An Open-Label Study of Adjunctive Modafinil in Patients With Sedation Related to Serotonergic Antidepressant Therapy

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Objective: In patients with major depressive disorder (MDD), excessive sleepiness and fatigue not only are major components of the disorder, but also may occur as side effects of antidepressant therapy. In addition, sedation may be a consequence of antidepressant regimens. The novel wake-promoting agent modafinil improves wakefulness and reduces fatigue across a variety of clinical disorders. This study assessed the use of modafinil as an adjunctive treatment in patients with MDD who reported sedation related to serotonergic antidepressant therapy.

Method: Data were collected between September 2001 and December 2003. Twenty men and women with DSM-IV–defined MDD were enrolled in this 3-week, open-label, single-center study. In addition to ongoing and stable treatment with selective serotonin reuptake inhibitors (SSRIs), clinic patients received modafinil once daily. Efficacy assessments were conducted at 1-week intervals.

Results: Sixteen patients (80%) completed the study. Modafinil plus SSRIs significantly improved overall depressive symptoms, as shown by reductions in mean Hamilton Rating Scale for Depression total scores ($p < .001$ vs. baseline). Adjunctive modafinil significantly improved subjective estimates of wakefulness on the Epworth Sleepiness Scale ($p < .001$, all weeks) and reduced fatigue on the Fatigue Severity Scale ($p = .009$). At the final visit, modafinil had improved overall health status and health-related quality of life, as shown by significant improvements in mean Medical Outcomes Study Short-Form 12-Item Health Survey total scores ($p = .007$) and in physical health ($p = .04$) and mental health ($p = .006$) subscores.

Conclusion: In patients with MDD who experience sedation as a side effect of antidepressant therapy, adjunctive modafinil improved wakefulness and reduced fatigue. Modafinil plus SSRIs also improved mood and quality of life.

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In patients with major depressive disorder (MDD), sleep problems, fatigue, or sedation may arise as a consequence of pharmacotherapies used to manage the underlying depression. Antidepressants have been associated with varying degrees of somnolence, fatigue, or related symptoms[1–5] that may occur early in treatment or as persistent or late-onset side effects.[6–9] These side effects detrimentally affect physical and mental function, undermining patients' compliance with treatment regimens[10] and contributing to diminished quality of life and global outcome. Using the lowest effective dose, administering medication in the evening, or switching to another antidepressant are common strategies used to alleviate drug-induced side effects. Alternatively, adjunctive therapies may be prescribed to address side effects caused by antidepressant medications when established therapies are otherwise effective and maintenance of benefits is desired. Psychostimulants have been used to augment suboptimal responses to antidepressants.[11,12] However, these agents have been shown to adversely affect cardiovascular, gastrointestinal, and central nervous system function,[13] and their use is associated with a risk of abuse.[13]

The novel wake-promoting agent modafinil is currently indicated for the treatment of excessive sleepiness in patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. Several reports have demonstrated that modafinil may have utility as an augmenting therapy in patients with MDD,[14–16] but no study to our knowledge has assessed the effects of modafinil in patients with depression who specifically experience side effects related to antidepressant medications. Therefore, we conducted a study to evaluate the effects of modafinil when used as an adjunc-

tive treatment in patients with MDD who experience sedating side effects as a consequence of ongoing serotonergic antidepressant therapy.

METHOD

Data were collected between September 2001 and December 2003. Patients recruited for the study included those aged 18 to 65 years with DSM-IV–defined MDD who reported sedation arising from the use of 1 or more antidepressant medications. A clear, subjective chronological accounting of symptom onset was required for study inclusion. Patients had to report that sedation, fatigue, low energy, and related symptoms were not part of their original depressive symptoms and that they developed after selective serotonin uptake inhibitor (SSRI) therapy was started. Side effects related to antidepressant therapy were not due to comorbid medical illness, disruption of nighttime sleep, concomitant medication use, or substance abuse. Patients were required to have been receiving stable and adequate dosing regimens of SSRIs for at least 30 days before the start of the study.

