A Multicenter, Placebo-Controlled Study of Modafinil Augmentation in Partial Responders to Selective Serotonin Reuptake Inhibitors With Persistent Fatigue and Sleepiness

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Background: Up to one half of depressed patients have partial or no response to antidepressant monotherapy. This multicenter, placebo-controlled study evaluated the efficacy of modafinil augmentation in major depressive disorder (MDD) patients with fatigue and excessive sleepiness despite selective serotonin reuptake inhibitor (SSRI) monotherapy.

Method: Patients (18–65 years) with a DSM-IV diagnosis of MDD and partial response to SSRI monotherapy (≥ 8 weeks) at a stable dose for ≥ 4 weeks were eligible. Patients had screening/baseline 31-item Hamilton Rating Scale for Depression (HAM-D) scores of 14 to 26, Epworth Sleepiness Scale (ESS) scores ≥ 10, and Fatigue Severity Scale (FSS) scores ≥ 4. Patients were randomly assigned to augmentation therapy with modafinil 200 mg/day or placebo for 8 weeks. Assessments included the ESS, Clinical Global Impressions-Improvement scale (CGI-I), 31- and 17-item HAM-D, FSS, Brief Fatigue Inventory (BFI), and Montgomery-Asberg Depression Rating Scale (MADRS).

Results: Of 311 enrolled patients who received ≥ 1 dose of study drug, 158 were randomly assigned to modafinil (70% women) and 153 to placebo (72% women); 85% of each treatment group completed the study. At final visit, modafinil significantly improved patients' overall clinical condition compared with placebo on the basis of CGI-I scores ($p = .02$), and there were trends toward greater mean reductions in ESS, 31- and 17-item HAM-D, and MADRS scores versus placebo. Modafinil significantly reduced BFI scores for worst fatigue at final visit ($p < .05$ vs. placebo). There were no significant differences between modafinil and placebo at final visit in FSS or BFI total scores. Adverse events significantly more common during modafinil compared with placebo treatment were nausea (9% vs. 2%; $p = .01$) and feeling jittery (4% vs. 1%; $p = .03$).

Conclusion: These findings suggest that modafinil is a well-tolerated and potentially effective augmenting agent for SSRI partial responders with fatigue and sleepiness.

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Major depressive disorder (MDD) is a highly prevalent and disabling medical condition.[1] It has been estimated that between 29% and 46% of depressed patients show only partial or no response to treatment after a single antidepressant trial,[2] and, even among responders, residual symptoms are rather common.[3] Remission is now widely considered to be the initial goal of antidepressant treatment,[4] yet rates of remission in efficacy trials with selective serotonin reuptake inhibitors (SSRIs) hover around 35%.[5] This suggests that, more often than not, clinicians are challenged to select the most appropriate next-step strategy to help patients enhance response, particularly considering that there is a paucity of published, adequately powered, placebo-controlled studies of SSRI augmentation that demonstrate significant improvement.[6–10]

Most of the time, clinicians' decisions regarding treatment approaches are guided by anecdotal reports, case series, and results of relatively small, uncontrolled clinical trials. Despite the prevalence of antidepressant nonre-

sponse, only a handful of controlled clinical trials have assessed next-step pharmacologic strategies for SSRI partial responders.[11] There are no published controlled data on the newer augmentation strategies, and when one surveys psychiatrists to assess their perceptions of what works, there is a poor relationship between the amount of clinical data available and what is used to manage partial or nonresponse in current psychopharmacologic practice.[12]

From the strategies available to manage antidepressant partial response, clinicians often choose to continue the antidepressant and to add an "augmenting" compound.[13] Such augmentation strategy involves the use of a pharmacologic agent that is not considered to be a standard antidepressant but that may enhance the effect of an antidepressant by a complementary mechanism. Alternatively, clinicians may choose to either switch to another antidepressant or combine the antidepressant that did not produce adequate response with another antidepressant, typically of a different class. Clinicians often favor augmentation and combination strategies over switching in cases of partial response, because patients may be reluctant to discontinue an antidepressant that has produced some benefit.

