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Modafinil Augmentation of Selective Serotonin Reuptake Inhibitor Therapy in MDD Partial Responders with Persistent Fatigue and Sleepiness

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Background. *Partial response, no response, or residual symptoms following antidepressant therapy is common in clinical psychiatry. This study evaluated modafinil in patients with major depressive disorder (MDD) who were partial responders to adequate selective serotonin reuptake inhibitor (SSRI) therapy and excessive sleepiness and fatigue.*
Methods. *This retrospective analysis pooled the data of patients (18–65 yrs) who participated in two randomized, double-blind, placebo-controlled studies of modafinil (6-week, flexible-dose study of 100–400 mg/day or 8-week, fixed-dose study of 200 mg/day) plus SSRI therapy. Patients (n = 348) met criteria for several residual symptoms (Epworth Sleepiness Scale [ESS] score ≥10; 17-item Hamilton Depression Scale [HAM-D] score between 4 and 25; and Fatigue Severity Scale [FSS] score ≥4).*
Results. *Compared to placebo, modafinil augmentation rapidly (within 1 week) and significantly improved overall clinical condition (Clinical Global Impression–Improvement), wakefulness (ESS), depressive symptoms (17-item HAM-D), and fatigue (FSS) (*$p < .01$ *for all). At final visit, patients receiving modafinil augmentation experienced statistically significant improvements in overall clinical condition, wakefulness, and depressive symptoms. Modafinil was well tolerated in combination with SSRI.*
Conclusions. *Results of this pooled analysis provide further evidence suggesting that modafinil is an effective and well-tolerated augmentation therapy for partial responders to SSRI therapy, particularly when patients continue to experience fatigue and excessive sleepiness.*

Keywords Modafinil, SSRI therapy, Augmentation, Major depressive disorder, Wakefulness, Fatigue

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INTRODUCTION

An estimated 29% to 46% of patients with major depressive disorder (MDD) who receive an initial course of antidepressant monotherapy experience no response or partial response to treatment, with residual symptoms commonly reported (1). Even for those patients considered to be full responders to antidepressant therapy, asymptomatic states are not always achieved. In one study, more than 80% of patients who responded to 8 weeks of treatment with fluoxetine experienced threshold or subthreshold MDD symptoms, with the most common symptoms being fatigue, sleep disturbance, and diminished interest or pleasure (2). The significance of such residual symptoms is reflected in a higher risk of subsequent depressive relapse or recurrence of the index episode (3,4).

In the absence of a true consensus regarding next-step interventions for partial responders based on a sufficient number of large-scale, randomized, controlled clinical trials, clinicians may be forced to rely on their own experience and/or the findings of uncontrolled reports to guide therapeutic management. Various strategies used to enhance suboptimal responses to antidepressants include maximizing the initial treatment regimen (i.e., increasing the antidepressant dosage and trial duration), switching to another antidepressant agent, and initiating combination or augmentation therapy (5–7). For partial responders, combination therapy (i.e., introducing a second antidepressant to ongoing treatment) or an augmentation strategy (i.e., adding an agent not considered to be a standard antidepressant) may be preferable to switching antidepressants, particularly when benefits with current antidepressant regimens have been achieved in the absence of bothersome or disabling adverse effects (6).

The wake-promoting agent modafinil is currently indicated for the treatment of excessive sleepiness in patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. Modafinil may be an appropriate augmentation therapy when patients with MDD respond partially to antidepressant medications but continue to experience residual symptoms, particularly excessive sleepiness and/or fatigue (8–11). A randomized, double-blind, placebo-controlled study of 136 partial responders to antidepressant medications found that modafinil 100 to 400 mg/day significantly improved excessive sleepiness and significantly reduced fatigue at earlier, but not later, time points versus placebo (9). At baseline in that study, 82% of patients experienced fatigue (scores ≥4 on the Fatigue Severity Scale), and 51% were pathologically sleepy (scores ≥10 on the Epworth Sleepiness Scale). A second placebo-controlled study of 311 patients with MDD who continued to experience excessive sleepiness and fatigue despite adequate SSRI monotherapy reported that modafinil significantly improved overall clinical condition (11). Patients treated with modafinil also showed trends toward greater improvements in wakefulness and depressive symptoms at the final visit compared with placebo, as well as a significant mean reduction in worst fatigue on one of the fatigue scales at the final visit versus placebo (11). Each of these double-blind studies employed distinct inclusion and exclusion criteria for selecting patients, but there was a substantial overlap in the populations evaluated within the two studies with regard to residual symptomatology. Therefore, to extend the findings of the controlled studies, we conducted a retrospective pooled analysis of those patients who were partial responders to SSRI therapy but continued to experience at least moderate levels of excessive sleepiness and fatigue and mild to moderate depressive symptoms.

