Adjunct Modafinil for the Short-Term Treatment of Fatigue and Sleepiness in Patients With Major Depressive Disorder: A Preliminary Double-Blind, Placebo-Controlled Study

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Background: Fatigue and sleepiness are primary symptoms of depression that may not resolve with antidepressant therapy. Modafinil is a novel agent that has been shown to improve wakefulness and lessen fatigue in a variety of conditions. In this study, we examined the utility of modafinil as an adjunct therapy to treat fatigue and sleepiness in patients with major depression who are partial responders to antidepressants.

Method: Patients with partial response to antidepressant therapy given for at least a 6-week period for a current major depressive episode (DSM-IV criteria) were enrolled in this 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients received once-daily doses (100–400 mg) of modafinil or matching placebo as adjunct treatment to ongoing antidepressant therapy. The effects of modafinil were evaluated using the Hamilton Rating Scale for Depression (HAM-D), the Fatigue Severity Scale (FSS), the Epworth Sleepiness Scale (ESS), the Clinical Global Impression of Change (CGI-C), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Adverse events were monitored throughout the study.

Results: One hundred thirty-six patients were randomized to treatment, with 118 patients (87%) completing the study. Most patients (82%) were fatigued, and one half of patients (51%) were sleepy. Modafinil rapidly improved fatigue and daytime wakefulness, with significantly greater mean improvements from baseline than placebo in fatigue (FSS) scores at week 2 ($p < .05$) and sleepiness (ESS) scores at week 1 ($p < .01$); the differences between modafinil and placebo at week 6 were not statistically significant. Assessment of the augmentation effects of modafinil (HAM-D, CGI-C, and SF-36) did not significantly distinguish modafinil from placebo. Modafinil was well tolerated in combination with a variety of antidepressants.

Conclusion: Modafinil may be a useful adjunct therapy for the short-term management of residual fatigue and sleepiness in patients who are partial responders to antidepressant therapy.

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Of the various symptoms of major depressive disorder (MDD), fatigue and sleep disturbances are among the most commonly reported. In surveys of depressed patients, fatigue, tiredness, and loss of energy were reported by 73% to 97% of patients,[1–3] a prevalence comparable in magnitude to that for core symptoms, such as depressed mood and diminished interest or pleasure.[2,3] In addition to being antecedent or primary complaints associated with acute depressive episodes, fatigue and sleep problems may be bothersome complications of therapy with antidepressants[4,5] and may be associated with coexisting conditions and medical illnesses.

Fatigue and sleep problems also may persist as residual symptoms despite adequate antidepressant therapy. Among those who were considered full responders to 20 mg of fluoxetine taken daily for 8 weeks in an open-label study, more than 30% of patients had 3 or more re-

sidual symptoms, with the 3 most common complaints being sleep disturbances (44%), fatigue (38%), and diminished pleasure (27%).[6] Over 90% of patients with posttreatment threshold or subthreshold fatigue or insomnia had experienced these symptoms prior to treatment. Considering that partial response to antidepressants predisposes patients to greater risk of relapse and greater probability of recurrent depression,[7–9] with attendant deficits in physical, psychological, and vocational functioning,[10,11] rapid resolution of residual symptoms may be a treatment goal of considerable importance to patients and their physicians.

Failure of antidepressant therapy to resolve the full constellation of depressive symptoms in partial responders has led to the use of adjunct therapies, particularly after various antidepressant combination and switching options have been considered or explored.[12] Reports have described the use of various agents, including lithium,[13–19] bupropion,[20–23] triiodothyronine,[16,24–27] atypical antipsychotics,[28,29] and psychostimulants.[30–36] Despite a lack of controlled conditions in many of these studies, recent literature reviews conclude that such adjunct therapy may be useful for treating patients with partial response to antidepressant therapy.[12,37]