Fatigue, lack of energy, tiredness, sleep disturbances, and impaired concentration are some of the most common symptoms reported by individuals with MDD.[14,15] Surveys show that a majority of patients report several of these symptoms (fatigue or loss of energy, 73%–97%; sleep disturbances, 63%–77%; impaired concentration, 51%–84%),[14–16] some of which may be categorized in the same degree as hallmark MDD symptoms such as depressed mood and diminished interest or pleasure.[14,15] In addition, many patients being treated for depression still experience fatigue, excessive sleepiness, and concentration impairments despite obtaining relief of other depressive symptoms.[17,18] SSRIs are also associated with treatment-related fatigue and excessive sleepiness.[19,20] Despite the frequent clinical perception that rates of treatment-emergent fatigue may vary across SSRIs, a double-blind study failed to show statistically significant differences among fluoxetine, sertraline, and paroxetine in rates of asthenia/fatigue.[21] Even the newer agents thought to be more activating may be associated with fatigue as a side effect; this has been generally thought to be a result of sleep disruption, with fatigue and sleepiness being a consequence of poor sleep continuity and sleep loss.[22–24]

Modafinil is a novel, wakefulness-promoting medication that has been approved for the treatment of excessive sleepiness associated with several sleep disorders. Its pharmacologic actions are different from those of the psychostimulants such as amphetamine and methylphenidate, although the precise mechanism of action is unknown.[25] Modafinil appears to exert its predominant pharmacologic action, "wake promotion," by selectively affecting areas of the brain believed to regulate normal wakefulness as compared with generalized effects on the central nervous system.[26,27] Because fatigue and excessive sleepiness are common complaints of antidepressant nonresponders, a number of clinical investigators have tried modafinil as an augmenting agent. In a retrospective case series, Menza et al.[28] reported the potential benefit of modafinil augmentation among antidepressant nonresponders (in dosages of up to 200 mg/day). A recent report by DeBattista et al.[29] found that modafinil (up to 400 mg/day for 4 weeks) as an augmenting agent for depressed patients (N = 31) not responding to SSRIs or venlafaxine resulted in statistically significant improvements across measures of depression and fatigue and 1 measure of cognitive function. Although these open-label studies do not prove that modafinil is an effective augmenting agent, the relative simplicity of this agent, especially when compared with either lithium or psychostimulants, reinforces the need for further research.[11] In particular, the residual symptoms of fatigue, excessive sleepiness, and lethargy may be important targets for augmentation with modafinil.[11]

This multicenter, placebo-controlled study was aimed at evaluating the efficacy of modafinil as an antidepressant treatment augmenting agent for patients who had not achieved remission and who had complained of symptoms of fatigue and excessive sleepiness despite adequate SSRI treatment.

MATERIALS AND METHOD

Patient Selection

Eligible patients, aged 18 to 65 years, had been previously diagnosed with MDD (single episode or recurrent) according to *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria and had symptoms of fatigue and excessive sleepiness despite adequate SSRI treatment. The current MDD episode was clinically assessed and confirmed using the Mini-International Neuropsychiatric Interview (MINI).[30] Patients had a partial response to an adequate course of SSRI monotherapy (≥ 8 weeks at a minimally effective dose) and had been on a stable monotherapy dose of SSRI for ≥ 4 weeks. At both screening and baseline, patients had a mean 31-item Hamilton Rating Scale for Depression (HAM-D-31)[31] score of between 14 and 26 (inclusive), an Epworth Sleepiness Scale (ESS)[32] score of ≥ 10, and a Fatigue Severity Scale (FSS)[33] score of ≥ 4. The risks and benefits of study participation were explained to each patient, and after all questions and concerns were addressed, written informed consent was obtained before any protocol activities were undertaken.

Patients were excluded from study participation if they had a current episode of MDD considered treatment-resistant (defined as having failed > 2 adequate trials of antidepressant treatment), a primary diagnosis of an Axis

I disorder other than MDD, or an Axis II disorder that may have interfered with conduct of the study (e.g., severe antisocial personality disorder). Other exclusion criteria included a significant risk for suicide; a history of psychosis or dysthymic disorder; a history of alcohol, narcotic, or other substance dependence (except for tobacco) within the past 12 months; or a diagnosis of fibromyalgia, chronic fatigue syndrome, or a primary sleep disorder. The presence of hypertension or a sitting pulse rate of > 100 bpm or < 50 bpm after resting for 5 minutes precluded study participation. Patients could not have an uncontrolled medical disorder, a clinically significant drug sensitivity or drug allergy to stimulants, a medical contraindication to the use of modafinil, or a history of prior use of modafinil.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study of modafinil augmentation. After a single-blind, placebo run-in period of 1 week, patients were randomly assigned (1:1) to receive augmentation therapy with either 200 mg modafinil, supplied as 100-mg tablets for oral administration, or matching placebo once daily in the morning for an 8-week period. During double-blind treatment, the dosage of modafinil was 100 mg/day on days 1 through 3 and 200 mg/day on days 4 through 56. The institutional review board of each site reviewed the study, and local ethics committees approved the protocol. This study was conducted in full accordance with the guidelines of the Declaration of Helsinki and its amendments.

