Adjunctive Modafinil at Initiation of Treatment With a Selective Serotonin Reuptake Inhibitor Enhances the Degree and Onset of Therapeutic Effects in Patients With Major Depressive Disorder and Fatigue

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Background: Benefit from selective serotonin reuptake inhibitor (SSRI) treatment in major depressive disorder (MDD) usually takes several weeks. Typically, a third of patients achieve remission and roughly half achieve response with acute treatment. This open-label study evaluated the efficacy and safety of modafinil treatment initiated with an SSRI in patients with MDD and fatigue.

Method: Twenty-nine patients with DSM-IV MDD, free from antidepressant therapy (≥ 4 weeks), were administered modafinil (titrated to 200 mg/day) and fluoxetine or paroxetine (20 mg/day) for 6 weeks. Assessments included the 21-item Hamilton Rating Scale for Depression (HAM-D), Structured Interview Guide for the HAM-D (SIGH-D), Fatigue Severity Scale (FSS), and Epworth Sleepiness Scale (ESS). The SIGH-D ratings were videotaped and rated by an independent rater masked to the visit schedule. Data were collected from August 2002 through March 2003.

Results: Modafinil combined with an SSRI at treatment initiation significantly improved mean total SIGH-D scores within 1 week (–9.3, $p < .001$), and this improvement was progressive throughout the study (–21.2 at week 6, $p < .001$). Forty-two percent (11 of 26) and 79% (19 of 24) of patients were responders, and 39% (10 of 26) and 58% (14 of 24) of patients were remitters (HAM-D) by week 2 and week 6, respectively. Adjunct modafinil rapidly and significantly reduced fatigue (FSS score reduction from baseline = 0.7 at week 1, $p < .01$) and improved wakefulness (ESS score reduction from baseline = 3.6 at week 1, $p < .01$). The combination caused few adverse events, with nausea and headache being the most common.

Conclusion: Modafinil combined with an SSRI at treatment initiation may enhance the onset and degree of symptom benefit in patients with MDD and fatigue. Treatment with adjunct modafinil was generally well tolerated, with most adverse effects being mild or moderate in severity.

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Major depressive disorder (MDD) has several domains of symptoms including emotional, cognitive, somatic, and behavioral.[1] Fatigue affects as many as 80% of patients,[2,3] and more than half report lack of energy, insomnia and/or hypersomnia, and cognitive impairment (e.g., poor concentration).[2,3] Patients who fail to remit with selective serotonin reuptake inhibitors (SSRIs) and other leading antidepressants often have inadequate relief of these symptoms.[4,5] Indeed, SSRIs may exacerbate one or more of these symptoms.[6–9]

Residual symptoms after an adequate trial of antidepressant therapy are strong predictors of relapse. Relapse and recurrence rates are at least 3 times higher in patients with residual symptoms compared with rates in those who achieve remission.[10,11] Resolution of residual symptoms and achievement of remission are thus important treatment goals.

Delay in achieving symptomatic benefit is a major limitation of the current antidepressant medications. For example, the response at 6 weeks to the SSRI fluoxetine is approximately 50%.[12] Fixed doses of fluoxetine 20 mg/day and paroxetine 20 mg/day have comparable antidepressant efficacy during the first 6 weeks of therapy.[13] Identifying a treatment strategy that demonstrates a more rapid onset of antidepressant effect has several potential advantages, including preventing premature treatment discontinuation, limiting the functional consequences of depression, and reducing the risk of suicide.[14]

Modafinil, a novel wake-promoting agent that works selectively through the sleep-wake centers of the brain,[15,16] improves wakefulness and reduces fatigue in various clinical disorders, including narcolepsy[17,18] and obstructive sleep apnea.[19,20] Previous reports[21–23] indicate that adjunctive modafinil reduced fatigue within 2 weeks in MDD patients with partial response to antidepressants.

The hypothesis for the present study was that modafinil and an antidepressant initiated together would provide rapid relief of depressive symptoms, including fatigue. This open-label study is the first to examine the efficacy, onset of action, and safety of SSRIs (fluoxetine or paroxetine) and adjunctive modafinil in patients with MDD who also had significant fatigue.