Exclusion criteria included a history of bipolar disorder or psychotic illness, current medical condition (including any that would predispose to fatigue or place the patient at risk in the opinion of the investigator) or use of medication that would preclude use of modafinil, active substance abuse with last use within the past year, or a significant risk of suicide as assessed by the investigator. Patients who were pregnant or trying to conceive were excluded from the study. Patients gave written informed consent at the time of enrollment. Twenty patients ranging in age from 31 to 62 years were enrolled.

An institutional review board approved this open-label, single-center study. Patients visited the clinic at baseline, during which previous diagnoses of depression made in accordance with DSM-IV criteria were confirmed using the Structured Clinical Interview for DSM-IV (SCID), and at weekly intervals during 3 weeks of modafinil treatment. Patients received open-label modafinil, supplied as 100-mg tablets, for administration once daily before or after the morning meal. Throughout the study, dosing was determined at the discretion of the investigators; individualized dose escalation was based on efficacy and tolerability. Patients could receive modafinil 50 mg/day (tablet cut in half) or 100 mg/day during week 1 of the study. During week 2, patients could receive modafinil 50 mg/day, 100 mg/day, or 200 mg/day. During week 3, patients could receive modafinil 50 mg/day, 100 mg/day, 200 mg/day, 300 mg/day, or a maximum allowable dosage of 400 mg/day.

Tests of efficacy were conducted at baseline and at 1-week intervals during modafinil treatment. Efficacy measures included a clinician-administered, 31-item Hamilton Rating Scale for Depression (HAM-D),[17–19] used to evaluate changes in depression. Other efficacy measures included the patient-rated, 8-item Epworth Sleepiness Scale (ESS),[20] used to assess changes from baseline in sleepiness, and the patient-completed, 9-item Fatigue Severity Scale (FSS),[21] used to assess changes from baseline in fatigue. Overall health status and health-related quality of life were monitored using the Medical Outcomes Study Short-Form 12-Item Health Survey (SF-12).[22] Summary measures for the SF-12 include a physical health component (physical functioning, role-physical, bodily pain, and general health) and a mental health component (vitality, social functioning, role-emotional, and mental health).

Clinician-observed and patient-reported adverse events were documented at each clinic visit. Physical examinations were performed and blood samples were collected for laboratory evaluation at baseline and at the end of the study.

Statistical Analysis

Efficacy analyses were performed using data collected from patients who received at least 1 dose of modafinil and had a baseline and at least 1 postbaseline assessment for any given efficacy variable. To estimate missing data, last-observation-carried-forward methodology was used; however, baseline data were not carried forward. Data available at the end of week 3 or at termination were used for the final visit summary. Seventeen patients (85%) were eligible for efficacy evaluations, with 3 patients excluded from analyses because of insufficient postbaseline data. Changes from baseline to postbaseline visits in mean HAM-D, ESS, FSS, and SF-12 scores or subscores were evaluated for significance using paired t tests (for normally distributed data) or the Wilcoxon signed rank test (for non-normal data). Statistical testing was 2-tailed and performed at a 5% level of significance. Statistical summaries detailing the proportion of HAM-D responders (i.e., those with a 50% or more decrease in score from baseline on the 31-item HAM-D) were compiled for all scheduled visits and the final visit. Patients receiving at least 1 dose of study medication were evaluated for safety. Clinical laboratory data were summarized using descriptive statistics.