Throughout double-blind treatment, patients continued to receive their current dosage of SSRI (defined as ≥ 8 weeks of a minimally effective dose with fixed-dose monotherapy for ≥ 4 weeks), as well as other concurrent medications not excluded by protocol. SSRIs were limited to fluoxetine (≥ 20 mg/day), paroxetine (≥ 20 mg/day), controlled-release paroxetine (≥ 25 mg/day), and sertraline (≥ 100 mg/day). All other antidepressant, anxiolytic, psychostimulant, and other psychotropic agents were prohibited during the study.

Assessments

Efficacy assessments included the ESS, FSS, Brief Fatigue Inventory (BFI),[34] Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales,[35] HAM-D-31, HAM-D-17, and the Montgomery-Asberg Depression Rating Scale (MADRS).[36] Assessments were made at screening, baseline, and weeks 1, 2, 4, 6, and 8.

Safety was assessed by summarizing and comparing the incidence rates of adverse events by treatment group, including severity and relationship to study medication. All observed adverse events were recorded; events occurring after the first dose of study medication (i.e., "treatment-emergent") regardless of the relationship to study drug were summarized and included in the safety assessment. Complete physical examinations (including body weight), laboratory assessments (including complete blood count, blood chemistry screen, thyroid function tests for women, and urinalysis; Quest Diagnostics Clinical Trials, Van Nuys, Calif.), and 12-lead electrocardiograms were conducted at screening and at the end of double-blind treatment. Vital signs (i.e., sitting blood pressure and heart rate) were monitored at screening, baseline, and weeks 1, 2, 4, 6, and 8. Urine drug testing was also conducted at screening to ensure that patients were not using agents prohibited according to the protocol. A positive result for any of these agents, including methylphenidate, amphetamines, pemoline, cocaine, codeine, barbiturates, methaqualone, morphine, methadone, propoxyphene, and phencyclidine, precluded the patient from enrollment or continued participation in the study.

Statistical Analysis

Demographic variables were summarized for all randomized patients using descriptive statistics, and between-group comparisons of continuous and discrete demographic variables were performed using analysis of variance and χ^2 tests (or Fisher exact test if warranted), respectively. The study was powered to detect a between-group difference of 1.1 units in the mean (assuming an estimated SD of 3.15) change from baseline in ESS score. Randomized patients with ≥ 1 postbaseline ESS measurement were evaluated for efficacy. The final visit was defined as week 8 or the last postbaseline observation. Comparisons of changes from baseline between treatment groups in ESS, FSS, BFI, HAM-D (both 17- and 31-item scores), and MADRS were performed for each visit using analysis of covariance, with the baseline score as a covariate and treatment and center as effects. Post hoc analyses were conducted for the subset of patients whose pretreatment score on the HAM-D-17 was above 13 (i.e., the study group's mean). The number of patients meeting criteria for remission (defined as a HAM-D-17 score < 8 at final visit) and those found at final visit to have minimal, much, or very much improvement on the CGI-I were analyzed using the Cochran-Mantel-Haenszel test adjusted for centers. Tests of treatment effect were 2-tailed and performed at a significance level of 5%. Patients receiving ≥ 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

A total of 513 patients were screened and 314 were randomized. Of the patients randomized, 3 (2 on placebo and 1 on modafinil) did not receive ≥ 1 dose of study drug

Table 1. Baseline Patient Characteristics

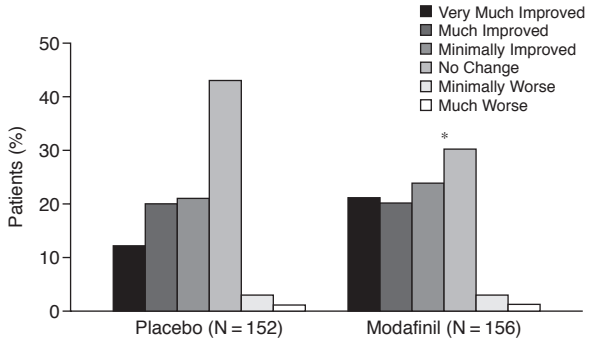
Characteristic	Placebo (N = 153)	Modafinil (N = 158)
Age, mean (range), y	42.3 (18–64)	42.0 (20–65)
Weight, mean (SD), kg	84.9 (23.9)	85.2 (20.4)
Body mass index, mean (SD), kg/m^2	29.5 (7.7)	30.0 (6.9)
Gender, N (%), female	110 (72)	110 (70)
Concomitant SSRI agent, N (%)		
Fluoxetine	56 (37)	59 (37)
Paroxetine	57 (37)	51 (32)
Sertraline	42 (27)	49 (31)
CGI-S rating, N (%)		
Slightly ill	35 (23)	26 (16)
Moderately ill	98 (64)	116 (73)
Markedly ill	14 (9)	11 (7)
Extremely ill	1 (< 1)	0 (< 1)
HAM-D-31 score, mean (SD)[a]	20.5 (3.5)	20.8 (3.5)
HAM-D-17 score, mean (SD)[a]	13.3 (2.9)	13.5 (3.2)
HAM-D-17 score ≥ 14, N (%)	69 (45)	73 (46)
MADRS score, mean (SD)[a]	17.4 (6.1)	18.2 (6.4)

