Notice of Correction 6/17/2011: Dr Yang's name was corrected in the byline on page 32 to appear without a middle initial, ie, Ronghua Yang, PhD. On page 37, the first number below 0 on the Y axis in Figure 3 was corrected to –1.0.

A Double-Blind, Placebo-Controlled Study of Armodafinil for Excessive Sleepiness in Patients With Treated Obstructive Sleep Apnea and Comorbid Depression

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Objective: Treatment of excessive sleepiness in the context of obstructive sleep apnea (OSA) may be particularly difficult in those with depression because depression and/or antidepressant medications may cause sleepiness and fatigue in addition to that due to the OSA. This study evaluating armodafinil, a nonamphetamine wakefulness-promoting medication, is the first trial for treatment of excessive sleepiness in patients with treated OSA and comorbid depression.

Method: Men and women with OSA diagnosed using *International Classification of Sleep Disorders* criteria being treated with continuous positive airway pressure and comorbid major depressive disorder or dysthymic disorder according to *DSM-IV-TR* criteria were enrolled into a 12-week, randomized, double-blind, parallel-group study between September 2007 and March 2009 at 60 outpatient sites. Patients maintained on stable monotherapy with a serotonergic antidepressant and with a 17-item Hamilton Depression Rating Scale score < 17 received placebo or armodafinil (target dose: 200 mg once daily). Coprimary outcomes were the proportion of patients with at least minimal improvement on the Clinical Global Impression of Change (CGI-C) as related to excessive sleepiness and mean change from baseline in Maintenance of Wakefulness Test mean sleep latency at final visit; the key secondary outcome was mean change in the Epworth Sleepiness Scale score.

Results: 249 patients were enrolled: 125 in the armodafinil group and 124 in the placebo group. The proportion of patients with at least minimal improvement on the CGI-C was statistically significantly greater in the armodafinil group (69%) compared with the placebo group (53%, $P = .012$). Mean (SD) increase in Maintenance of Wakefulness Test sleep latency was numerically but not significantly greater following armodafinil (2.6 [7.1] min) versus placebo (1.1 [7.6] min, $P = .30$) treatment. Mean decrease in Epworth Sleepiness Scale score was greater in the armodafinil group (–6.3 [4.8]) than in the placebo group (–4.8 [4.9], nominal $P = .003$). Headache, dry mouth, and insomnia were the most common adverse events occurring with armodafinil treatment. There was no clinically significant effect on depression in either group as measured by the Quick Inventory of Depressive Symptomatology–Self-Report 16.

Conclusions: Armodafinil significantly improved overall clinical condition related to excessive sleepiness as rated by the CGI-C and was well tolerated in patients with treated OSA and comorbid depression.

Trial Registration: clinicaltrials.gov Identifier: NCT00518986

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In patients with obstructive sleep apnea (OSA), partial or complete collapse of the upper airway during sleep results in frequent arousals and sleep fragmentation.[1] Excessive sleepiness is the most common presenting symptom in patients with OSA.[1] Although continuous positive airway pressure (CPAP) reduces apneic events and sleepiness,[2,3] many patients experience residual excessive sleepiness despite treatment of the underlying obstruction.[4]

Mood disorders are common comorbidities in patients with OSA. Prevalence rates reported for mood disorder in patients with OSA are as high as 63%, with most studies reporting rates in the range of 30% to 50%.[5] Patients with OSA and major depressive disorder (MDD) have shown an increased duration of apnea compared with those without MDD,[6] and injuries to specific cortical and subcortical brain regions have been associated with higher levels of depressive symptoms in patients with OSA.[7] Higher levels of sleepiness or fatigue are also associated with depression in patients with OSA.[8–10]

The presence of depression may complicate the treatment of excessive sleepiness in patients with OSA. Depression may contribute to sleepiness because sleepiness is a common symptom in depressed patients without OSA and may persist even after mood symptoms have responded to therapy.[11] An added burden of sleepiness may also accompany depression because it may be a side effect of antidepressant treatment. Patients with depression are typically treated with

