

# Modafinil as Adjunctive Therapy in Depressed Outpatients

SUHAYL NASR, M.D.

Nasr Psychiatric Services, PC, Michigan City, Indiana, USA

*The wake-promoting agent modafinil (PROVIGIL®) may prove useful as an adjunctive treatment in patients with suboptimal responses to antidepressant regimens. This retrospective chart review describes the use of modafinil as an adjunct to antidepressant therapy in 78 outpatients in a general psychiatric practice and discusses in detail treatment outcomes for 3 patients. Statistically significant improvements in mean Carroll Depression Rating Scale scores ( $p < 0.01$ ), Visual Analog Scale scores for overall feeling ( $p < 0.003$ ), and Clinical Global Impression of Severity ratings ( $p < 0.001$ ) were demonstrated following treatment with modafinil. Treatment with modafinil rapidly improved wakefulness, fatigue, and everyday functioning in individual cases. Modafinil was well tolerated in combination with antidepressants and other medications. These findings suggest that adjunctive modafinil may improve treatment outcomes when used with antidepressant therapy in depressed patients, particularly in those with problematic sleepiness or fatigue.*

**Keywords** Modafinil; Depression; Fatigue; Wakefulness; Sleepiness; Adjunct.

## INTRODUCTION

In clinical trials of antidepressants, up to 75% of patients have generally responded to therapy, with response defined as either a 50% reduction from baseline in a standard depression rating scale score or a reduction in score to or below a predetermined threshold. For those who do not respond to a first course of antidepressant therapy, switching to another antidepressant affords an additional 20% chance of response (1). Patients who continue to fail to respond to antidepressant monotherapy or who have a partial response may require alternative or additional pharmacologic interventions, including the use of augmentation therapy. Controlled clinical studies have demonstrated the benefits of lithium (2–7) and triiodothyronine (4) when these agents were used in combination with antidepressant medications. The adjunctive use of psychostimulants, such as methylphenidate and dextroamphetamine, has also been described in case studies (8). However, careful monitoring is required with these

agents owing to concerns about abuse and a potential for the development of dependence, tolerance, or untoward side effects.

Currently considered a standard treatment for excessive sleepiness in patients with narcolepsy (9), the wake promoting agent modafinil has been shown to improve wakefulness in patients with a variety of sleep disorders (10–15) and to improve fatigue in patients with multiple sclerosis (16). In a retrospective case series of patients with major depression or bipolar affective disorder who had a partial response to antidepressant therapy, 5 of 7 patients achieved a 50% or more reduction in depression rating scale scores when modafinil was used in conjunction with antidepressant therapy, with the remaining patients achieving an approximately 40% reduction (17). Improvements in fatigue were noted in all 7 patients. In a large-scale, double-blind, placebo-controlled clinical trial of patients with major depressive disorder and a partial response to antidepressant therapy, adjunctive modafinil was shown to significantly improve sleepiness and fatigue symptoms associated with depression (18).

This article reviews the use of modafinil as a treatment adjunct to antidepressant therapy in outpatients in a general psychiatric practice. General findings from a series of consecutive cases are presented and treatment outcomes for 3 patients are described in detail.

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Address correspondence to Suhayl Nasr, M.D., Nasr Psychiatric Services, PC, 2814 S. Franklin Street, Michigan City, IN 46360. E-mail: sjnasr@msn.com