MATERIALS AND METHODS

Patient Selection

Patients with a *Diagnostic and Statistical Manual-IV*–defined diagnosis of MDD participated in one of two randomized, double-blind, placebo-controlled studies that evaluated modafinil augmentation of antidepressant therapy for a depressive episode with symptoms of excessive sleepiness and fatigue. Both studies were conducted in the United States and followed protocols that had been approved by local ethics committees, with prior written informed consent obtained from each patient; both studies were carried out in accordance with the Declaration of Helsinki. Full eligibility requirements for the two studies have been described in detail (9,11). Briefly, patients (n = 136) in the first study (9) were aged 19 to 64 years and had documented partial response to antidepressant therapy (predominantly SSRIs) of ≥ 6 weeks' duration and screening/baseline scores between 14 and 28 (inclusive) on the 21-item Hamilton Rating Scale for Depression (HAM-D) (12,13). Patients (n = 311) in the second study (11) were aged 18 to 65 years, had documented partial response to an adequate course of SSRI monotherapy (minimally effective dose for ≥ 8 weeks), and had been receiving a stable dose of an SSRI for ≥ 4 weeks. Patients in the second study had screening/baseline 31-item HAM-D scores between 14 and 26 (inclusive), an Epworth Sleepiness Scale (ESS) (14) total score of ≥ 10, and a Fatigue Severity Scale (FSS) (15) average score of ≥ 4 (11).

The population selected for this pooled analysis included patients from the two double-blind studies receiving SSRI therapy (sertraline, fluoxetine, or paroxetine), who had a baseline ESS score of ≥ 10, an FSS score of ≥ 4, and a 17-item HAM-D score between 4 and 25 (inclusive). The threshold scores chosen for the ESS and FSS correspond to the presence of at least moderate excessive sleepiness (14) and fatigue (15), respectively. Seventeen-item HAM-D scores in the established range correspond to mild to moderate levels of depressive illness, with partial response to antidepressant treatment (i.e., having residual symptoms). Patients included in the pooled analysis received other clinically relevant medications not excluded by protocol in addition to their SSRI therapy.

Study Design and Assessments

This retrospective pooled analysis of the overlapping population from 2 double-blind studies evaluated SSRI partial responders who experienced at least moderate levels of the above-mentioned depressive symptoms. In the first study, patients were randomized to receive modafinil 100 to 400 mg/day, based on efficacy or tolerability, or matching placebo in addition to existing antidepressant therapy for 6 weeks (9). In the second study, patients received fixed-dose modafinil 200 mg/day or placebo in addition to existing SSRI monotherapy for 8 weeks (11). In both studies, patients received a dose of 100 mg/day of modafinil or placebo equivalent for the first 3 days of double-blind treatment. During the studies, efficacy assessments were conducted at baseline and at 1- or 2-week intervals. The assessments included the Clinical Global Impression–Improvement (CGI-I) (16), ESS, FSS, and 17-item HAM-D. Safety and tolerability were evaluated throughout these double-blind studies by monitoring adverse events and conducting physical examinations, laboratory evaluations, electrocardiograms, and vital sign assessments. This pooled analysis evaluated the safety and tolerability of modafinil compared with placebo.

Statistical Analysis

Patients who met retrospectively defined evaluable criteria, had received at least one dose of study drug, and had at least one post-baseline primary efficacy measurement (ESS) were included in the pooled efficacy analyses for those visits that matched in the two studies (Week 1, Week 2, and final visit [Week 6 or earlier in one study and Week 8 or earlier in the other study]). Demographic variables were summarized using descriptive statistics, with continuous variables compared between groups using analysis of variance and discrete variables analyzed using the Cochran-Mantel-Haenszel chi-square test or Fisher's exact test. Statistical summaries detailing the proportion of patients achieving CGI-I response (i.e., those with a response of much improved or very much improved) were compiled by treatment group and analyzed using the Cochran-Mantel-Haenszel chi-square test. Mean changes from baseline to post-baseline time points and final visit (last scheduled visit or termination) in ESS, FSS, and 17-item HAM-D scores were compared for between-group statistical differences using analysis of variance, with treatment as the factor. Statistical tests were 2-tailed and performed at a significance level of 5%. Patients who received at least one dose of study medication were included in the pooled safety analysis.