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selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs),[12,13] and while these are effective medications, they are commonly associated with daytime somnolence.[14–17] In a large prospective survey of those patients prescribed an SSRI, "drowsiness/fatigue" was the most common adverse event leading to SSRI discontinuation.[15] Comorbid depression may also influence clinical outcomes in general, as has been well documented by the increased risk for poor outcomes in patients with cardiovascular disease and depression.[18,19]

Armodafinil is a nonamphetamine, wakefulness-promoting medication. It is the *R*- and longer-lasting isomer of modafinil.[20] Armodafinil significantly improved wakefulness in patients with excessive sleepiness associated with treated OSA in 2 placebo-controlled, double-blind studies,[21,22] as well as in studies of shift work disorder (Roth et al[23] and data on file, Cephalon, Inc, Frazer, Pennsylvania) and narcolepsy.[24] Because treatment of excessive sleepiness in patients with OSA may be more challenging in the context of comorbid depression, it is important to evaluate the efficacy of armodafinil in this population. This study, evaluating the efficacy and tolerability of armodafinil in patients with CPAP-treated OSA and stable comorbid MDD or dysthymic disorder requiring antidepressant monotherapy, is the first study of a treatment for excessive sleepiness focused exclusively on this patient population.

METHOD

Study Design

This 12-week, randomized, double-blind, parallel-group, placebo-controlled study was conducted from September 2007 through March 2009 at 60 outpatient sites in the United States. Written informed consent was obtained from each participant before any study-specific procedures were performed and after procedures and potential adverse events of study drug were explained. The protocol was approved by the appropriate health authorities and the independent ethics committee/institutional review board at each site. The study was conducted in full accordance with the Good Clinical Practice: Consolidated Guidance approved by the International Conference on Harmonization[25] and any applicable national and local laws and regulations.

Clinic visits occurred during a 1-week, single-blind, placebo run-in, screening period; at baseline; and at weeks 4, 8, and 12 of double-blind treatment with armodafinil or placebo. Patients were contacted by telephone at week 2 to review medication usage and adverse events and also were asked to complete an Epworth Sleepiness Scale (ESS) at week 2. Except for the screening period, all clinic visits included an overnight sleep study. Patients arrived for their sleep study between 7 PM and 8 PM, were in bed by 10 PM, and were awakened at 7 AM the following morning. Recurring assessments were performed at the same time of day for all in clinic study visits.

Patients

Eligible patients were men and women aged 18 to 65 years who met *International Classification of Sleep Disorders* (*ICSD*)[1] diagnostic criteria for OSA and had a complaint of excessive sleepiness despite regular use of CPAP therapy. Patients were required to have a stable regimen of CPAP for ≥ 4 weeks that was effective as evidenced by an apnea-hypopnea index of ≤ 10[26–29] at the baseline visit and as judged by the investigator. Regular use of CPAP (≥ 4 hours/night on ≥ 70% of nights)[30] was confirmed during a 1-week evaluation period by review of data from the CPAP device. A Clinical Global Impressions-Severity of Illness scale (CGI-S)[31] score relative to excessive sleepiness of ≥ 4 (at least moderately ill) and an ESS[32] score of ≥ 10 were also required.

Eligible patients were also required to have a diagnosis of MDD or dysthymic disorder, according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria and a 17-item Hamilton Depression Rating Scale (HDRS-17)[33] score of < 17 at screening and baseline. If HDRS-17 scores changed by ≥ 6 points between screening and baseline, patients were not permitted to continue in the study. Stable monotherapy with study-approved SSRIs or SNRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine, or duloxetine) was required for ≥ 8 weeks at the time of screening. During the 1-week, single-blind, placebo run-in screening period, all patients were administered the Mini International Neuropsychiatric Interview (MINI)[34] and HDRS-17 by a psychiatrist or licensed clinical psychologist. On the basis of clinical assessment, the primary diagnosis of MDD or dysthymic disorder was confirmed by the psychiatrist or licensed clinical psychologist, who also evaluated patients to ascertain that the patient was stable in regard to depressed mood and had shown a clinical response to the SSRI or SNRI.