METHOD

Patient Selection

Eligible patients (N = 29) had MDD (single episode or recurrent) according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition,[1] criteria (determined by the Mini-International Neuropsychiatric Interview[24]) as well as significant fatigue (Fatigue Severity Scale [FSS] score of ≥ 4).[25] Patients were aged 18 to 65 years and had no previous exposure to modafinil. At screening and at baseline, patients had a score of ≥ 15 on the Structured Interview Guide for the Hamilton Rating Scale for Depression (SIGH-D).[26] Patients had taken no antidepressant therapy for at least 4 weeks prior to the study. Written informed consent was obtained from each patient before study entry. Data were collected from August 2002 through March 2003.

Patients were excluded from study participation if they had an Axis I disorder other than MDD or an Axis II disorder that would interfere with conduct of the study. Other exclusion criteria included failure of 2 adequate antidepressant trials for the current episode of MDD; a significant risk for suicide assessed clinically; a history of psychosis; a history of alcohol, narcotic, or other substance dependence within the past 30 days; the presence of hypertension or a sitting pulse rate of ≥ 110 bpm or < 50 bpm after resting for 5 minutes; an uncontrolled general medical disorder; a drug allergy to central nervous system stimulants; a medical contraindication to the use of modafinil; or use of an antidepressant within 4 weeks prior to baseline.

Study Design

This open-label pilot study was conducted at a primary care and psychiatric research center using a protocol approved by the Independent Ethics Committee/ Institutional Review Board. During the study, patients attended the center at screening, baseline (day 0), and weekly for 6 weeks. Both modafinil and the SSRI were administered at fixed doses. Modafinil was initiated at a dose of 100 mg in the morning on days 1 through 3 and titrated from day 4 to a maximum dose of 200 mg in the morning. If clinically indicated, the modafinil dosage was reduced to 100 mg/day or the dosing schedule changed to 100 mg in the morning and 100 mg at noon. Patients were simultaneously started on treatment with fluoxetine 20 mg/day or paroxetine 20 mg/day for 6 weeks on the basis of clinical choice.

Assessments

Efficacy evaluations were conducted at screening, baseline, and weeks 1, 2, 3, 4, 5, and 6. Changes in depressive symptoms were analyzed using SIGH-D total score evaluations. The SIGH-D scale was used because of its additional items assessing cognitive and "reverse" vegetative symptoms, including symptoms associated with fatigue and sleepiness. SIGH-D evaluations were performed by a single qualified rater and were videotaped for rating by an independent rater blinded to the sequence of the tapes. The 21-item Hamilton Rating Scale for Depression (HAM-D)[27] total scores were analyzed to evaluate changes in depressive symptoms, response rates (i.e., proportion of patients with a > 50% decrease at any postbaseline visit), and remission rates (i.e., proportion of patients with a score of ≤ 7 at any postbaseline visit).

Changes in fatigue were measured using the FSS, a 9-item instrument that assesses the effects or consequences of fatigue.[25] FSS scores for individual items range from 1 to 7 (lower scores indicating less fatigue); the average of the 9 items is the total FSS score. An FSS total score of ≥ 4 is considered to be indicative of clinically significant fatigue. Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS),[28] a brief, validated questionnaire that measures the propensity of patients to sleep or doze during 8 common daytime situations. Total scores for the ESS range from 0 to 24, with lower scores indicating less sleepiness. Scores ≥ 10 are considered to be indicative of clinically significant sleepiness. Fatigue, motivation, and concentration were evaluated using self-rated visual analogue scales (VAS). Self ratings of health-related quality of life were determined at baseline and at week 6 using the 36-item Medical Outcomes Study Short-Form Health Survey (SF-36).[29]