The wake-promoting agent modafinil has been shown to improve wakefulness in patients with narcolepsy[38–40] and obstructive sleep apnea when used as an adjunct to nasal continuous positive airway pressure therapy[41–43] and to lessen fatigue in patients with multiple sclerosis.[44,45] Additionally, Menza et al.[46] reported on a retrospective case series of 7 patients with MDD or bipolar depression who had a partial response or nonresponse to antidepressant treatment in which the addition of modafinil, 100 to 200 mg/day, was associated with decreases in fatigue and decreases in Hamilton Rating Scale for Depression (HAM-D) scores within 1 to 3 weeks. In a prospective but open-label study of patients with major depression who experienced an incomplete response to an adequate trial of antidepressant medication, decreases in fatigue and depression were demonstrated when modafinil, 100 to 400 mg/day, was added to the treatment regimen.[47] While the results of these 2 pilot studies suggest a possible role for modafinil as an adjunct to antidepressant therapy, these were not blinded, placebo-controlled clinical studies. Therefore, a double-blind, placebo-controlled, pilot study was undertaken to determine the effects of adjunct modafinil on fatigue and sleepiness and to assess its safety in patients who responded only partially to antidepressant medications.

METHOD

Patient Selection

Eligible patients, aged 18 to 65 years, had been previously diagnosed with MDD (single episode or recurrent) without psychotic features in accordance with DSM-IV criteria, with clinical assessment and confirmation by the Mini-International Neuropsychiatric Interview.[48] Patients exhibited partial response to antidepressant therapy for at least 6 weeks, as evidenced by clinical history. At screening and at baseline, patients scored between 14 and 28, inclusive, on the 21-item HAM-D. Written informed consent was obtained from each patient before entry into the study.

Patients were excluded from study participation if they had a diagnosis of any Axis I disorder other than MDD or an anxiety disorder. Patients with a diagnosis of any Axis II disorder that would, in the opinion of the investigator, interfere with the conduct of the study also were excluded. Other exclusion criteria included a history or current diagnosis of dysthymia, a history of any psychotic disorder, or significant risk for suicide. The presence of hypertension or a sitting pulse rate of > 100 b.p.m. or < 50 b.p.m. after resting for 5 minutes precluded study participation. Patients could not have uncontrolled medical disorders, clinically significant drug sensitivity or drug allergy to stimulants, or medical contraindications to the use of modafinil. Patients had not received modafinil previously.

Study Design

This 6-week, randomized, double-blind, placebo-controlled study was conducted at 15 centers in the United States using a protocol approved by their respective institutional review boards. During the study, patients attended the clinic at screening, at baseline on day 0, and on treatment days 1, 7, 14, and 42, with telephone contact on day 28. Patients were assigned to receive modafinil, supplied as 100-mg tablets for oral administration, or matching placebo once daily in the morning. During week 1 of double-blind treatment, the dosage of modafinil was 100 mg/day on days 1 through 3 and 200 mg/day on days 4 through 7. On day 7, the modafinil dosage for week 2 was determined based on efficacy and tolerability demonstrated during week 1, with the dosage maintained at 200 mg/day or titrated downward to 100 mg/day or upward to 300 mg/day. During weeks 3 to 6, patients continued to receive the dosage from week 2 or the dosage could be adjusted upward or downward by 100 mg/day based on efficacy and tolerability, with 400 mg the maximum allowable daily dose. Throughout double-blind treatment, patients continued to receive their current dosage and formulation of antidepressant medication and other clinically relevant concurrent medications not excluded by protocol.

Assessments

Efficacy evaluations were conducted at baseline and weeks 1, 2, and 6 (or termination visit). Changes in fatigue were assessed using the Fatigue Severity Scale (FSS),[49] a 9-item instrument that assesses the effects or

Table 1. Fatigue Severity Scale (FSS)[a]

1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my 3 most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

[a]Reprinted with permission from Krupp et al.[49] Scores for each item range from 1 (strongly disagree) to 7 (strongly agree). The final FSS score is the average score.

Table 2. Epworth Sleepiness Scale (ESS)[a]

Sitting and reading
Watching TV
Sitting, inactive, in a public place (ie, a theatre or a meeting)
As a passenger in a car for an hour without a break
Lying down to rest in the afternoon
Sitting and talking to someone
Sitting quietly after a lunch without alcohol
In a car, while stopped for a few minutes in traffic

[a]Reprinted from Johns.[50] Scores for each situation range from 0 (would never doze) to 3 (high chance of dozing). The total ESS score is the sum of the individual item scores.

consequences of fatigue. FSS scores for individual items range from 1 to 7 (lower scores indicate less fatigue); the mean of the 9 items is the final FSS score (Table 1). Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS).[50] The ESS measures the propensity of patients to sleep or doze during 8 commonly encountered daytime situations. Total scores for the ESS range from 0 to 24, with lower scores indicating less sleepiness (Table 2).