In general, patients were excluded for having conditions believed to significantly increase their risk for harm or interfere with study conduct or interpretation of results. Exclusion criteria included a confirmed or suspected diagnosis of any currently active sleep disorders other than OSA (including polysomnography [PSG] revealing periodic leg movements of > 10/h, suggestive of periodic limb movement disorder), current treatment-resistant depression (defined as failing ≥ 2 adequate trials of an antidepressant), a diagnosis of an Axis I disorder (confirmed by the MINI: eating disorder, psychotic disorder, delirium, dementia, substance-related disorders, or moderate to severe hypochondriasis) or Axis II disorder (confirmed by the MINI, as applicable) that could interfere with the conduct of the study (eg, severe antisocial or borderline personality disorders, mental retardation), or any clinically significant uncontrolled psychiatric condition. Patients with any history of bipolar disorder, psychotic depression, schizophrenia, schizoaffective disorder, or any other psychotic disorders were also specifically excluded. Additionally, patients with a score ≥ 2 on the suicidality item

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of the HDRS-17, with any history of suicidal ideation, or who were believed to be at imminent risk of self-harm were excluded. A history of substance abuse or dependence in the past year or a positive urine drug screen without medical explanation were also considered reasons for exclusion.

Patients who had previously taken armodafinil at any time, had taken modafinil within 1 month of the study baseline visit, or had a history of hypersensitivity to modafinil were excluded. Patients were also excluded for taking monoamine oxidase inhibitors, psychotropics (except the study-approved SSRIs and SNRIs), anticoagulants, anticonvulsants, investigational drugs, and > 800 mg/d of caffeine within 2 to 4 weeks of study entry. Current consumption of > 600 mg/d of caffeine was not permitted. Psychotherapy was not allowed unless it was initiated > 8 weeks before study entry.

Study Drug

Patients were randomly assigned to armodafinil or matching placebo in a 1:1 ratio, stratified by center. Patients took armodafinil or placebo once daily, before 8 AM. Armodafinil was initiated at a dose of 50 mg (1 tablet) and titrated in 50-mg increments on days 2, 5, and 8 to a target dose of 200 mg (4 tablets) daily. After 3 days at the target dose, the dose could be further increased to 250 mg on the basis of the investigator's and patient's perception of efficacy. The dose could also be decreased after the target dose was reached, on the basis of tolerability; patients unable to tolerate 150 mg daily were discontinued. Once a dose was decreased, it could not be increased, and no adjustments were permitted after week 3.

Assessments

Efficacy. The primary efficacy outcomes were the proportion of patients with at least minimal improvement as rated by investigators on the Clinical Global Impression of Change (CGI-C)[31] and the mean change from baseline in the Maintenance of Wakefulness Test (MWT)[35] mean sleep latency at final visit (week 12 or last postbaseline visit). The CGI-C is the clinician's rating of the patient's condition, in this case as related to the severity of excessive sleepiness associated with OSA, compared with a baseline measure of severity (CGI-S). The CGI-C is scored on a 7-point scale ranging from very much improved to very much worse. The CGI-C was performed at weeks 4, 8, and 12. The MWT is an objective measure of sleepiness that measures the ability of the patient to stay awake.[35] It was administered for 30 minutes at 9 AM, 11 AM, 1 PM, and 3 PM. Sleep latency was defined as the time to onset of the first of 3 consecutive epochs of stage 1 sleep or the time to onset of any epoch stages 2, 3, and 4 or rapid eye movement (REM) sleep. If a patient fell asleep, he or she was awakened immediately and then prevented from falling asleep again throughout the reminder of the 30-minute period. The MWT was performed at baseline and weeks 4, 8, and 12.