Safety and Tolerability

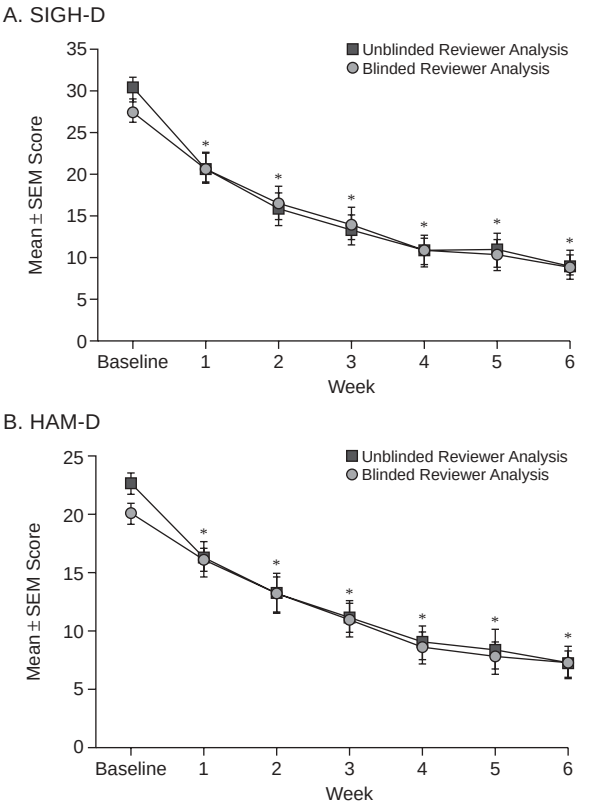
Safety was assessed by recording all reported adverse events by day of onset, type, severity, and relationship to study medication. Complete physical examinations were conducted at screening and week 6. Vital signs (sitting blood pressure, pulse rate, respiration rate, and body temperature) were monitored at screening, baseline, and weeks 1, 2, 3, 4, 5, and 6. Blood and urine samples were collected for evaluation of clinical laboratory parameters, and a 12-lead electrocardiogram (ECG) was conducted at the screening visit.

Table 1. Baseline Characteristics of Patients With Major Depressive Disorder and Fatigue

Variable	Modafinil + Fluoxetine or Paroxetine (N = 29)
Age, mean (SD), y	36.2 (8.6)
Weight, mean (SD), lb	173.1 (57.5)
Gender, N (%), female	21 (72.4)
Race, N (%), white	19 (65.5)
Duration of disease, mean (SD), y	2.7 (3.9)
HAM-D score, mean (SD)	22.6 (4.9)[a]
SIGH-D score, mean (SD)	29.9 (7.4)[a]
FSS score, mean (SD)[b]	5.2 (0.8)[a]
ESS score, mean (SD)[c]	10.3 (4.9)

[a]N = 28.
[b]Scores ≥ 4 denote significant fatigue.
[c]Scores ≥ 10 denote significant sleepiness.
Abbreviations: ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, HAM-D = Hamilton Rating Scale for Depression, SIGH-D = Structured Interview Guide for the HAM-D.

Figure 1. Blinded and Unblinded Mean 21-Item Hamilton Rating Scale for Depression (HAM-D) and Structured Interview Guide for the HAM-D (SIGH-D) Total Scores for Baseline and Weeks 1 Through 6



*p < .001 for change from baseline (both unblinded and blinded reviewer analyses).

Statistics

All patients who received at least 1 dose of modafinil and had at least 1 postbaseline efficacy measurement were evaluated for efficacy. Continuous variables were analyzed using a paired t test for normally distributed data or Wilcoxon signed rank test for non-normally distributed data. The number of HAM-D responders was analyzed using the Wilcoxon signed rank test. Patients receiving at least 1 dose of study drug were included in the safety analysis. Descriptive statistics were used to summarize safety measures.

RESULTS

Patients

Baseline characteristics of patients are summarized in Table 1. In general, the baseline severity of depressive symptoms was moderate. The mean baseline FSS score was 5.2, indicating moderate to severe fatigue. Patients with chronic neurologic conditions, such as multiple sclerosis and systemic lupus erythematosus, also report similar intensity of fatigue.[25] Approximately half (57%) of the patients had clinically significant daytime sleepiness (i.e., an ESS score of ≥ 10) at baseline.

Treatment Outcomes

Fifteen patients were treated with fluoxetine, and 14 were treated with paroxetine. No significant differences were found between the modafinil and fluoxetine treatment group and the modafinil and paroxetine treatment group on any of the efficacy evaluations. Therefore, results are presented as changes from baseline for the combined SSRI treatment group.