RESULTS

Patient Characteristics and Disposition

Of the 450 patients who were randomized to receive treatment in the double-blind studies (447 of whom received at least one dose of study drug), 348 patients (placebo, n = 168; modafinil, n = 180) met the defined criteria for excessive sleepiness, fatigue, depression, and SSRI use. Baseline characteristics for these patients are shown in Table 1. No significant differences were observed between the groups for demographics and baseline test scores. Most patients (79%) were rated by the investigator as at least moderately ill at the baseline visit of their respective study. The mean excessive sleepiness and fatigue baseline scores demonstrated that patients had at least moderate levels of excessive sleepiness (14) and fatigue (15).

Of the 348 patients who met criteria, 300 (86%) completed their respective study. One hundred seventy-nine (> 99%) modafinil-treated patients received a ≥ 200-mg dose (one of the double-blind studies was fixed-dose). Patients discontinued for the following reasons: adverse event (n = 15), loss to follow-up (n = 11), consent withdrawn (n = 7), insufficient efficacy (n = 4), protocol violation (n = 4), and other (n = 2). Of the patients who discontinued owing to at least one adverse event, 10 patients (6%) received modafinil combined with an SSRI and 5 patients (3%) received placebo combined with an SSRI.

Table 1 Baseline Characteristics

Characteristic	Placebo (n = 168)	Modafinil (n = 180)
Mean (SD) age, y	42.6 (10.9)	42.3 (11.3)
Age range, y	18.0–64.0	20.0–65.0
Gender, n (%)		
Male	44 (26)	55 (31)
Female	124 (74)	125 (69)
Ethnicity, n (%)		
Caucasian	149 (89)	172 (96)
African American	9 (5)	3 (2)
Asian	2 (1)	2 (1)
Other	8 (5)	3 (2)
Concomitant SSRI, n (%)		
Sertraline	45 (27)	56 (31)
Fluoxetine	62 (37)	64 (36)
Paroxetine	61 (36)	60 (33)
Overall clinical condition/illness severity (CGI-S), n (%)		
Normal	1 (< 1)	0 (0)
Borderline ill	4 (2)	5 (3)
Slightly ill	37 (22)	26 (14)
Moderately ill	110 (65)	136 (76)
Markedly ill	15 (9)	13 (7)
Severely ill	1 (< 1)	0 (0)
Mean (SD) ESS total score[a]	14.5 (3.3)	14.4 (3.3)
Mean (SD) FSS score[a]	5.7 (0.8)	5.6 (0.8)
Mean (SD) 17-item HAM-D score[a]	13.5 (3.0)	14.0 (3.4)

CGI-S, Clinical Global Impression–Severity of Illness; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HAM-D, Hamilton Depression Rating Scale; SSRI, selective serotonin reuptake inhibitor.
[a]Scores were available for 167 (placebo) and 178 (modafinil) patients.

Efficacy Outcomes

Overall Clinical Condition

The percent of patients who were CGI-I responders was significantly greater for modafinil combined with an SSRI than placebo combined with an SSRI at Week 1 (21%, modafinil vs. 10%, placebo; $p = .003$) and at final visit (42% modafinil vs. 31%, placebo; $p = .035$) (Figure 1). Although the trend favored modafinil over placebo, there were no statistically significant differences between treatment groups in the percent of patients who were CGI-I responders at Week 2 (26%, modafinil vs. 23%, placebo), Week 4 (33%, modafinil vs. 29%, placebo), Week 6 (45%, modafinil vs. 37%, placebo), or Week 8 (45%, modafinil vs. 34%, placebo).