Changes in overall depression were evaluated using the 21-item HAM-D (HAM-D-21)[51,52]; scores on the first 17 items (HAM-D-17) were also recorded. The 4 items comprising the HAM-D retardation subscale (i.e., depressed mood, psychomotor retardation, work and activities, and genital symptoms) also were evaluated. Overall clinical condition and illness severity were established at baseline using the investigator-rated Clinical Global Impression of Severity (CGI-S), and changes in illness severity were assessed using the Clinical Global Impression of Change (CGI-C).[53] Investigator ratings for the 7-point CGI-C range from "very much improved" to "very much worse."

Patient-assessed, health-related quality of life was determined at baseline and at week 6 using the Medical Outcomes Study Short-Form Health Survey (SF-36), a 36-item instrument that is applicable for a wide variety of populations and interventions.[54,55] Physical and mental component summary scores were calculated from 8 SF-36 domains (i.e., general health, mental health, physical functioning, role-emotional, role-physical, social functioning, vitality, and bodily pain). Domain scores range from 0 (lowest quality of life) to 100 (highest quality of life); higher scores correspond to a more favorable overall health status.

Safety was assessed by recording all observed and reported adverse events by treatment group, day of onset, type, severity, and relationship to study medication. Treatment-emergent (i.e., of all causes) adverse events were those occurring during double-blind treatment after the first dose of study drug was administered. Complete physical examinations and 12-lead electrocardiograms were conducted at screening and at week 6. Vital signs (sitting and standing blood pressure and pulse rates) were monitored at screening, at baseline, and at weeks 1, 2, and 6. Blood and urine samples were collected for evaluation of clinical laboratory parameters at the screening visit, at the baseline visit, and at weeks 1, 2, and 6.

Statistical Analysis

Demographic variables were summarized for all randomized patients using descriptive statistics, and between-group comparisons of continuous and nominal demographic variables were performed using analysis of variance (ANOVA) and chi-square tests, respectively. Randomized patients with at least 1 postbaseline efficacy measurement were evaluated for efficacy. Comparisons of changes from baseline between treatment groups in FSS, ESS, HAM-D, and SF-36 scores were performed for each visit using analysis of covariance (ANCOVA), with the baseline score as a covariate and treatment and center as factors. CGI-C data were analyzed using a Cochran-Mantel-Haenszel statistic adjusted for center. Tests of treatment effect were 2-tailed and performed at a significance level of 5%. Patients receiving at least 1 dose of study drug were included in the safety analysis. Clinical laboratory and vital signs data were summarized using descriptive statistics, and the proportion of patients with clinically significant values was summarized by treatment group.

RESULTS

Patients

Baseline characteristics of patients are summarized in Table 3. A total of 136 patients were randomized to treatment, with 69 patients in the adjunct modafinil group and 67 patients in the adjunct placebo group. Between treatment groups, there were no significant differences with respect to age, race, or gender. The ratio of women to men was 2.0:1 and 2.7:1, respectively, for the modafinil and placebo groups, similar to gender ratios for major depressive disorder observed in the general population.[56] During the study, 127 patients (93%) were taking a single antidepressant, and 9 patients (7%) were taking 2 or more antidepressants. The majority of patients (78%) were re-

Table 3. Baseline Characteristics of Patients Receiving Antidepressants Who Were Treated Adjunctively With Placebo or Modafinil[a]