Depression

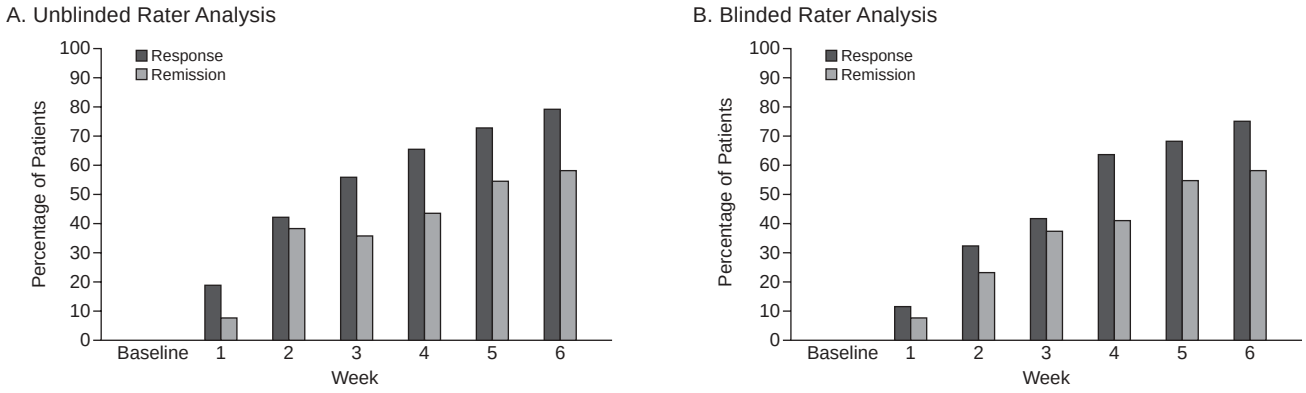
Statistically significant reductions in mean SIGH-D scores (Figure 1A) and HAM-D scores (Figure 1B) were evident by week 1 and at every subsequent week. The results of the blinded and unblinded reviews were similar.

Response (> 50% HAM-D score reduction) was achieved by 42% of patients (11 of 26) at week 2, 65% (15 of 23) by week 4, and 79% (19 of 24) at week 6 (Figure 2A). Remission (HAM-D score of ≤ 7) was achieved by 39% (10 of 26) of patients at week 2, 44% (10 of 23) at week 4, and 58% (14 of 24) at week 6 (Figure 2A). The post hoc analysis of the HAM-D blinded reviewer data (Figure 2B) shows similar percentages of patients who achieved response (32% [8 of 25] at week 2, 64% [14 of 22] at week 4, and 75% [18 of 24] at week 6) and remission (23% [6 of 26] at week 2, 41% [9 of 22] at week 4, and 58% [14 of 24] at week 6).

Fatigue Severity Scale

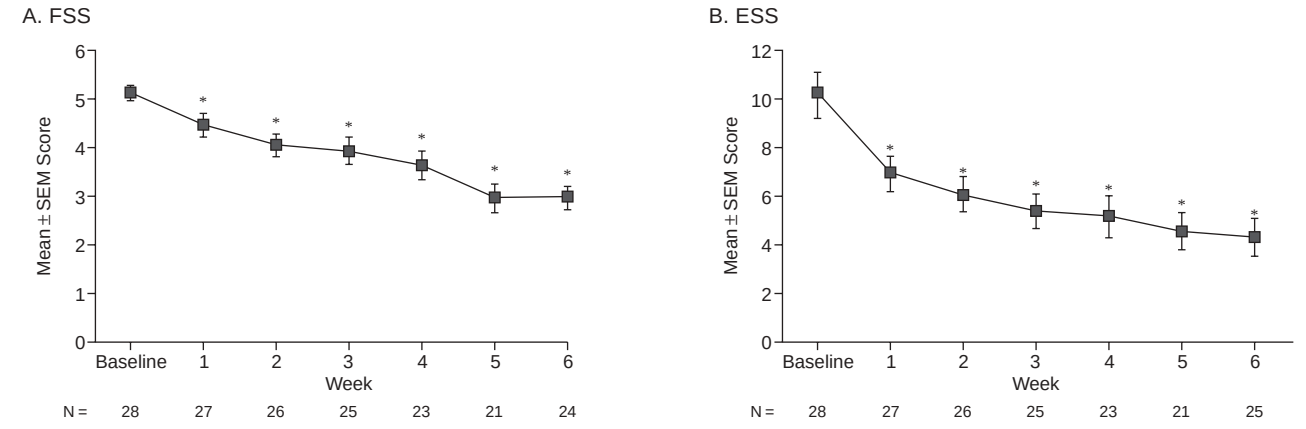
Modafinil combined with an SSRI significantly reduced mean FSS scores at week 1 through week 6 (Figure 3A). Seventy-one percent (17 of 24) of patients met the responder criterion (i.e., an average FSS score of < 4 at any postbaseline visit) for reduced fatigue at week 6.