Epworth Sleepiness Scale

Modafinil combined with an SSRI improved wakefulness, as shown by significantly greater reductions in mean ESS scores compared with placebo combined with an SSRI at Week 1 (–2.5, modafinil vs. –1.5, placebo; $p = .007$) and final visit (–4.1, modafinil vs. –3.1, placebo; $p = .04$) (Figure 2). Although the trend favored modafinil over placebo, there were no statistically significant differences between treatment groups for reductions in mean ESS scores at Week 2 (–2.6, modafinil vs. –2.3, placebo), Week 4 (–3.4, modafinil vs. –2.8, placebo), Week 6 (–4.0, modafinil vs. –3.2, placebo), or Week 8 (–4.3, modafinil vs. –3.4, placebo).

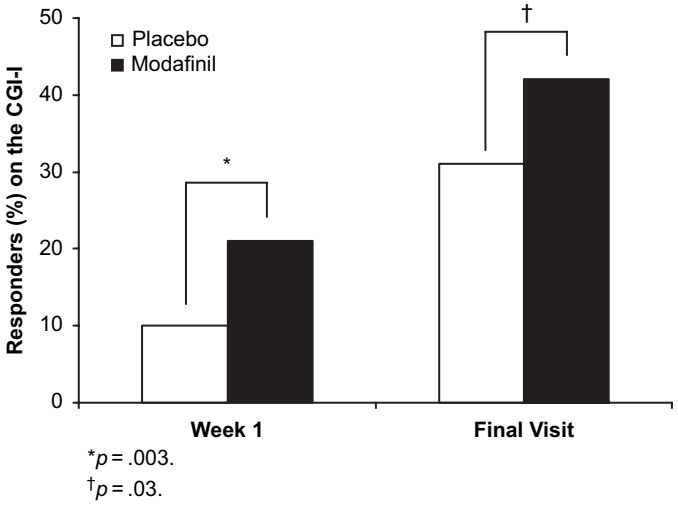

Figure 1 Percent of Responders (i.e., Those with a Response of Much Improved or Very Much Improved) on the Clinical Global Impression–Improvement (CGI-I) for Placebo and Modafinil (All Patients).

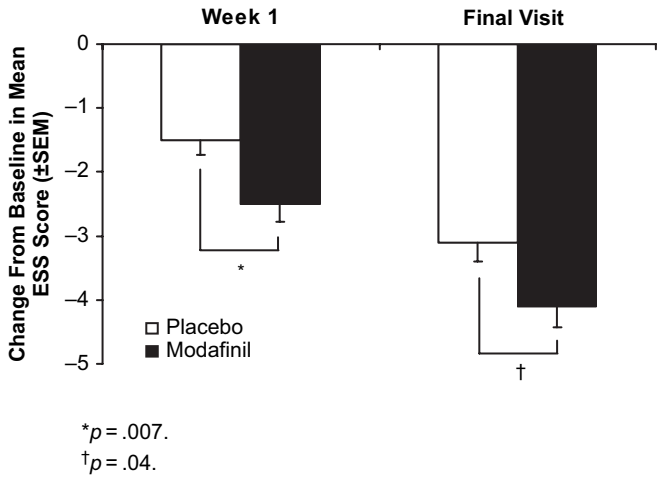

Figure 2 Mean (± SEM) Changes from Baseline in Epworth Sleepiness Scale (ESS) Scores between Placebo and Modafinil (All Patients).

Fatigue Severity Scale

Modafinil combined with an SSRI rapidly and significantly reduced fatigue compared with placebo combined with an SSRI, as shown by greater reductions in mean FSS scores at Week 1 (–0.6, modafinil vs. –0.3, placebo; $p = .007$) (Figure 3). However, the between-group differences in mean FSS scores at Week 2 (–0.6, modafinil vs. –0.6, placebo), Week 4 (–0.8, modafinil vs. –0.8, placebo), Week 6 (–1.1, modafinil vs. –0.8, placebo), Week 8 (–1.2, modafinil vs. –0.9, placebo), and final visit (–1.0, modafinil vs. –0.8, placebo; Figure 3) were not statistically significant.