The key secondary efficacy outcome was the mean change from baseline to final visit in ESS score.[32] The ESS is a self-assessed measure of the propensity to fall asleep in 8 everyday situations. Scores range from 0 to 24, with higher scores indicating greater sleepiness. A score ≥ 10 has been used to define excessive sleepiness.[36] The ESS was performed at screening, during the telephone contact (week 2), and at weeks 4, 8, and 12. The proportion of responders on ESS at final visit (as defined by achieving an ESS score < 10) was another secondary efficacy outcome.

Tolerability. Adverse events were recorded at all patient contacts. Use of CPAP was monitored throughout the study. Vital signs were measured at all clinic visits. Electrocardiography (ECG), clinical laboratory testing, and physical examinations were performed at screening and final visit.

Nocturnal PSG was performed at baseline and final visit. Additionally, a patient diary assessing sleep latency, sleep disturbance, duration of sleep, and sleep quality over the previous week was completed at baseline and weeks 4, 8, and 12.

To assess tolerability as related to the patient's MDD or dysthymia diagnosis, the Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR-16)[37] was performed at baseline and at all follow-up patient contacts. The QIDS-SR-16 is a 16-item self-rated scale of the severity of depression symptoms based on the *DSM-IV* criteria symptom domains. Patients with a total score ≥ 21 (indicating severe depression) or a score of 2 or 3 on item 12 (suicidality item) were to be immediately withdrawn from the study per protocol.

Statistical Analysis

The sample size calculation was based on a mean difference of 3.0 minutes in MWT sleep latency with SD of 7.65 ($\Delta = 0.392$). On the basis of a 2-sided significance level of .05 and 80% power, a total of 232 patients (116 per group) were planned to be enrolled to assure that at least 104 patients per group had postbaseline assessments of MWT or CGI-C.

The safety analysis set included all patients who received at least 1 dose of study drug. The efficacy analysis set included all patients who received at least 1 dose of study drug and completed at least 1 postbaseline MWT or CGI-C assessment. For the efficacy analysis, a last-observation-carried-forward approach was used for the final visit.

The CGI-C response rate at final visit was analyzed using the Pearson χ^2 test. Changes from baseline to final visit in MWT mean sleep latency (mean of 4 time points: 9 AM, 11 AM, 1 PM, and 3 PM) and ESS score were analyzed using analysis of covariance (ANCOVA) with study drug as a fixed factor and the baseline value as covariate. The Hochberg procedure[38] was used to control the overall Type I error rate at the .05 level for the primary outcomes. According to the Hochberg procedure, if the *P* values for both primary outcomes are ≤ .05, the treatment effect is considered significant for both outcomes. If 1 *P* value is > .05

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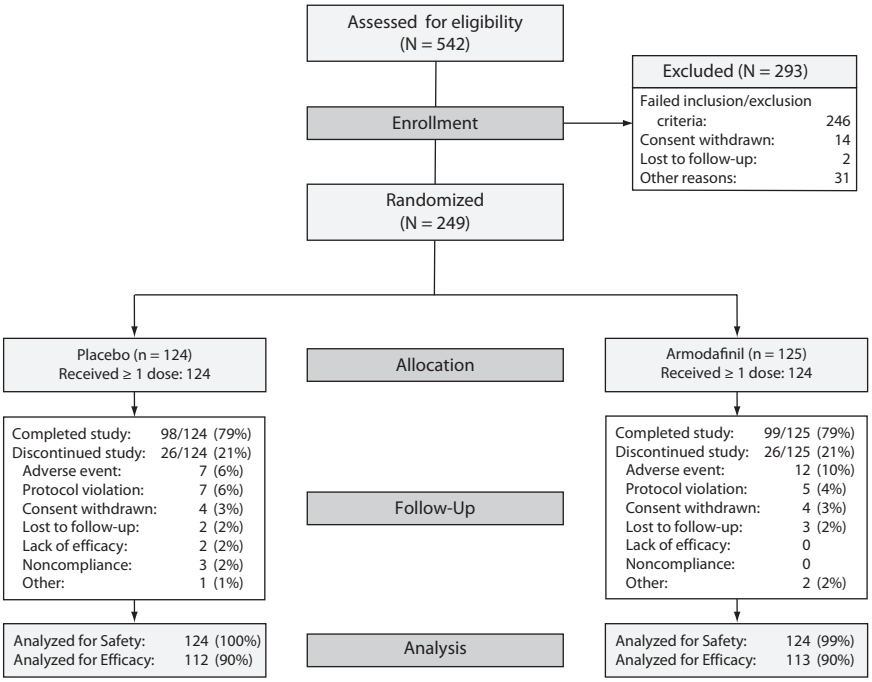
Figure 1. Patient Disposition