[a]N = 152, placebo; N = 156, modafinil.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

Table 2. Reasons for Discontinuing the Study, N (%)

Variable	Placebo (N = 155)	Modafinil (N = 159)
Subjects who discontinued study	25 (16)	24 (15)
Reason		
Adverse event	5 (3)	9 (6)
Lack of efficacy	2 (1)	1 (1)
Consent withdrawal	3 (2)	4 (3)
Protocol violation	2 (1)	2 (1)
Noncompliance	5 (3)	0 (0)
Lost to follow-up	7 (5)	7 (4)
Other	1 (1)	1 (1)

Figure 1. Clinical Global Impressions-Improvement Scale Rating at Final Visit in All Patients



*p = .02 for difference in overall distribution of scores between modafinil and placebo groups.

and were therefore excluded from the safety analyses. The safety analysis set, then, included 311 patients, with N = 158 randomly assigned to modafinil (mean [SD] age = 42.0 [11.2] years; 70% women; mean [SD] body mass index [BMI] = 30.0 [6.9]) and N = 153 to placebo (mean age = 42.3 [10.9] years; 72% women; mean BMI = 29.5 [7.7]). Table 1 lists study group demographic and pretreatment characteristics. Three patients (2 receiving modafinil and 1 receiving placebo) were excluded from the efficacy analyses (because they had no on-therapy ESS assessment). The efficacy analysis set therefore included 308 patients, with 156 randomly assigned to modafinil (mean [SD] HAM-D-31 score = 20.8 [3.5]; mean HAM-D-17 score =13.5 [3.2]; mean MADRS score = 18.2 [6.4]) and 152 to placebo (mean HAM-D-31 score = 20.5 [3.5]; mean HAM-D-17 score = 13.3 [2.9]; mean MADRS score = 17.4 [6.1]). Of 311 patients randomly assigned to treatment, 135 (85%) of modafinil-treated patients and 130 (85%) of placebo-treated patients completed the study. Table 2 lists the reasons for discontinuation.

Efficacy

Modafinil significantly improved overall clinical condition compared with placebo on the basis of CGI-I scores at week 1 (p = .049), week 8 (p = .01), and final visit (Figure 1; p = .02). The percentage of patients rated as at least minimally improved was significantly greater for the modafinil group than the placebo group at week 8 (70% vs. 55%, respectively; p = .006) and final visit (65% vs. 53%, respectively; p = .03). At final visit, 64 (41%) of the modafinil-treated patients met CGI-I response criteria (i.e., much or very much improved) compared with 48 (32%) of the placebo-treated patients (p < .09).

Table 3 shows that modafinil-treated patients achieved significantly greater mean reductions in ESS scores (p = .02) and FSS scores (p = .04) compared with placebo-treated patients at week 1. There was a trend toward a significantly greater (p = .08) mean reduction in ESS scores in modafinil-treated versus placebo-treated patients at final visit, whereas no significant differences were observed in mean reductions in FSS and BFI total scores at final visit between the 2 groups. However, there was a significant reduction in mean BFI scores assessing the worst level of fatigue during the last 24 hours for modafinil-treated patients compared with placebo-treated patients at week 8 (p = .01) and final visit (p = .048).

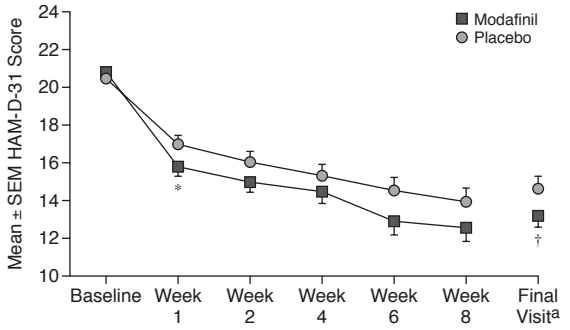
As shown in Figures 2 and 3, there were trends at final visit toward significantly greater (p < .08) mean reductions in HAM-D-31 and HAM-D-17 scores in modafinil-treated patients compared with placebo-treated patients. Remission rates (HAM-D-17 score < 8 at final visit) were 44% (N = 68) in modafinil-treated patients and 36% (N = 55) in placebo-treated patients (p = .2). Additionally, the mean (SD) reduction in MADRS scores at final visit was 6.2 (7.8) for modafinil-treated patients and 4.5 (8.4) for placebo-treated patients, which was not statistically significant (p = .1) but which followed the positive trend seen with the other depression rating scales.