Hamilton Rating Scale for Depression

Modafinil combined with an SSRI rapidly and significantly improved depressive symptoms compared with placebo

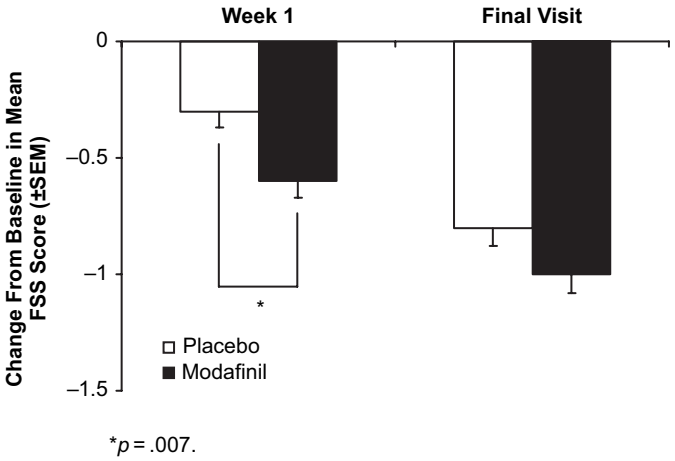

Figure 3 Mean (± SEM) Changes from Baseline in Fatigue Severity Scale (FSS) Scores between Placebo and Modafinil (All Patients).

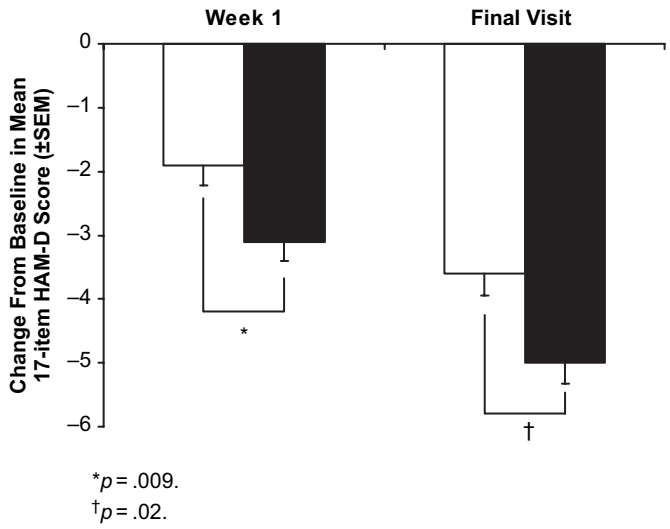

Figure 4 Mean (± SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

combined with an SSRI, as shown by greater reductions in 17-item HAM-D mean scores at Week 1 (−3.1, modafinil vs. −1.9, placebo; $p = .009$) (Figure 4). Significant between-group differences in favor of modafinil were also observed at Week 2 (−3.8, modafinil vs. −2.8, placebo; $p = .02$), Week 6 (−5.2, modafinil vs. −3.8, placebo; $p = .02$), and final visit (−5.0, modafinil vs. −3.6, placebo; $p = .02$, Figure 4). However, differences between treatment groups at Week 4 (−3.8, modafinil vs. −3.1, placebo) and Week 8 (−5.0, modafinil vs. −3.9, placebo) were not statistically significant.

Safety Outcomes

Table 2 summarizes adverse events that occurred at rates ≥ 5% in either treatment group. As shown, the most common adverse events reported more frequently by patients taking modafinil than those taking placebo were headache, nervousness, and nausea. Most adverse events were mild to moderate in intensity. One patient in the modafinil group experienced a serious adverse event (i.e., non-cardiac chest pain) that was considered by the investigator to be unrelated to modafinil treatment. No deaths were reported. There were no clinically significant trends observed for clinical laboratory tests, vital signs, or physical examinations.

Table 2 Adverse Events at Rates ≥5% in Either Treatment Group[a]

	Number (%) of Patients	
Adverse Event	Placebo (n = 168)	Modafinil (n = 180)
Headache	26 (15)	32 (18)
Nervousness	7 (4)	20 (11)
Infection	16 (10)	17 (9)
Nausea	3 (2)	16 (9)
Insomnia	14 (8)	13 (7)
Diarrhea	12 (7)	12 (7)
Dizziness	3 (2)	11 (6)
Dry mouth	5 (3)	10 (6)
Hypertension	9 (5)	6 (3)
Pain	8 (5)	4 (2)

[a]Patients may have reported > 1 adverse event type.