and the other is ≤ .025, the outcome with a *P* value ≤ .025 is claimed to be significant. If both primary outcomes are significant and the *P* value for the key secondary outcome is ≤ .05, it is considered significant. If only 1 of the primary outcomes is significant, the key secondary outcome cannot be considered significant. Other secondary outcomes are to be tested according to a predefined hierarchy procedure for a claim of statistically significant treatment difference. However, nominal *P* values are reported in this article even if statistical significance cannot be claimed. Summary statistics and *P* values are reported for all outcomes.

Tolerability outcomes were summarized using descriptive statistics for continuous variables and patient counts and percentages for categorical variables.

RESULTS

Patients

Two hundred forty-nine patients were randomly assigned to treatment: 125 to the armodafinil group and 124 to the placebo group. Twenty-one percent of both treatment groups discontinued the study prematurely (Figure 1). Thirty-nine patients (31%) were receiving 250 mg of armodafinil at their final visit.

Baseline demographics were comparable across groups (Table 1). The mean body mass index (BMI) was 37.3 kg/m^2 in the armodafinil group and 36.2 kg/m^2 in the placebo group. Escitalopram was the most commonly prescribed antidepressant, reported by 21% of patients receiving armodafinil and 26% of patients receiving placebo. The mean (SD) HDRS-17 scores at baseline were 6.7 (4.1) for those in the armodafinil group and 6.3 (4.0) for those in the placebo group. Mean (SD) baseline ESS scores were 14.3 (3.1) in the armodafinil group and 15.3 (3.4) in the placebo group.

Efficacy

The proportion of patients with at least minimal improvement on CGI-C at final visit was significantly greater in the armodafinil group than in the placebo group (69% vs 53%, *P* = .012); this proportion was also numerically higher for those in the armodafinil group at weeks 4, 8, and 12 (Figure 2).

For the coprimary outcome, change from baseline to final visit in MWT mean sleep latency, mean change was greater in the armodafinil group (2.6 [7.1] minutes) compared with placebo (1.1 [7.6] minutes), but the difference was not statistically significant (95% CI, –0.80 to 2.54; *P* = .304). Changes at weeks 4, 8, and 12 were also numerically greater for those in the armodafinil group than for those in the placebo group (Table 2).

In a subgroup analysis, CGI-C response and MWT mean sleep latency were analyzed by depression type. For patients with MDD, the proportion of patients rated as minimally improved, much improved, or very much improved on the CGI-C was 70% (73/105) following armodafinil versus 54% (56/103) following placebo at the final visit (nominal *P* = .024). In the much smaller subgroup with dysthymic

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Table 1. Baseline Demographics and Clinical Characteristics of Patients With Treated Obstructive Sleep Apnea and Comorbid Depression