Figure 2. Percentages of Patients With Response (defined as > 50% decrease in HAM-D total score) and Remission (defined as HAM-D score of ≤ 7) at Baseline and Weeks 1 Through 6



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 3. Mean Fatigue Severity Scale (FSS) and Epworth Sleepiness Scale (ESS) Total Scores for Baseline and Weeks 1 Through 6



*p < .01 for change from baseline.

Epworth Sleepiness Scale

Modafinil combined with an SSRI reduced mean ESS scores at week 1 through week 6 (Figure 3B). Eighty-eight percent (22 of 25) of patients met the responder criterion (i.e., an ESS total score of < 10 at any postbaseline visit) for improved wakefulness at week 6.

Visual Analogue Scales

Modafinil combined with an SSRI improved self-reported mood, anxiety, energy/fatigue, motivation, concentration, and sleepiness in each of the individual mean VAS scores from baseline to weeks 1 through 6 (Figure 4A–F).

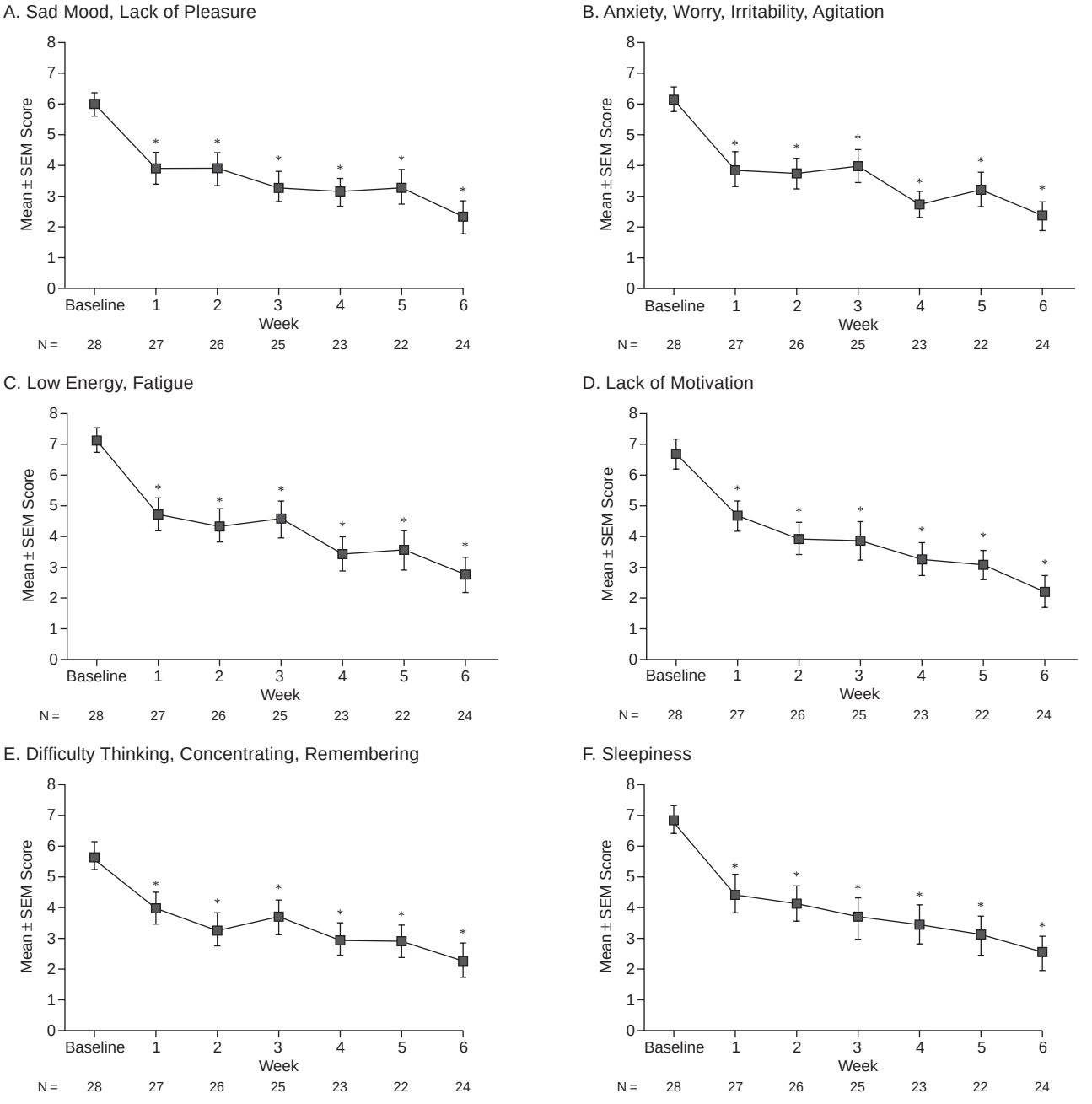
Quality of Life

Modafinil combined with an SSRI significantly improved quality of life in all 8 mean ± SD component scores of the SF-36 (physical functioning = 15.6 ± 20.1, role-physical = 41.7 ± 50.0, bodily pain = 20.0 ± 21.7, general health = 14.6 ± 18.6, vitality = 34.1 ± 27.4, social functioning = 31.0 ± 28.9, role-emotional = 45.7 ± 46.4, mental health = 27.5 ± 21.6; each $p < .001$). Significant benefit was also demonstrated by the mean SF-36 summary component scores (physical = 6.1 ± 8.2, mental = 17.0 ± 14.1; both $p \leq .001$).

Safety and Tolerability

Adjunctive modafinil with an SSRI was tolerated by most patients. Adverse events were mild to moderate in severity, with no serious adverse events reported during the study. Globally, 59% of patients experienced at least 1 adverse event. The most frequently reported adverse events were nausea (41%) and headache (24%), and these were generally transient. No clinically significant differ-

Figure 4. Mean Visual Analogue Scale (VAS) Scores for Baseline and Weeks 1 Through 6



*p < .01 for change from baseline.

ences were found in any vital signs, body weight changes, ECG, heart rate, blood pressure, or laboratory parameters.