RESULTS

Patients

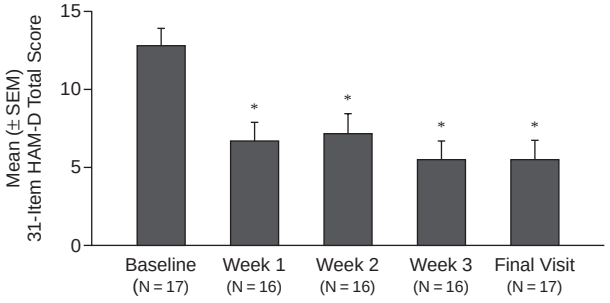
Patient characteristics and test scores at baseline are shown in Table 1. During the study, patients were receiving therapeutic doses of SSRIs as antidepressant monotherapy. The baseline mean HAM-D score indicated that depression in these patients was generally well controlled. On average, patients were mildly to moderately sleepy and moderately to severely fatigued at baseline, as reflected in mean ESS and FSS scores. On an individual

Table 1. Baseline Characteristics and Test Scores of Patients Receiving Adjunctive Modafinil for SSRI-Related Sedation

Variable	N
Characteristic	
Patients	20
Gender, male/female	9/11
	Mean (SD)
Age, y	45.4 (8.5)
Age at diagnosis, y	38.6 (9.4)
Test	
31-item HAM-D score[a] (range, 4.0–21.0)	13.2 (4.4)
ESS score[b] (range, 4.0–23.0)	11.7 (5.6)
FSS score[c] (range, 1.7–6.6)	5.1 (1.3)
SF-12 score (range, 24.0–51.0)	39.5 (8.1)

[a]HAM-D total scores were available for 19 patients.
[b]The ESS total score is the sum of 8 individual item scores. ESS total scores range from 0 to 24, with higher scores corresponding to a greater degree of sleepiness. For individuals who are sleepy, ESS total score is ≥ 10.
[c]Scores for individual FSS items range from 1 to 7, with higher scores indicating more fatigue. The final FSS score was calculated as the mean of the individual items. For individuals who are fatigued, FSS score is ≥ 4.
Abbreviations: ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, HAM-D = Hamilton Rating Scale for Depression, SF-12 = Medical Outcomes Study Short-Form 12-Item Health Survey, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Total Scores at Baseline and During 3 Weeks of Adjunctive Modafinil for SSRI-Related Sedation

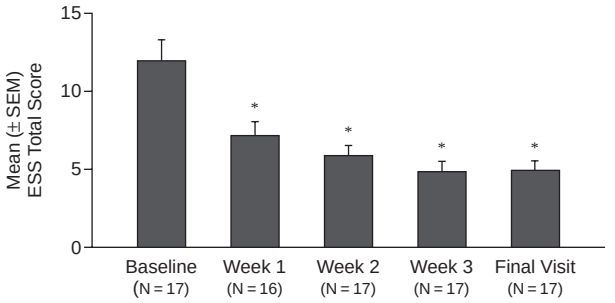


*p < .001 for the change from baseline.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

basis, 13 patients (65%) had ESS scores of ≥ 10, and 16 patients (80%) had FSS scores of ≥ 4. The mean baseline SF-12 total score suggested that the overall burden of illness for most patients was fair to good.

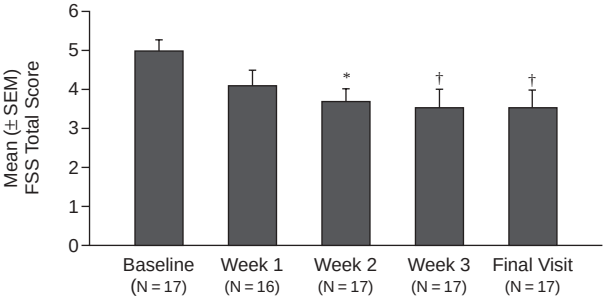
Sixteen patients (80%) completed the study. Three patients withdrew consent, and 1 patient was lost to follow-up. The final daily modafinil dosages were 50 mg/day for 2 patients, 100 mg/day for 7 patients, 200 mg/day for 5 patients, and 300 mg/day for 5 patients. One subject did not start modafinil, as we discovered a new cardiac murmur in the patient. The duration of modafinil exposure ranged from 4 to 30 days.