Table 3. Sleepiness and Fatigue Scores for Placebo (N = 152) Versus Modafinil (N = 156), Mean (SD)

	ESS			FSS			BFI (total)			BFI (worst[a])		
Rating	Placebo	Modafinil	p Value[b]	Placebo	Modafinil	p Value[b]	Placebo	Modafinil	p Value[b]	Placebo	Modafinil	p Value[b]
Baseline	14.7 (3.3)	14.5 (3.3)	…	5.8 (0.8)	5.6 (0.8)	…	6.1 (1.7)	6.0 (1.8)	…	8.0 (1.6)	7.8 (1.8)	…
Week 1	13.1 (4.0)	12.2 (4.3)	.02	5.4 (1.0)	5.1 (1.2)	.04	5.5 (2.0)	5.2 (2.2)	.25	7.5 (2.1)	7.1 (2.2)	.08
Week 2	12.6 (4.4)	12.1 (4.3)	.26	5.1 (1.1)	5.1 (1.3)	.77	5.3 (2.1)	5.4 (2.3)	.45	7.1 (2.2)	7.2 (2.1)	.43
Week 4	12.0 (4.6)	11.2 (4.4)	.18	5.0 (1.3)	4.8 (1.4)	.56	5.3 (2.3)	5.0 (2.4)	.62	7.2 (2.5)	6.8 (2.3)	.32
Week 6	11.4 (4.7)	10.7 (4.8)	.24	4.8 (1.3)	4.5 (1.5)	.22	4.9 (2.3)	4.4 (2.5)	.12	6.7 (2.5)	6.2 (2.5)	.09
Week 8	11.4 (4.9)	10.2 (4.7)	.08	4.8 (1.5)	4.5 (1.6)	.14	5.0 (2.3)	4.5 (2.5)	.16	7.0 (2.4)	6.2 (2.6)	.01
Final visit	11.5 (4.8)	10.5 (4.7)	.08	4.9 (1.5)	4.6 (1.6)	.29	5.1 (2.4)	4.8 (2.5)	.49	7.1 (2.4)	6.5 (2.6)	< .05
Change from baseline at final visit	–3.2 (4.5)	–4.0 (4.8)	.08	–0.9 (1.4)	–1.0 (1.4)	.29	–1.1 (2.4)	–1.2 (2.5)	.49	–0.9 (2.6)	–1.4 (2.7)	< .05

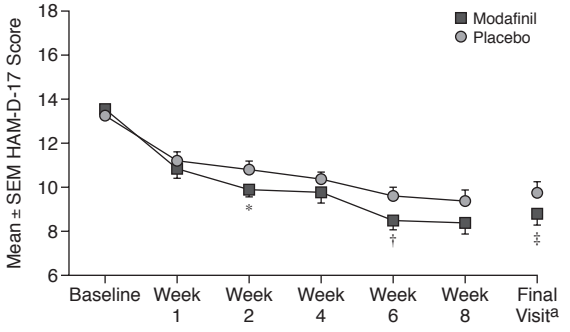
[a]Worst level of fatigue during the past 24 hours.
[b]Reflects change from baseline for placebo versus modafinil.
Abbreviations: BFI = Brief Fatigue Inventory, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale.

Figure 2. Change in 31-Item Hamilton Rating Scale for Depression (HAM-D-31) Scores With Modafinil Augmentation Versus Placebo (all patients, baseline to final visit)



[a]Modafinil, N = 156; placebo, N = 152 at endpoint.
*p = .03; mean difference in change = 1.4.
†p = .07; mean difference in change = 1.7.
Abbreviation: SEM = standard error of the mean.

Figure 3. Change in 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Scores With Modafinil Augmentation Versus Placebo (all patients, baseline to final visit)



[a]Modafinil, N = 151; placebo, N = 149 at endpoint.
*p = .07; mean difference in change = 1.1.
†p = .06; mean difference in change = 1.1.
‡p < .08; mean difference in change = 1.2.
Abbreviation: SEM = standard error of the mean.