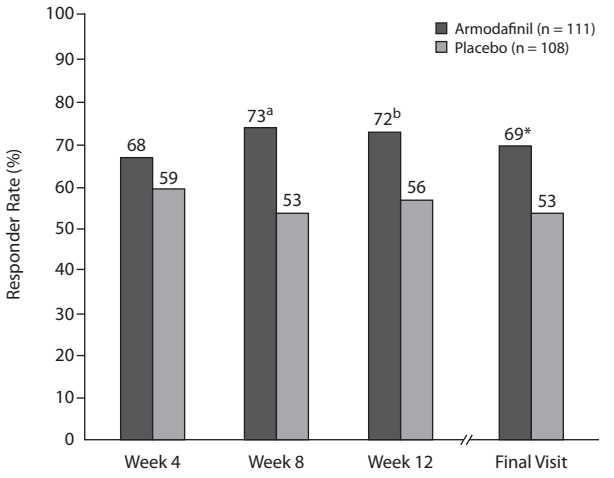
Characteristic	Armodafinil (n = 125)	Placebo (n = 124)
Age, mean (SD), y	49.5 (10.3)	49.5 (9.7)
Sex, n (%)		
Men	57 (46)	58 (47)
Women	68 (54)	66 (53)
Race, n (%)		
White	113 (90)	112 (90)
Black	9 (7)	9 (7)
Asian	1 (1)	2 (2)
Other	1 (1)	1 (1)
BMI, mean (SD), kg/m^2	37.3 (7.9)	36.2 (7.8)
Depression diagnosis, n (%)		
MDD	117 (94)	114 (92)
Dysthymic disorder	8 (6)	10 (8)
Concomitant SSRI/SNRI, n (%)[a]		
Citalopram	24 (19.4)	16 (12.9)
Duloxetine	8 (6.5)	11 (8.9)
Escitalopram	26 (21.0)	32 (25.8)
Fluoxetine	20 (16.1)	25 (20.2)
Paroxetine	6 (4.8)	10 (8.1)
Sertraline	26 (21.0)	20 (16.1)
Venlafaxine	14 (11.3)	12 (9.7)
HDRS-17 score, mean (SD)	6.7 (4.1)	6.3 (4.0)
QIDS-SR-16 score, mean (SD)[a]	7.9 (4.1)	7.8 (4.2)
CPAP, mean (SD), h/night[a]	6.9 (1.6)	7.0 (1.3)
Baseline CGI-S rating, n (%)		
Moderately ill	64 (51)	74 (60)
Markedly ill	46 (37)	38 (31)
Severely ill	14 (11)	12 (10)
Extremely ill	1 (1)	0
Maintenance of Wakefulness Test score, mean (SD)[b]	20.0 (8.5)	21.3 (7.9)
Epworth Sleepiness Scale score, mean (SD)[b]	14.3 (3.1)	15.3 (3.4)

[a]From safety population: n = 124 for armodafinil, n = 124 for placebo.
[b]From efficacy population: n = 113 for armodafinil group; n = 112 for placebo group.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, CPAP = continuous positive airway pressure, HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder, QIDS-SR-16 = Quick Inventory of Depressive Symptomatology—Self-Report, SNRI = serotonin norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

disorder, 63% (5/8) were at least minimally improved on the CGI-C following armodafinil versus 33% (3/9) following placebo (nominal $P = .229$). Mean (SD) change from baseline to final visit in MWT following armodafinil versus placebo was 2.5 (7.1) versus 1.2 (7.8) minutes in patients with MDD (nominal $P = .268$) and 3.7 (7.9) versus 0.8 (5.5) minutes in patients with dysthymic disorder (nominal $P = .811$).

For the key secondary outcome, change from baseline to final visit in ESS score, the mean (SD) decrease in score was greater in the armodafinil group (–6.3 [4.8]) than in the placebo group (–4.8 [4.9]; 95% CI, –3.13 to –0.66; nominal $P = .003$; Figure 3). Mean changes in ESS score were also numerically greater in the armodafinil group at the earliest time point evaluated (week 2) and at all subsequent study visits (Figure 3). The proportion of ESS responders (ESS < 10) at final visit was 66% in the armodafinil group and 48% in the placebo group (nominal $P = .006$).

Figure 2. Proportion of Patients With at Least Minimal Improvement on the Clinical Global Impression of Change by Visit



[a]$P = .02$, [b]$P \leq .01$. Nominal P values are reported for weeks 8 and 12, and statistical significance cannot be claimed on the basis of these P values.
*$P \leq .01$. Differences between groups at final visit are statistically significant.