Twenty-three (79%) of 29 patients completed the study. Three patients discontinued early because of adverse events possibly related to medications: 1 patient reported agitation, anorexia, and headache; 1 patient reported headache and difficulty concentrating; and 1 patient reported insomnia, nausea, and nervousness. All 3 of these patients were taking concomitant fluoxetine. Additionally, 1 patient was withdrawn due to protocol noncompliance, and 2 patients were lost to follow-up.

DISCUSSION

Respondents (N = 1884) to a patient survey detailing the symptoms, disability, and treatment of depression identified the ideal antidepressant as causing no daytime drowsiness, allowing normal sleep, not adversely affect-

ing concentration, and reducing depression in a few days.[3] The disability associated with depression is state dependent and can exist even when a few symptoms are present.[30] In the present study, in patients with MDD and prominent fatigue, combining modafinil with an SSRI resulted in improvement across the spectra of symptoms, including fatigue, (subjective) wakefulness, concentration, and mood. Symptoms of fatigue/lack of energy (94%), lack of motivation (86%), and inability to concentrate (64%),[2] which are prominent in cohorts with MDD, are often worsened by antidepressants or respond only secondarily to treatment.

Enhancing the emergence of antidepressant benefit is also a clinically important consideration. In this study, response (> 50% reduction in HAM-D-21 scores) was achieved by 42% of patients by the end of week 2, 65% by week 4, and 79% by week 6. With all the caveats of comparing data from different studies, the proportion of responders defined similarly for fluoxetine and paroxetine was less than 50% at week 4 in 2 open-label studies in MDD.[13,31] Examining remission, defined as ≤ 7 on the HAM-D-17, Nierenberg et al.[5] report a remission rate of 50.2% with open-label fluoxetine at week 8. In the present study, remission rates (defined as ≤ 7 on the HAM-D-21) for weeks 2, 4, and 6 were 39%, 44%, and 58%, respectively. Modafinil with an SSRI thus potentially provides a more rapid and larger effect in achieving response and remission in MDD.