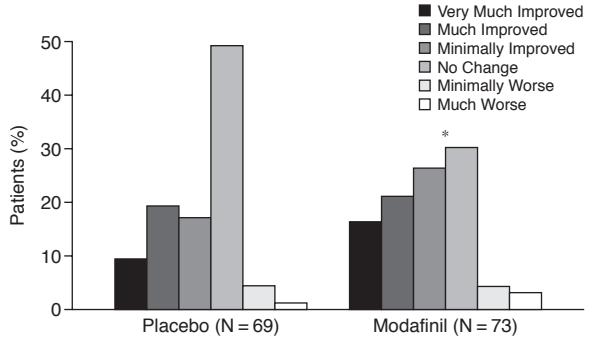
In the subanalysis of patients with HAM-D-17 baseline scores of ≥ 14, 73 patients were randomly assigned to modafinil and 69 to placebo. Modafinil significantly improved overall clinical condition on the CGI-I compared with placebo at final visit (Figure 4; p = .05). The percentage of patients rated as at least minimally improved was significantly greater for the modafinil group than the placebo group at week 8 (69% vs. 47%, respectively; p = .02) and final visit (63% vs. 45%, respectively; p = .03). Modafinil-treated patients had a significantly greater (p = .03) mean (SD) reduction in ESS scores at final visit (4.0 [4.9]) compared with placebo-treated patients (3.0 [4.1]). There were no significant differences in mean reductions in FSS or BFI total scores between modafinil-treated patients (1.0 [1.3] and 1.1 [2.3], respectively) and placebo-treated patients (0.9 [1.4] and 1.2 [2.3], respectively). As shown in Figures 5 and 6, there was a significantly greater (p = .05) mean reduction in HAM-D-17 scores at final visit in modafinil-treated patients compared with placebo-treated patients, whereas no significant difference on the HAM-D-31 was observed. The mean reduction in MADRS scores at final visit was 6.0 (8.4) for modafinil-treated patients and 4.6 (8.9) for placebo-treated patients (p = .4).

Safety

Table 4 summarizes adverse events that occurred at rates of ≥ 5% in either treatment arm. As shown, the most common adverse events spontaneously reported with modafinil were headache, nausea, dizziness, and dry mouth. Nausea (Table 4; p = .01 vs. placebo) and feeling jittery (N = 6 [4%] for modafinil vs. N = 2 [1%] for placebo; p = .03) were the only adverse events significantly more common during modafinil augmentation therapy.

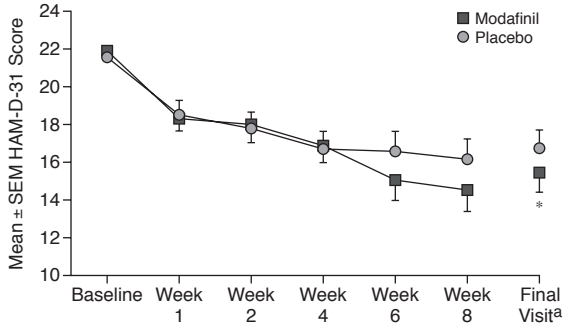
There were no clinically significant treatment-related abnormalities in mean changes from pretreatment in physical examination findings, vital signs, and laboratory test data (Table 5). There was 1 serious event of noncar-

Figure 4. Clinical Global Impressions-Improvement Scale (CGI-I) Rating at Final Visit in Patients With a HAM-D-17 Score ≥ 14 at Baseline



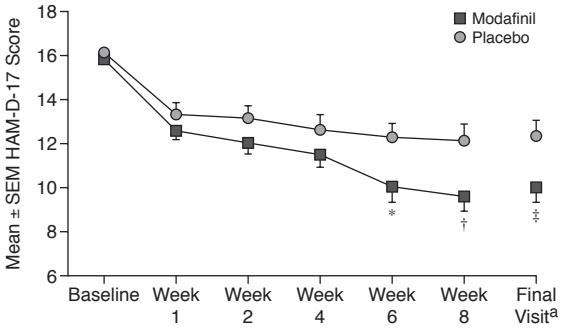
*p = .05 for difference in overall distribution of scores between modafinil and placebo groups.

Figure 5. Change in 31-Item Hamilton Rating Scale for Depression (HAM-D-31) Scores With Modafinil Augmentation Versus Placebo (patients with baseline HAM-D-17 score ≥ 14, baseline to final visit)



[a]Modafinil, N = 73; placebo, N = 69 at endpoint.
*p = .23; mean difference in change: 1.7.
Abbreviation: SEM = standard error of the mean.