## METHODS

The records of the first 99 office patients in a general psychiatric practice who were given modafinil for any length of time were reviewed retrospectively, with approval from the local hospital's institutional review board. Patients' records, collected over a 9-month period from Nasr Psychiatric Services (Michigan City, IN) and a local university, were evaluated for diagnoses, number and type of prior and concomitant medications, depressive illness severity, initial and final dosages of modafinil, duration of modafinil treatment, test scores and improvement ratings, and untoward side effects. As part of routine office procedure at Nasr Psychiatric Services, patients completed the Carroll Depression Rating Scale (CDRS) (19,20), a self-administered variant of the 17-item Hamilton Depression Rating Scale, before (CDRS1) and after (CDRS2) treatment with modafinil. Patients were considered to be in remission if they obtained a score of 7 or less on the CDRS2. Patients evaluated at Nasr Psychiatric Services also routinely completed a visual analog scale (VAS) in response to the question "how are you feeling today?" Patients placed a mark along a line labeled "worst ever" at the left and "best ever" at the right. VAS ratios (distance of mark from left divided by the length of the line) were calculated before (VAS1) and after (VAS2) modafinil treatment. The overall clinical condition of patients at both centers was rated by the clinician using the Clinical Global Impression of Severity (CGI-S) (21). CGI-S assignments ranged from 1 (normal) to 7 (among the most extremely ill). CGI-S ratings were recorded before (CGI-S1) and after (CGI-S2) modafinil. Improvement in depressive symptoms was assessed using the Clinical Global Impression of Change (CGI-C) (21) for patients at both sites. CGI-C ratings ranged from 1 (very much improved) to 7 (very much worse). Paired sample *t*-tests were used to compare mean CDRS scores, VAS scores, and CGI-S ratings before and after treatment. Statistical tests were two-tailed and performed at a 5% significance level.

## RESULTS

### General Findings

A total of 99 charts were reviewed. Seventeen patients had taken modafinil samples but did not wish to call or pay for more drug; they were excluded from review because their duration of treatment (i.e., less than 2 weeks) was considered insufficient for meaningful clinical assessment. Four other patients were excluded because they received modafinil for reasons other than as an adjunct to antidepressant therapy. Characteristics and medications for patients whose charts were reviewed are shown in Table I. Patients

**Table I** Characteristics and Medications For Patients Receiving Modafinil

<i>Characteristic</i>	
Number of patients	78
Mean age; yr (range)	44 (15–75)
Gender, male/female; n	29/49
Depression diagnoses; n (%) <sup>a</sup>	
Unipolar depression	59 (76) <sup>b</sup>
Bipolar depression	13 (17)
Other	6 (7)
<i>Medications</i>	
Mean number of concurrent medications (SD)	2.6 (1.4)
Concomitant antidepressant; n (%) <sup>c</sup>	
Bupropion	12 (15)
Venlafaxine	11 (14)
Citalopram	11 (14)
Sertraline	10 (13)
Fluoxetine	8 (10)
Paroxetine	4 (5)
Fluvoxamine	3 (4)
Mirtazapine	5 (6)
Nefazodone	4 (5)
Other	20 (26)

<sup>a</sup>Patients had 1 or more concurrent conditions.

<sup>b</sup>Twenty-nine patients had recurrent major depression.

<sup>c</sup>Some patients were taking more than 1 antidepressant at the time of modafinil treatment.

ranged in age from 15 to 75 years and took modafinil for at least 1 month; post-treatment ratings were performed between 1 and 5 months after starting modafinil. All patients presented with depression with or without concomitant psychiatric or medical disorders. In general, patients were treatment resistant (i.e., failed to achieve remission after trials with adequate doses of 3 antidepressants of at least 2 types and at least one combination of two antidepressants or one antidepressant and an augmenting agent) and considered partial or incomplete responders to antidepressant therapy based on clinical assessment.

Seventy-one patients (91%) had significant fatigue and/or sleepiness and previously failed adjunctive treatment with stimulants such as amphetamine or methylphenidate or other medications such as bupropion for reasons including headache, tachycardia, hypertension, jitteriness, and hypomania. Of the 68 patients assigned a CGI-S rating by the clinician at the initial visit, 56 patients (82%) were considered to be markedly ill, severely ill, or among the most extremely ill. Starting and final dosages of modafinil ranged from 50 to 200 mg/day and 100 to 800 mg/day, respectively, with a mean (SD) final dosage of 249 (122) mg/day taken as a single or split dose.