All of the patients in the study had moderate to severe fatigue at baseline, and close to two thirds had responded by the end of the study. The average baseline ESS total score (10.3) for all patients indicated that sleepiness was clinically significant in this patient population (mean age = 36.2 years). Modafinil treatment rapidly improved symptoms associated with fatigue and sleepiness in this patient population.

Approximately 10% of patients discontinued treatment because of adverse events. This is comparable to other studies with SSRIs administered as single agents. Although 3 subjects taking fluoxetine-modafinil discontinued due to adverse effects compared with none taking paroxetine-modafinil, the small number of subjects in this study prevents any definitive conclusion. Of note, in the DeBattista et al. study,[22] there was no reported problem with the fluoxetine-modafinil combination, although in that study, subjects had been taking fluoxetine for at least 6 weeks before modafinil was initiated. Compounds that induce or inhibit cytochrome P450 (CYP) activity are unlikely to have major effects on the pharmacokinetics of modafinil.[32] Modafinil does cause reversible inhibition of CYP2C19 and modest induction of CYP3A4,[32] but neither fluoxetine nor paroxetine are metabolized through these pathways. Thus, drug-drug interactions are an unlikely explanation for the observation of adverse events.

Limitations of this study include an open-label design with a small number of patients.

Important questions are why and when a combination strategy of an SSRI and modafinil should be instituted at the initiation of treatment of major depression. The rationale for employing this strategy would be the greater proportion of remitters with combination treatment (if the results of this study are confirmed in a randomized controlled trial) and the general failure of SSRI monotherapy to alleviate the symptom of fatigue.[5] One could argue for sequential augmentation with modafinil after a trial of an acute course with an SSRI. However, clinicians often choose to start with a combination of medications if a specific symptom is significant and not expected to respond to the antidepressant, e.g., a sedative-hypnotic is commonly initiated with an SSRI in the management of MDD. An additional follow-up question for systematic enquiry is how long modafinil should be continued with the SSRI in the management of MDD.

Why should the combination of an SSRI and modafinil be potently effective in treating MDD? Pharmacodynamic explanations are fraught with potential risks given our limited understanding of pathophysiology and mechanisms of treatment response. In syndromes such as MDD, diverse neurobiological pathways presumably mediate different symptom domains as well as response components. If only a subset of such pathways is normalized by a treatment, would that be the equivalent of response that falls short of remission? In some patients, addressing certain pathways may result in the secondary response of other circuits and/or mental functions and, consequently, in remission. The known pharmacologic properties of SSRIs and modafinil are fundamentally different, and therefore their pharmacodynamic combination may be more likely to address enough pathways to assure remission. The primary benefits of SSRIs may be derived from the buffering of pathologic negative emotional responses, particularly those resulting from a sensitization of the stress response,[33] as well as enhancement of neurogenesis in the hippocampus.[34] Modafinil, on the other hand, has powerful effects on internally oriented vigilance, with consequent enhancement of energy, motivation, and executive functions including cognitions.[16] Thus, an SSRI-modafinil combination would be synergistic and enhance the likelihood of achieving remission.

This 6-week open-label study suggests that adjunct treatment with modafinil enhances the degree and onset of symptom relief achieved in MDD patients with significant fatigue. After initiating modafinil with fluoxetine or paroxetine, these patients had a significant improvement of depressive symptoms, as assessed by total HAM-D and SIGH-D scores, within 1 week of initiation that progressed throughout the rest of the study. The combination appeared to rapidly reduce fatigue and improve (subjective) wakefulness, mood, concentration, and quality of

life. By week 6, response in depression was achieved by up to 79% of patients and remission by up to 58%. Treatment with modafinil in combination with an SSRI resulted in few adverse effects, most of mild to moderate intensity. These results indicate that adjunctive modafinil may be beneficial when initiating SSRI treatment in MDD patients with fatigue; however, additional studies using a randomized controlled design are warranted.

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

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