Figure 2. Epworth Sleepiness Scale (ESS) Total Scores at Baseline and During 3 Weeks of Adjunctive Modafinil for SSRI-Related Sedation



*p ≤ .001 for the change from baseline.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 3. Fatigue Severity Scale (FSS) Scores at Baseline and During 3 Weeks of Adjunctive Modafinil for SSRI-Related Sedation



*p = .003 for the change from baseline.
†p = .009 for the change from baseline.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Efficacy Outcomes

Modafinil in conjunction with SSRIs rapidly and significantly improved HAM-D total scores at week 1, a treatment effect that was maintained at all subsequent time points (p < .001) (Figure 1). The mean (SD) reduction from baseline to final visit in the HAM-D total score was –7.3 (3.6) points (p = .0001). At the final visit, 12 of 17 patients (71%) were responders, as defined by a reduction of 50% or more from baseline in the HAM-D total score.

Adjunctive modafinil rapidly and significantly improved wakefulness as early as week 1, with the effect sustained across all weeks of the study (p ≤ .001) (Figure 2). At the final visit, the mean (SD) ESS total score had decreased from baseline by –7.1 (4.6) points (p < .0001).

Treatment with adjunctive modafinil reduced subjective estimates of fatigue (Figure 3). Statistically significant changes from baseline in the mean FSS score were demonstrated at weeks 2 (p = .003) and 3 (p = .009) and at the final visit (p = .009).

Table 2. Mean SF-12 Scores at Baseline and During Treatment With Adjunctive Modafinil for SSRI-Related Sedation

	Score			Change			p
Rating Scale	N	Mean	(SD)	N	Mean	(SD)	Value[a]
SF-12 total score							
Baseline	17	40.9	(8.0)				
Week 1	16	44.1	(6.3)	16	3.2	(7.1)	.09
Week 2	16	44.9	(7.6)	16	4.1	(8.0)	.06
Week 3	17	47.1	(7.1)	17	6.1	(8.1)	.007
Final visit	17	47.1	(7.1)	17	6.1	(8.1)	.007
SF-12 physical health score							
Baseline	17	21.2	(4.1)				
Week 1	16	21.1	(3.2)	16	0	(3.4)	1.00
Week 2	16	21.9	(2.9)	16	0.7	(2.5)	.20
Week 3	17	22.9	(2.8)	17	1.7	(3.1)	.04
Final visit	17	22.9	(2.8)	17	1.7	(3.1)	.04
SF-12 mental health score							
Baseline	17	19.8	(4.4)				
Week 1	16	22.9	(4.0)	16	3.2	(4.8)	.02
Week 2	16	23.1	(5.4)	16	3.4	(6.0)	.04
Week 3	17	24.2	(5.0)	17	4.4	(5.8)	.006
Final visit	17	24.2	(5.0)	17	4.4	(5.8)	.006

[a]Change from baseline.
Abbreviations: SF-12 = Medical Outcomes Study Short-Form 12-Item Health Survey, SSRI = selective serotonin reuptake inhibitor.

Improvements in overall health status and health-related quality of life also were demonstrated with modafinil plus SSRIs (Table 2). Mean SF-12 total scores were significantly improved at week 3 ($p = .007$) and at the final visit ($p = .007$). Physical health subscores were significantly improved at week 3 ($p = .04$) and at the final visit ($p = .04$). Mental health subscores were significantly improved at all postbaseline time points.

Safety Outcomes

Modafinil was well tolerated in combination with other medications. Adverse events with the highest incidence rates were dry mouth (11 of 20 patients [55%]) and insomnia (3 of 20 patients [15%]). Most adverse events were mild or moderate in nature. There were no serious adverse events. No patients discontinued treatment with modafinil because of adverse events. No clinically significant changes from baseline in laboratory parameters or physical examination findings were demonstrated.