For the 52 patients with pre-and post-treatment CDRS scores, modafinil significantly reduced the mean CDRS score ( $p < 0.01$ , CDRS2 versus CDRS1) (Table II). On an

**Table II** Scores/Ratings for Patients Receiving Modafinil

Assessment	Score/Rating <sup>a</sup>	<i>p</i> Value <sup>b</sup>
CDRS1 <sup>c</sup>	19.4 (9.1)	
CDRS2 <sup>d</sup>	16.9 (9.9)	<0.01
VAS1 <sup>c</sup>	0.40 (0.19)	
VAS2 <sup>d</sup>	0.49 (0.19)	<0.003
CGI-S1 <sup>c</sup>	5.4 (1.0)	
CGI-S2 <sup>d</sup>	2.9 (1.3)	<0.001
CGI-C <sup>d</sup>	1.9 (0.9)	

CDRS1 = Carroll Depression Rating Scale, before modafinil; CDRS2 = Carroll Depression Rating Scale, after modafinil; VAS1 = visual analog scale, before modafinil; VAS2 = visual analog scale, after modafinil; CGI-S1 = Clinical Global Impression of Severity, before modafinil; CGI-S2 = Clinical Global Impression of Severity, after modafinil; CGI-C = Clinical Global Impression of Change.

<sup>a</sup>Mean value with SD in parentheses.

<sup>b</sup>*p* value for the change from initial visit.

<sup>c</sup>CDRS1 scores, VAS1 scores, and CGI-S1 ratings were available for 68, 65, and 68 patients, respectively.

<sup>d</sup>CDRS2 scores, VAS2 scores, CGI-S2 ratings, and CGI-C ratings were available for 52, 44, 68, and 68 patients, respectively.

individual basis, scores improved for 36 patients, remained unchanged for 2 patients, and worsened for 14 patients. For those who improved, the mean (SD) CDRS score was reduced from 19.9 (9.3) at baseline to 14.2 (8.8) following modafinil treatment ( $p < 0.001$ ). Eleven patients had post-treatment CDRS scores of 7 or less. For the 44 patients with pre- and post-treatment VAS scores, modafinil significantly improved the mean VAS score ( $p < 0.003$ , VAS2 versus VAS1) (Table II). VAS scores improved for 31 patients and worsened for 13 patients. For those who improved, the mean (SD) VAS score increased from 0.34 (0.16) at baseline to 0.53 (0.17) following modafinil ( $p < 0.001$ ). Modafinil improved overall clinical condition, as shown by a statistically significant change in the mean CGI-S depressive illness rating ( $p < 0.001$ , CGI-S2 versus CGI-S1) (Table II). On average, illness severity improved from a rating of markedly ill at baseline to a rating of slightly ill following modafinil. Of the 68 patients assigned a CGI-C rating by the clinician, 63 patients (93%) were rated as clinically improved (i.e., minimally improved, much improved, or very much improved) compared with their level of illness established at the initial visit. Of the 63 patients who improved, 49 patients (78%) were considered by the clinician to be much or very much improved.

Modafinil was well tolerated in combination with a variety of antidepressants and other concomitant medications, including antipsychotic medications and anti-anxiety agents. Adverse events were mild to moderate in intensity. One patient had preexisting tremors that appeared to worsen during the modafinil treatment period. Another patient, a 15-year-old boy, developed hypertonia while receiving modafinil 200 mg once daily and was withdrawn from

treatment. The hypertonia was considered by the investigator not related to modafinil, as he experienced several episodes while on other medications following discontinuation of modafinil. These episodes were determined to be related to anxiety/anger/somatization and were not neurological in nature; they improved with psychotherapy and a combination of divalproex sodium and venlafaxine XR. Eighteen patients discontinued modafinil treatment because of insufficient efficacy. For these patients, the mean modafinil dosage was 265 mg/day.

## CASE SERIES

The following cases are representative of the types of responses observed when modafinil was used as an adjunct to antidepressant therapy. Overall, treatment with modafinil rapidly improved wakefulness, fatigue, and everyday functioning in these individual cases.