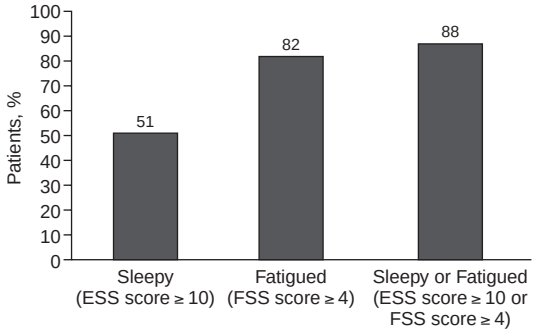
Characteristic	AD + Placebo (N = 67)	AD + Modafinil (N = 69)
Age, mean (range), y	45 (23–64)	45 (19–64)
Gender		
Female	49 (73)	46 (67)
Male	18 (27)	23 (33)
Concomitant AD therapy		
Monotherapy	61 (91)	66 (96)
Polytherapy (2 or more ADs)	6 (9)	3 (4)
Concomitant AD class and agent[b]		
SSRI	50 (75)	56 (81)
Citalopram	12 (18)	9 (13)
Fluoxetine	19 (28)	14 (20)
Paroxetine	14 (21)	17 (25)
Sertraline	5 (7)	16 (23)
Tricyclics	1 (2)	0 (0)
Amitriptyline	1 (2)	0 (0)
Other	21 (31)	15 (22)
Bupropion	5 (7)	5 (7)
Mirtazapine	2 (3)	1 (1)
Nefazodone	4 (6)	5 (7)
Trazodone	3 (4)	1 (1)
Venlafaxine	9 (13)	3 (4)
CGI-S rating[c]		
Slightly ill	8 (12)	6 (9)
Moderately ill	51 (77)	55 (81)
Markedly ill	6 (9)	7 (10)
Extremely ill	1 (2)	0 (0)
HAM-D score, mean (SD)[d]		
Items 1–21	19.0 (3.5)	19.2 (3.4)
Items 1–17	16.8 (3.4)	17.0 (3.2)
FSS score, mean (SD)[d]	5.0 (1.3)	5.1 (1.3)
ESS score, mean (SD)[d]	10.5 (4.9)	9.5 (4.5)

[a]Values shown as N (%) unless otherwise noted.
[b]N (%) of patients receiving SSRIs and other ADs exceeds the total N (%) of patients because some patients were taking 2 or more ADs.
[c]CGI-S scores at baseline were available for 66 of 67 patients randomized to placebo and 68 of 69 patients randomized to modafinil.
[d]HAM-D, FSS, and ESS scores at baseline were available for all 67 patients randomized to placebo and 68 of 69 patients randomized to modafinil.
Abbreviations: AD = antidepressant, CGI-S = Clinical Global Impression of Severity, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

ceiving selective serotonin reuptake inhibitors as monotherapy or in combination with other antidepressants.

Disease severity was recorded at baseline for 134 of 136 patients using the CGI-S. Most patients (adjunct modafinil group, 55 patients [81%]; adjunct placebo group, 51 patients [77%]) were rated by a clinician as moderately ill, as would be expected for patients required by protocol to be partial responders to current antidepressant pharmacotherapy and in accordance with baseline HAM-D-21 scores (3 patients scored outside of the protocol-specified range of 14–28, inclusive [scores of 12, 12, and 29]). At baseline, mean scores for the HAM-D-21 and HAM-D-17 were similar between the treatment groups, as were mean FSS and ESS scores. The majority of patients (82%) were fatigued, with baseline FSS scores of 4 or more, and one half of patients (51%) were sleepy,

Figure 1. Percentages of Patients With Pathological Sleepiness or Fatigue as Determined From Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS) Scores



as evidenced by baseline ESS scores of 10 or more (Figure 1).

Of those randomized, 118 patients (87%) (adjunct modafinil, 59 patients; adjunct placebo, 59 patients) successfully completed the study. Reasons for study discontinuation included adverse event (adjunct modafinil group, N = 3; adjunct placebo group, N = 4), lack of efficacy (modafinil, N = 3; placebo, N = 2), withdrawn consent (modafinil, N = 1), noncompliance (modafinil, N = 2), and lost to follow-up (modafinil, N = 1; placebo, N = 2).