Figure 6. Change in 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Scores With Modafinil Augmentation Versus Placebo (patients with baseline HAM-D-17 score ≥ 14, baseline to final visit)



[a]Modafinil, N = 85; placebo, N = 65 at endpoint.
*p = .04; mean difference in change = 1.9.
†p = .04; mean difference in change = 2.4.
‡p = .05; mean difference in change = 2.2.
Abbreviation: SEM = standard error of the mean.

Table 4. Adverse Events at Rates ≥ 5% in Either Treatment Arm, N (%)

Adverse Event	Placebo (N = 153)	Modafinil (N = 158)
Headache	24 (16)	21 (13)
Nausea	3 (2)	15 (9)[a]
Dizziness	3 (2)	11 (7)
Dry mouth	5 (3)	10 (6)
Nasopharyngitis	5 (3)	9 (6)
Insomnia	7 (5)	7 (4)
Diarrhea	10 (7)	6 (4)
Upper respiratory tract infection	9 (6)	5 (3)
Hypertension	7 (5)	4 (3)

[a]p = .01 vs. placebo.

diac chest pain in the modafinil group, which was considered by the investigator not to be related to treatment with modafinil. Finally, there was a mean (SD) decrease in weight of 0.6 (2.9) kg on modafinil treatment and a mean increase of 0.4 (2.2) kg on placebo treatment ($p < .0001$). Overall, 14 (10%) of 146 modafinil-treated patients for whom weight data were available at baseline and final visit gained ≥ 4 lb during the 8-week study compared with 31 (22%) of 144 placebo-treated patients ($p = .01$).

DISCUSSION

Our findings provide evidence in support of the uncontrolled, preliminary reports of usefulness of modafinil as an augmentor of antidepressants by Menza et al.[28] and by DeBattista and colleagues,[29] particularly among patients with relatively greater pretreatment symptom severity. Overall clinical condition was significantly improved with modafinil compared with placebo, and trends toward improvements were observed on the ESS, HAM-D, and MADRS at final visit. When these analyses were carried out among patients who scored ≥ 14 on the HAM-D-17 at pretreatment, significant differences were observed in the overall clinical condition and HAM-D-17 and ESS scores. This suggests that the benefit of modafinil augmentation was more pronounced among more symptomatic patients. The choice of a HAM-D-17 score of ≥ 14 as a threshold is noteworthy, because it essentially defines the lower boundary of symptom severity in MDD.[37] This choice of score is also consistent with the threshold for inclusion of patients with MDD in the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, funded by the National Institute of Mental Health.[38] In addition, as the minimum required period of stability on SSRI monotherapy prior to randomization was only 4 weeks, it is possible that patients with scores of < 14 were more likely to continue to improve by

Table 5. Vital Signs and Electrocardiogram Intervals, Mean (SD)

	Baseline		Final	
Variable	Placebo	Modafinil	Placebo	Modafinil
Vital signs				
Sitting heart rate, bpm	71.0 (9.1)	71.8 (9.0)	69.9 (8.2)	73.8 (9.1)
Sitting systolic BP, mm Hg	119.1 (13.3)	118.9 (13.5)	118.6 (12.9)	120.7 (13.4)
Sitting diastolic BP, mm Hg	75.5 (9.8)	75.8 (10.0)	75.7 (9.5)	77.1 (8.5)
Weight, kg	84.9 (23.9)	85.3 (20.4)	84.3 (24.0)	84.4 (20.9)
Body temperature, °C	36.7 (0.4)	36.6 (0.4)	36.7 (0.4)	36.7 (0.4)
Electrocardiogram intervals				
Heart rate, bpm	64.1 (9.1)	65.0 (9.1)	66.7 (9.4)	69.0 (9.0)
PR interval, msec	161.5 (66.1)	157.8 (25.2)	159.1 (20.8)	156.2 (20.7)
QRS interval, msec	87.0 (9.4)	87.4 (11.4)	88.9 (32.9)	86.9 (11.1)
QT interval, msec	404.7 (29.3)	399.0 (28.8)	395.2 (28.6)	388.9 (28.9)

Abbreviation: BP = blood pressure.

simply extending the SSRI treatment, whether or not they received active modafinil.