### Case 1

Mr. A, a 22-year-old college senior who has been under a clinician's care for the past 3 years, has a history of chronic depression. His symptoms included hypersomnia, poor concentration, excessive fatigue, lack of motivation, increased appetite and weight gain, low mood, and hopelessness. His course of treatment included antidepressant therapy and weekly psychotherapy. The patient received several trials of various medications, given alone or in combination, at the following daily doses: sertraline 200 mg, bupropion 400 mg, buspirone 30 mg, nefazodone 600 mg, citalopram 40 mg, mixed amphetamine salts 30 mg, clonazepam 3 mg, venlafaxine 225 mg, and St. John's Wort 900 mg. When given nortriptyline 150 mg/day and alprazolam 3 mg/day, along with levothyroxine 75 µg/day to successfully treat hypothyroidism, his aforementioned symptoms started to improve but did not completely resolve. After taking these medications for 6 months with partial improvement and following discussion of other treatment options (including electroconvulsive therapy), he agreed to start treatment with modafinil, which was initiated at a dosage of 100 mg/day and then increased to 200 mg/day after 1 week. Before the start of modafinil, the patient was rated by the clinician as severely ill. Within 2 weeks of treatment with modafinil, the patient became very alert and was considered very much improved. He finished his coursework and graduated on schedule. He stopped attending psychotherapy with clinician's consent and obtained very high income-producing employment. Before leaving a clinician's care, the patient was maintained for several months on modafinil 200 mg/day, with no evidence of tolerance.

### Case 2

Mr. B is a 33-year-old white single man who is a graduate student. He had been having difficulty with attention and concentration for some time and had experienced symptoms of anxiety, depression, irritability, and lethargy. During previous employment, the patient underwent neuropsychological testing and was found to have decreased rote verbal learning and memory. He had fluctuations in attention and some asymmetry in his motor performance, with his right side being somewhat weaker than his left side. He has had electroencephalograms that showed sleep fragmentation but no conclusive evidence of any primary sleep disorder. In various trials of single or multiple medications, the patient was given dextroamphetamine, methylphenidate, mixed amphetamine salts, and clonazepam, as well as bupropion, paroxetine, and fluoxetine. All of these medications provided limited benefit. The patient was started on gabapentin 900 mg/day and sertraline 100 mg/day. His mood improved, but he continued to experience difficulty with sleep, energy, and attention span. With the addition of bupropion 300 mg/day to his treatment regimen, improvements in energy, attention, and concentration were noted over 4 months. However, the patient continued to fall asleep during his classes and was not able to spend adequate time attending to his schoolwork. To address the excessive residual sleepiness, modafinil was started initially at a dosage of 100 mg/day, replacing bupropion, then increased to 200 mg/day after 1 week. Within 2 weeks of treatment, improvements in wakefulness and further improvements in energy, attention, and concentration were noted. As rated using the CGI-C, the patient was considered to be very much improved following modafinil. The patient reported a "remarkable" recovery, stating "you saved my life." He was able to complete his graduate studies on schedule and obtained highly compensated employment. He also became engaged to his girlfriend of 2 years, who had been hesitant to commit to their relationship. The patient continued treatment with modafinil 200 mg/day for several months, without the development of tolerance, before being lost to follow up.

### Case 3

Mr. C is a 74-year-old white married man with a lifelong history of bipolar affective disorder and alcoholism in remission. He recently had been diagnosed with cerebral vascular dementia secondary to chronic hypertension. The patient was maintained on a combination of oxcarbazepine, rivastigmine, sertraline, mirtazapine, and clonazepam. He had been doing well with regard to his mood, sleep, appetite and memory. However, he continued to experience lethargy and difficulty with executive cognitive function and had to

give control of his sizeable estate to a financial planner because he was unable to keep track of his investments. Bupropion (sustained release) 150 mg taken three times daily induced hypomania and stimulants induced irritability and more confusion. The patient was initially started on modafinil 200 mg taken once daily in the morning, and the dosage was increased after 1 week to include a 100-mg dose taken in the afternoon. Before the start of modafinil treatment, the patient was considered to be among the most extremely ill of patients. Following modafinil treatment, the patient's overall condition was considered very much improved. His CDRS score improved from 30 at the initial visit to 16 following treatment. The patient no longer required daytime naps and his lethargy was much improved. He also experienced a recovery of his cognitive functioning. These improvements were noted within 2 to 6 weeks of starting modafinil treatment. He took back his investment portfolio and was beginning to make sound decisions. His family corroborated his improvement and used his research for their investments as well. The patient has continued with adjunctive modafinil 400 mg/day for 16 months, without the development of tolerance.