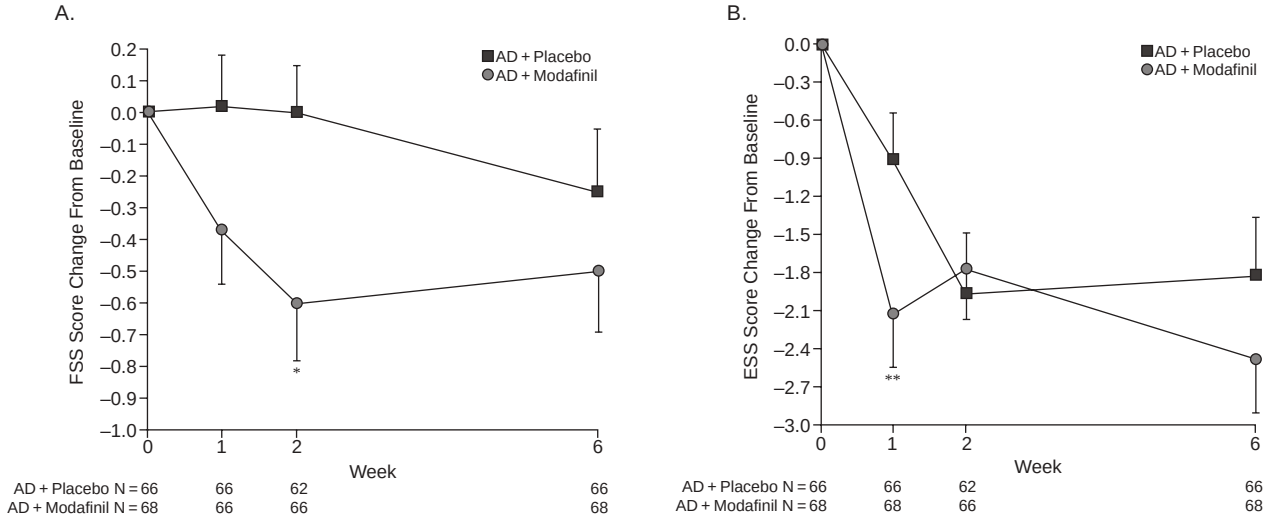
Dosing

During the first week of the study, patients in the active modafinil group received protocol-specified daily modafinil doses of 100 mg (days 1–3) and 200 mg (days 4–7). A change in dosing was implemented for most patients after week 1 in accordance with the protocol and at the investigator's discretion. At week 2, 22 (32%) of 69 patients in the modafinil arm were taking modafinil 200 mg (2 tablets), and 39 patients (57%) were taking modafinil 300 mg (3 tablets). At study endpoint, 21 patients (30%) in the modafinil group were taking modafinil 100 or 200 mg, 21 patients (30%) were taking 300 mg, and 21 patients (30%) were taking 400 mg.

Efficacy Outcomes

Modafinil was shown to rapidly lessen fatigue compared with placebo. Reductions from baseline in FSS scores were demonstrated with modafinil at each post-baseline timepoint, with a statistically significant treatment effect favoring modafinil over placebo evident at week 2 ($p < .05$) (Figure 2A). Although the mean improvement in fatigue in the modafinil group was sustained from week 2 to week 6, mean fatigue scores in the placebo group declined from week 2 to week 6. Consequently, the difference between modafinil and placebo was no longer statistically significant at week 6. Treatment with

Figure 2. Mean Change (± SEM) From Baseline in (A) Fatigue Severity Scale (FSS) Scores and (B) Epworth Sleepiness Scale (ESS) Scores After Treatment With Antidepressants (ADs) Plus Modafinil or ADs Plus Placebo[a]



[a]Mean (± SEM) baseline FSS scores for placebo and modafinil groups were 5.0 (± 0.2) and 5.1 (± 0.2), respectively. Mean baseline ESS scores for placebo and modafinil groups were 10.5 (± 0.6) and 9.5 (± 0.6), respectively.
*p < .05.
**p < .01.

Table 4. Change From Baseline in HAM-D Scores

	HAM-D-21			HAM-D-17		
Comparison	N	Mean (SEM) Change From Baseline	p Value[a]	N	Mean (SEM) Change From Baseline	p Value[a]
Week 1						
AD + placebo	67	–3.66 (0.51)		67	–3.25 (0.48)	
AD + modafinil	68	–4.06 (0.51)	NS	68	–3.62 (0.45)	NS
Week 2						
AD + placebo	63	–6.21 (0.62)		63	–5.49 (0.59)	
AD + modafinil	65	–5.83 (0.50)	NS	65	–5.23 (0.47)	NS
Week 6						
AD + placebo	67	–6.40 (0.76)		67	–5.57 (0.70)	
AD + modafinil	68	–6.94 (0.67)	NS	68	–6.10 (0.56)	NS

[a]Versus AD + placebo group.
Abbreviations: AD = antidepressant, HAM-D = Hamilton Rating Scale for Depression, NS = not significant.

modafinil also improved wakefulness, as shown by a statistically significant reduction in mean ESS score relative to placebo after 1 week of treatment ($p < .01$) (Figure 2B). While the change from baseline in mean ESS score at week 6 was greater for modafinil than for placebo, the difference between the treatment groups was not statistically significant.