The 2 most-studied augmentation strategies for partial responders to antidepressants are the addition of lithium or thyroid hormone; however, these agents are rarely used in general clinical practice.[12,39] The most-studied augmentation strategy for SSRIs is the addition of buspirone, but 2 double-blind, placebo-controlled studies failed to demonstrate a benefit of buspirone over placebo.[6,7] No placebo-controlled studies investigating reboxetine or bupropion augmentation of SSRIs[39] are available, and there is only 1 small but positive trial of mirtazapine augmentation of SSRIs.[40]

A previous double-blind report[41] found that modafinil rapidly and significantly improved wakefulness (mean ESS scores) within 1 week and significantly reduced fatigue (mean FSS scores) within 2 weeks compared with placebo. Although the differences between the treatment groups were no longer statistically significant at week 6,[41] a post hoc analysis[42] of a subset of patients who experienced, at baseline, symptoms of excessive sleepiness (score of ≥ 10 on the ESS) and/or at least moderate fatigue (score of ≥ 5 on the FSS) found greater effects for modafinil in improving overall clinical condition and wakefulness and reducing fatigue. The current study replicated these findings in patients with excessive sleepiness and fatigue and found even more pronounced significant improvements in overall clinical condition with sustained improvement at final visit and significant reductions in the worst level of fatigue.

It is not uncommon in placebo-controlled antidepressant trials to achieve statistical significance in some but not all outcome measures. In fact, diagnostic misclassification, issues concerning inclusion/exclusion criteria, outcome measures' lack of sensitivity to change, measurement errors, waxing and waning of the natural course of illness, the regression toward the mean phenomenon, patient and clinician expectations about the trial, and nonspecific therapeutic effects all contribute to confounding the efficacy assessments in antidepressant trials and to decreasing the chances of detecting a treatment-placebo difference.[38]

The main limitation of this study is the retrospective ascertainment of SSRI nonresponse, which has been associated with a high risk of misclassification of resistance and may result in larger placebo responses.[43] We note that, perhaps because of this issue, there is no positive published, adequately powered, placebo-controlled study of SSRI augmentation.[6–9] In this light, our findings are noteworthy. The 8-week duration of the present trial may have partly protected against the delayed effect of recent increases in SSRI dosing prior to randomization, but, at the same time, may have increased the chances of spontaneous responses/remissions. Another limitation of the study is the use of a fixed-dose design, which assumes that "one dose fits all" and does not take into consideration the great variability in both metabolism and BMI in the studied population, thereby leading to potential underdosing in some subjects.

The safety/tolerability data from this study suggest that modafinil treatment is very well tolerated, with a dropout rate and overall tolerability profile comparable to placebo. Modafinil was not associated with adverse effects on blood pressure or heart rate. Because weight gain is a common adverse event that may emerge or persist after a month of SSRI treatment,[44] it is of interest that modafinil-treated patients tended to lose weight on average, while placebo-treated patients tended to gain weight. In addition, modafinil lessened the proportion of patients who gained ≥ 4 lb during the 8-week trial. No significant effect on weight (gain or loss) has been observed in multicenter, placebo-controlled trials evaluating modafinil in excessive sleepiness associated with various sleep disorders, even in obese patients.[45–47] Together, these findings suggest that modafinil may help prevent weight gain during SSRI treatment.

In vitro, modafinil has been observed to produce a reversible inhibition of cytochrome P450 (CYP)2C19 in human liver microsomes and a small, but concentration-dependent, induction of CYP1A2, CYP2B6, and CYP3A4 activities and suppression of CYP2C9 activity in primary

cultures of human hepatocytes.[48] Therefore, the levels of CYP2D6 substrates (e.g., SSRIs), which have ancillary routes of elimination through CYP2C19, may be increased by coadministration with modafinil, particularly among those subjects with a CYP2D6 deficiency.[48] However, only about 7% to 10% of white individuals lack any CYP2D6 activity due to deletions and frame-shift or splice-site mutations of the gene.[49] There was no apparent evidence of abuse with modafinil in this study. A recently published article reviewing the abuse liability of modafinil reported that various evidentiary sources suggest the agent has limited potential for abuse.[50] The chemical and pharmacologic properties of modafinil and preclinical studies indicate little to no addictive potential.[51]

In summary, the findings of this double-blind, placebo-controlled study suggest that modafinil is a safe and possibly effective augmenting agent for SSRIs in patients who are partial responders. Further studies of the role of modafinil as an augmenting agent in patients with greater symptom severity (i.e., score of ≥ 14 on the HAM-D-17 at pretreatment) are warranted.

Drug names: amphetamine (Adderall and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), methadone (Methadose, Dolophine, and others), methylphenidate (Metadate, Ritalin, and others), mirtazapine (Remeron), modafinil (Provigil), morphine (Kadian, Avinza, and others), paroxetine (Paxil and others), pemoline (Cylert and others), propoxyphene (Darvon, Kesso-gesic, and others), sertraline (Zoloft), venlafaxine (Effexor).

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