DISCUSSION

The results of this study suggest that modafinil may be an effective and well-tolerated adjunctive treatment in patients with MDD who report sedation as a result of ongoing serotonergic antidepressant therapy. Modafinil in conjunction with SSRIs significantly improved depression, as shown by rapid and sustained reductions in HAM-D scores, with a concomitant and significant improvement in wakefulness and a reduction in fatigue across the study. Modafinil was well tolerated, with a safety profile similar to those observed in controlled clinical studies of modafinil use in patients with depression[15] and patients with sleep disorders.[23–25]

Others have evaluated the effects of modafinil augmentation in patients with MDD.[14–16] In a recent double-blind, placebo-controlled study that assessed the efficacy and safety of modafinil in partial responders to antidepressant therapy, adjunctive modafinil was shown to rapidly and significantly improve symptoms of fatigue and excessive sleepiness while being well tolerated.[15] Although modafinil-related improvements were sustained, they were not distinguishable from placebo at the end of the study, nor were significant differences noted between modafinil and placebo on depression rating scale scores. The controlled study[15] did not determine whether partial responders experienced excessive sleepiness or fatigue as residual symptoms or developed these as a consequence of their antidepressant regimens. The positive results of our study may reflect greater homogeneity with respect to symptom etiology, as patients reported that their sedation and related symptoms developed after SSRI therapy was initiated. While a chronological accounting demonstrated that onset of these symptoms coincided with SSRI use, it is possible that patients may have experienced mild but unacknowledged or unreported fatigue as a residual symptom and that an increase in fatigue severity related to the introduction of SSRIs may have prompted its eventual report by patients.

In our study, all patients reported sedation as a side effect of antidepressant therapy. The fact that only 65% of patients reported excessive sleepiness and 80% of patients reported pathologic fatigue suggests that sedation may not be fairly characterized as either excessive sleepiness or fatigue.

The aims of antidepressant therapy include reduction in symptoms and the likelihood of relapse or recurrence, restoration of psychosocial functioning, and optimization of side effect profiles and compliance.[8] In the present study, modafinil plus SSRIs afforded improvements that are consistent with these goals. At the end of our study, nearly three quarters of patients met the criterion for HAM-D responders when modafinil was added to their antidepressant regimens. The improved rate of response and general symptom reduction on the HAM-D with adjunctive modafinil are noteworthy findings, as unresolved symptoms may hinder recovery or contribute to subsequent depressive relapse or recurrence.[8,26] The fact that adjunctive modafinil not only alleviated SSRI-induced side effects but also improved physical and mental health and health-related quality of life suggests that its addition to antidepressant therapy may be of benefit in promoting patient adherence by reducing noncompliance due to medication side effects as a potential cause for relapse.

While modafinil was well tolerated in combination with SSRIs, caution is advised whenever combination

pharmacotherapy is prescribed because of a potential for drug-drug interactions. In an in vitro study,[27] modafinil induced cytochrome P450 (CYP) 3A4 activity and therefore may decrease circulating blood levels of medications (e.g., citalopram) that are metabolized via this enzyme. Modafinil also was shown in vitro[27] to inhibit the activity of cytochrome CYP2C19, an enzyme that provides an ancillary pathway for some drugs (e.g., fluoxetine, paroxetine) in CYP2D6-deficient patients; blood levels of concomitantly administered agents metabolized via this enzyme may increase in some patients.

Generalization of these findings is limited by the open-label nature of modafinil treatment, exclusion of a control group, and selective entry criteria for study participants. The small sample size and short treatment duration also may have influenced study outcomes, further limiting generalization.

In this, the first prospective trial of the effects of modafinil in patients with MDD who report sedation related to ongoing serotonergic antidepressant therapy, we have shown that modafinil improves wakefulness, reduces fatigue, and improves depression and health-related quality of life. These positive findings, as well as the effects of adjunctive modafinil on responder rates, warrant further systematic study.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), modafinil (Provigil), paroxetine (Paxil and others).

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