No significant differences between adjunct modafinil and placebo were demonstrated in HAM-D scores (Table 4). At each timepoint, reductions from baseline in HAM-D-21 and HAM-D-17 scores were similar in magnitude for both treatment groups. No significant treatment differences were observed when individual items of the HAM-D were evaluated for mean end-of-study changes from baseline. However, a trend suggesting a treatment difference in favor of modafinil was noted in the individual item of psychomotor retardation ($p = .089$).

Patients' overall clinical condition, as assessed by the CGI-C for depression, improved in about two thirds (67%) of all patients. While the percentage of patients rated as clinically improved was greater for the modafinil group than the placebo group at each postbaseline timepoint, the differences between the treatment groups were not statistically significant. At week 6, CGI-C ratings improved for 50 (74%) of 68 patients receiving modafinil compared with 41 (61%) of 67 patients receiving placebo.

No significant between-group differences were demonstrated for the end-of-study change from baseline in mental or physical composite scores or any domain scores of the SF-36.

Table 5. Treatment-Emergent Adverse Events Experienced by ≥ 5% of Patients in Either Treatment Group During Double-Blind Treatment[a]

	AD + Placebo (N = 67)		AD + Modafinil (N = 69)	
Adverse Event	N	%	N	%
Headache	8	12	15	22
Nervousness	3	4	14	20
Insomnia	9	13	13	19
Infection	8	12	7	10
Diarrhea	5	7	5	7
Rhinitis	4	6	5	7
Anxiety	4	6	5	7
Somnolence	3	4	5	7
Hypertonia	0	0	5	7[b]
Nausea	5	7	3	4
Asthenia	5	7	2	3
Myalgia	4	6	1	1

[a]Includes randomized patients who received at least 1 dose of study drug.
[b]Jaw clenching (N = 3), muscle tension (N = 1), spasms in right sternocleidomastoid muscle (N = 1).

Safety Outcomes

During the 6-week treatment period, 102 (75%) of 136 patients experienced an adverse event. Adverse events were generally mild or moderate in nature. No serious adverse events were reported during the course of the study. Treatment-emergent adverse events occurring in 5% or more of patients in either treatment group are shown in Table 5. A greater percentage of patients in the modafinil group than patients in the placebo group reported headache (22% vs. 12%) and nervousness (20% vs. 4%). The incidence of other adverse events was not appreciably different between the treatment groups. Modafinil was not associated with sexual side effects, as determined from adverse event reporting and responses to item 14 of the HAM-D. Treatment with modafinil had no effect on body weight.

Three patients (4%) in the modafinil group and 4 patients (6%) in the placebo group discontinued treatment because of adverse events. Of the 3 patients receiving modafinil who discontinued owing to adverse events, all experienced events considered by the investigator to be treatment related. The treatment-related adverse events leading to study discontinuation in the modafinil group included headache (N = 1), dry mouth (N = 1), and heart palpitation and shortness of breath (N = 1). There were no significant differences between modafinil and placebo in vital signs, including sitting and standing systolic blood pressure, sitting or standing diastolic blood pressure, and heart rate. No clinically meaningful differences in laboratory test results were noted between the treatment groups.

DISCUSSION

In this 6-week study, adjunct treatment with modafinil rapidly improved fatigue in patients with a current episode of major depression and a partial response to antidepressant therapy, with statistically significant improvement demonstrated after 2 weeks of double-blind treatment. Rapid and significant modafinil-related improvement in wakefulness also was demonstrated relative to placebo after 1 week of treatment. Adjunct treatment with modafinil was well tolerated. While improvements in fatigue and wakefulness with modafinil were sustained, there were no significant differences between modafinil and placebo at week 6. These data suggest that adjunct modafinil may be beneficial when used as a short-term pharmacotherapy for fatigue and sleepiness in patients undergoing treatment for depression. However, these data do not support long-term benefits of modafinil over placebo in this depressed population of partial responders to antidepressant therapy.

