of depression, anxiety, inattentiveness, and apathy. She met all 5 Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for ADHD, with 6 symptoms of inattentiveness and 7 symptoms of

hyperactivity-impulsivity. Ms G reported being in psychotherapy. Prior trials of psychotropic therapy had failed to produce a therapeutic effect. Before initiating modafinil, the Modified Fatigue Impact Scale (MFIS) score was 76 (Cognitive 37, Physical 31, and Psychosocial 8); the maximum MFIS score is 84, with higher scores indicating greater impairment. In spite of significant symptoms, the patient had insight, was well compensated, and maintained a high level of functioning. After 3 weeks of treatment with modafinil 50 mg every morning, the MFIS score was reduced to 43 (Cognitive 22, Physical 16, and Psychosocial 5). The patient reported an improvement in concentration, fatigue, and motivation. She has continued treatment with modafinil 50 mg taken every morning for the past 2 years. Since receiving modafinil treatment, Ms G’s overall clinical condition has improved from mildly ill at baseline to normal, not at all ill, after modafinil treatment. She has tolerated the medication well.

DISCUSSION

The patients included in the current retrospective chart review exhibited a broad range of psychiatric and general medical conditions. Nonetheless, they shared common treatment-resistant hypoarousal symptoms characterized by some combination of excessive sleepiness, fatigue, cognitive impairments, and poor motivation. The response rate reported here is similar to the 84% response rate recently reported by Cochran in a series of 25 patients with fatigue associated with neurological illnesses who were treated with modafinil²⁸ and consistent with the findings of Markovitz et al in an open-label study of 27 patients with depression who experienced lethargy and/or apathy and had either no response or a partial response to antidepressant therapy (81% of patients demonstrated improve-

ment in symptomatology).²⁹ It may be questioned whether some patients in the current study had undiagnosed sleep disorders, such as obstructive sleep apnea; however, the reviewer believes that the number of patients falling in this category was relatively small.

Cognitive impairments associated with executive dysfunction responded well to modafinil treatment. Based upon clinical assessments, various facets of executive functioning, such as sustained attention, working memory, visual spatial processing, prioritizing, planning, and time management, appeared to be improved with modafinil. Notably, modafinil was generally effective in those patients with concentration impairments and in teenagers with ADHD who were not good candidates for psychostimulant therapy because of a history of treatment resistance, intolerance, or substance abuse, in combination with an SSRI or venlafaxine XR. Other therapeutic effects of modafinil consistently reported by patients included improvements in apathy, initiative, energy, and motivation. Many patients reported feeling “better able to get started in the morning” and exhibited improvements in daily functioning. Patients with psychotic illnesses demonstrated improvement in negative symptoms with modafinil without exacerbation of positive symptoms. A number of patients who responded to modafinil had a chronic medical illness accompanied by a constellation of behavioral problems characterized by social withdrawal, depression, and fatigue. Some patients reported an improvement in mood; however, it was unclear if this was a direct effect upon mood from modafinil or a secondary improvement resulting from the drug’s wake-promoting or other cortical-activating effects. Interestingly, a number of patients who were given modafinil for somnolence associated with analgesic

treatment volunteered that modafinil treatment seemed to have analgesic properties; such effects, however, may be related to better adherence to analgesic regimens. These observations also warrant further investigation. Future studies are recommended in each of the therapeutic areas discussed in this article. A prospective study of modafinil by the author is currently underway.

CONCLUSIONS

The results of the current chart review suggest that modafinil may be an effective adjunctive strategy for patients with certain psychiatric, neurological, and medical conditions who experience a constellation of treatment-resistant hypoarousal symptoms characterized by some combination of excessive sleepiness, fatigue, cognitive impairment, and motivational and mood dysfunction. Although these symptoms are often seen as a part of primary sleep disorders, in this study, they were frequently a secondary component to psychiatric and general medical conditions. For many patients, inadequate management of these symptoms may result in failure to achieve adequate response, recovery, and remission from psychiatric and somatic illnesses and severe impairment of functioning. The positive outcomes observed in the current patient population suggest that modafinil may represent a new pharmacological tool for the treatment of cognitive and motivational impairments.

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