### DISCUSSION

The general findings described in this report suggest that there may be a therapeutic advantage to adding modafinil to the treatment regimens of patients who have a poor or partial response to their antidepressant medications. Statistically significant improvements in mean VAS and CDRS scores were demonstrated, with 11 patients in this generally treatment-resistant population achieving remission after modafinil treatment. The majority of patients were rated as clinically improved with regard to their depressive symptoms. The range of final modafinil dosages and the mean final modafinil dosage were similar to those reported previously in studies of depressed patients (17,18). As with other studies (16,18), treatment with modafinil was well tolerated in combination with multiple, concurrent medications.

As is routine in this practice, patients completed the CDRS before and after the start of modafinil treatment. The CDRS contains elements that are influenced by sleepiness and fatigue, as well as multiple elements that are unrelated to these symptoms. Sleepiness and fatigue may occur as symptoms of depression or as side effects of medications used to treat depression or other concurrent illness. Modafinil has been shown in clinical studies to improve wakefulness (11,13–15, 18) and fatigue (16,18,22). In the present study, improvements in overall clinical condition for the majority of patients were likely due to the beneficial effects of modafinil on sleepiness, fatigue, and energy (as in the profiled cases) rather than improvement in overall mood. It

remains to be determined in controlled studies whether modafinil is an effective augmentation therapy for mood or other core depressive symptoms, as suggested previously in a case report (17) and an open-label study (23) of patients with depression.

For the 3 patients profiled in this report, modafinil-related improvements in wakefulness and fatigue were associated with substantial improvements in functioning. In addition, one patient reported improvement in attention and another showed improvement in cognitive functioning when modafinil was added to antidepressant therapy. Improvements in attention and cognitive functioning were not evident when psychostimulants were given previously. While these findings are intriguing, they are preliminary observations, and this report did not assess the degree to which modafinil improved wakefulness, reduced fatigue, or improved energy or cognition. Others have shown that adjunctive modafinil improves wakefulness (18), reduces fatigue (17,18,23), and enhances cognition (23) in patients with depression and a partial response to antidepressant medications. Finally, the difficulty of treating chronic depression with adequate doses and duration of medications was highlighted in the first case report. It was not until modafinil was added to the patient's treatment regimen that his recovery was optimized and there was no longer a need for ancillary services.

Although the mechanisms through which modafinil exerts its wake-promoting effects have not been established, its structure and pharmacologic profile distinguish it from amphetamines and methylphenidate, psychostimulants that are used as treatments for sleep disorders or as adjuncts to antidepressant therapy. Preclinical studies have shown that psychostimulants activate widespread dopaminergic pathways in the brain (24). In contrast, modafinil activates discrete hypothalamo-cortical neurons associated with wakefulness and cognitive processing (24,25). This selective activity may explain differences observed between the psychostimulants and modafinil in tolerability. While the majority of patients (91%) in this study had previously failed adjunctive treatment with psychostimulants for reasons including tachycardia or behavioral agitation, modafinil use was not associated with these effects, in agreement with the findings of controlled clinical studies (11,13,14). In addition, modafinil in this and other studies (11–18,26) was shown to be well tolerated, with few treatment discontinuations related to adverse events. Modafinil has a low potential for abuse compared with the psychostimulants (27–29). The continuous use of modafinil over the course of several months was not associated with the development of tolerance. This finding is consistent with those of long-term studies that have evaluated the effects of modafinil for up to 88 weeks (26,30).

## CONCLUSION

In summary, modafinil may be effective and well tolerated as an adjunctive therapy in patients with a partial but insufficient response to antidepressant therapy, particularly in those with problematic sleepiness or fatigue. Prospective controlled trials will be valuable in further delineating a role for modafinil in the treatment of depressed patients.

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