DISCUSSION

Results of this pooled analysis support the use of modafinil as an augmentation therapy in patients with MDD and with partial response to SSRI therapy, particularly when excessive sleepiness and fatigue occur as persistent, residual symptoms. Modafinil combined with SSRIs rapidly (i.e., within 1 week) and significantly improved overall clinical condition, wakefulness, and depressive symptoms and significantly reduced fatigue compared with placebo ($p < .01$ for all). Additionally, modafinil-related improvements in overall clinical condition, wakefulness, and depressive symptoms were significant at final visit ($p < .05$ for all). Given that these two studies were designed to test the efficacy of an augmentation agent (i.e., patients already were receiving and had responded partially to SSRI therapy), the sustained nature and magnitude of change in overall clinical condition and depressive symptoms are particularly noteworthy. Although changes from baseline in sleepiness and fatigue scales were seemingly modest, these are also prominent for patients who were retrospectively selected on the basis of a common set of criteria for symptoms (i.e., at least moderate levels of excessive sleepiness and fatigue and mild to moderate depressive symptoms).

Although the reduction in fatigue attributable to modafinil was maintained at final visit, it was not distinguishable from placebo. This finding may reflect limitations imposed by study design (e.g., the use of modafinil dosages and dosing schedules not optimized for managing fatigue and the variable duration of prior antidepressant therapy) (9). Alternatively, it may relate to other factors (e.g., diagnostic misclassification, rising or dwindling severity of symptoms over the natural course of illness, patient and clinician expectations) that may contribute to a placebo response, thereby confounding interpretation of efficacy assessments and decreasing the likelihood of detecting treatment differences in clinical trials (17). Another possible explanation is that of a partial loss of benefit during continued administration of modafinil with respect to fatigue; however, the reduction in fatigue at Week 1 following initiation of modafinil, as determined by the FSS score, is slightly less than the reduction in fatigue at the final visit, suggesting that the lack of significance in the difference between modafinil and placebo at the final visit is unlikely to be due to the development of tolerance to the pharmacological effect of modafinil.

Several pharmacotherapies are currently used to improve responses to SSRI therapy. Buspirone is commonly used to

augment SSRI responses in treatment-resistant depressed patients, although one randomized, double-blind trial of buspirone used in combination with SSRIs did not distinguish buspirone from placebo (18), and another controlled study reported sustained improvement following buspirone augmentation only for a subset of patients with severe depression (19). In a survey conducted at an academic psychopharmacology practice, bupropion, methylphenidate, and dextroamphetamine were considered the most effective agents for SSRI augmentation (20). However, the use of psychostimulants as augmentation agents may be limited by their substantial side effect profiles and potential for abuse.

In patients with MDD, sleep problems and fatigue may be premonitory or primary depressive symptoms that occur as commonly as depressed mood or diminished interest or pleasure (21–23). These symptoms may persist in patients who are treated for depression and are otherwise considered responders to established antidepressant regimens (2), or may remit but return during recurring depressive episodes. Fatigue and excessive sleepiness also may be related to comorbid conditions or treatment with SSRIs (24,25) and other medications that disrupt or attenuate sleep. A recent open-label study suggested that modafinil may effectively address treatment-emergent effects like sedation, excessive sleepiness, and fatigue in patients with MDD (26). Controlled studies examining its utility in alleviating drug-related side effects are warranted.

Treatment with modafinil was well tolerated, with a low rate of discontinuation due to adverse events. Modafinil was not associated with adverse effects on blood pressure or heart rate, consistent with the safety results reported in the placebo-controlled studies in MDD patients (9,11). This is also consistent with the previous findings of randomized, placebo-controlled clinical trials in patients with primary sleep disorders (27–29).

A factor that limits the interpretation of our findings is the incongruence of some of the visit schedules in the double-blind studies, resulting in decreased statistical power at Weeks 4 and 8. Other limitations include the fixed but not optimized dosing schedule of one study, the mild severity of mood symptoms and excessive sleepiness, and the lack of systematic confirmation of symptom stability prior to randomization. The possibility of spontaneous responses and remissions over the course of augmentation therapy also may have affected study outcomes.

Taken together, the results of this retrospective, pooled analysis suggest that modafinil may be an effective and well-tolerated augmentation therapy in partial responders to SSRI therapy, particularly when patients continue to experience fatigue and excessive sleepiness as persistent, residual symptoms. Additional controlled studies, including those addressing the limitations of this retrospective analysis, exploring dosing strategies or examining the effects of modafinil augmentation on early response and particularly in MDD patients with a higher pretreatment depression severity score, would provide useful information regarding the role of modafinil in the treatment of depression.

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