There are several possible explanations for why the early statistically significant advantages of modafinil over placebo were not demonstrated at week 6. There may be a limitation in the wake-promoting effectiveness of modafinil treatment in this population; however, this would be inconsistent or contrary to studies for the treatment of excessive sleepiness in other clinical models, which clearly demonstrated sustained wake-promoting effects. Another explanation may be that limitations imposed by the study design may have contributed to the lack of statistically significant effects versus placebo at the later timepoint. These include modafinil dosages and dosing schedules that may have not been optimized for managing fatigue and sleepiness and the inclusion of some patients without fatigue or sleepiness. The variable duration and choice of prior antidepressant therapy also may have affected fatigue and sleepiness outcomes. Because some patients were allowed to enter the study after having taken antidepressants for at least 6 weeks and because symptom stability was not systematically confirmed prior to randomization, it is possible that the beneficial effects of antidepressants may have continued to accrue over the course of double-blind treatment for some patients, regardless of whether the patient was randomized to modafinil or placebo.

Multiple studies of modafinil have now been completed that demonstrate sustained benefits in wakefulness in narcolepsy,[38–40] idiopathic hypersomnia,[57] and obstructive sleep apnea.[43] In open-label studies conducted in narcolepsy patients, improvements in fatigue were maintained during 6 weeks of treatment,[58] and improvements in vitality were demonstrated for up to 88 weeks[59,60] with modafinil 200 or 400 mg/day. There has been no evidence for the development of tolerance in narcolepsy patients who have received long-term treatment with modafinil.[61,62]

An item analysis of the HAM-D supports the theory that the effects of modafinil in depression may be specific to its effects on fatigue and sleepiness. Of the individual HAM-D items, modafinil was shown to most notably affect psychomotor retardation (i.e., slowness of thought

and speech, impaired ability to concentrate, and decreased activity). That modafinil appeared to have a greater effect on psychomotor retardation is consistent with improvements in fatigue and sleepiness. Additional controlled studies that specifically address the effects of modafinil on concentration, energy, and psychomotor retardation are warranted.

Given the rapid onset of action for modafinil demonstrated in this study and the relatively long latency to response for antidepressant medications, an area for further investigation is whether modafinil may prove useful for treating fatigue or sleepiness in patients who are starting or switching antidepressant therapy, affording early symptomatic relief. Modafinil may also prove effective as a treatment option for patients who develop fatigue as a side effect of ongoing antidepressant therapy or in response to diminishing antidepressant effectiveness. Additional research is necessary to assess the utility of modafinil in this therapeutic area.

This study provides preliminary evidence suggesting that modafinil improves fatigue and sleepiness when used as a short-term adjunct treatment for patients with major depression who are partially responsive to antidepressants. Just as adjunctive benzodiazepines may be useful in the short-term relief of agitation and anxiety in depressed patients, modafinil may be useful as a short-term adjunctive treatment in the relief of fatigue and psychomotor retardation in depression. However, this study did not differentiate at baseline whether the fatigue and sleepiness were part of the underlying depression, secondary to their pharmacotherapy, or related to both medication and the underlying depression. Thus, it is possible that modafinil may work preferentially on fatigue secondary to medications and perhaps be less effective in treating the core retardation of major depression.

Adjunctive therapy with modafinil did not have broader antidepressant effects over and above placebo-expectancy factors. Treatment with modafinil was well tolerated in combination with a variety of antidepressants, with most adverse events mild or moderate and few patients discontinuing the study because of modafinil-related adverse events. Additional double-blind, placebo-controlled trials are required to establish optimal modafinil dosing regimens for the treatment of fatigue and related symptoms and to determine whether these short-term improvements in fatigue can be sustained. Other studies aimed at examining the effects of modafinil in patients receiving long-term antidepressant therapy and in patients with primary fatigue disorders and concomitant depression may further delineate what role modafinil may play in the treatment of depression-related fatigue and sleepiness.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), liothyronine (Cytomel, Triostat), modafinil (Provigil).

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