Table 2. Change From Baseline in Mean Sleep Latency on Maintenance of Wakefulness Test in Patients With Treated Obstructive Sleep Apnea and Comorbid Depression

Visit	Armodafinil	Placebo	*P* Value	95% CI for Difference
Week 4				
Change, mean (SD), min	3.0 (7.8)	–0.4 (7.0)	.0019	1.06 to 4.59
n	108	105		
Week 8				
Change, mean (SD), min	2.3 (7.4)	0.9 (6.5)	.3145	–0.84 to 2.61
n	104	100		
Week 12				
Change, mean (SD), min	2.9 (7.1)	1.0 (7.5)	.2196	–0.67 to 2.90
n	96	95		
Final visit				
Change, mean (SD), min	2.6 (7.1)	1.1 (7.6)	.3043	–0.80 to 2.54
n	109	105		

Tolerability

The most commonly reported adverse events were headache, dry mouth, and insomnia (Table 3). Most events were rated by the investigator as mild or moderate in nature. The only psychiatric events reported by > 1 patient in the armodafinil group were insomnia, anxiety, and worsening of MDD (Table 4). The worsening of depression was rated as mild or moderate in all cases, was rated by the investigator as related to treatment in 1 case (armodafinil), and did not lead to study discontinuation for any patients. Three of the 4 patients with worsening MDD as an adverse event showed a 1-point improvement on the QIDS-SR-16 at final visit,

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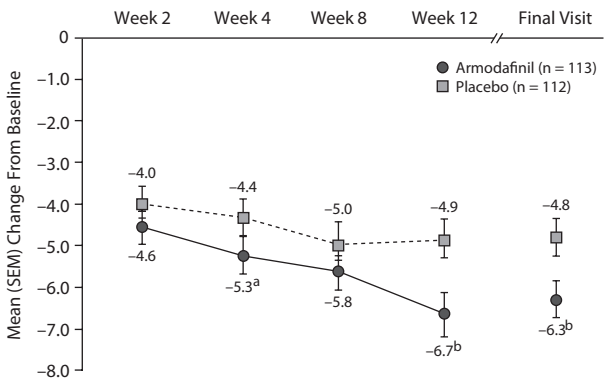
Figure 3. Change in Epworth Sleepiness Scale Score by Visit



[a]$P = .04$, [b]$P = .003$. Nominal P values are reported for weeks 4 and 12 and final visit, and statistical significance cannot be claimed on the basis of these P values.

Table 4. Selected Psychiatric Adverse Events, n (%)[a]

Adverse Event	Armodafinil (n = 124)	Placebo (n = 124)
Insomnia	9 (7)	2 (2)
Anxiety	6 (5)	1 (1)
Major depression	3 (2)	1 (1)
Agitation	1 (1)	1 (1)
Nervousness	1 (1)	1 (1)
Middle insomnia	1 (1)	0
Hypervigilance	1 (1)	0
Sleep disorder	1 (1)	0
Hallucination	1 (1)	0
Restlessness	0	3 (2)
Aggression	0	1 (1)
Early morning awakening	0	1 (1)
Suicidal ideation	0	0
Mania	0	0
Hypomania	0	0

[a]Includes all events classified as *psychiatric disorders* under the MedDRA coding system that occurred in > 1 patient and other selected psychiatric events of interest.

Table 3. Adverse Events Reported in ≥ 5% of Patients and More Frequently With Armodafinil Than With Placebo, n (%)

Adverse Event	Armodafinil (n = 124)	Placebo (n = 124)
Headache	14 (11)	9 (7)
Dry mouth	10 (8)	0
Insomnia[a]	9 (7)	2 (2)
Nausea	8 (6)	5 (4)
Anxiety	6 (5)	1 (1)

[a]Does not include 1 patient with middle insomnia and 1 patient with dyssomnia who received armodafinil and 1 patient with early morning awakening who received placebo per MedDRA adverse event coding system.

whereas 1 showed a 4-point worsening. Small decreases from baseline (improvements) in mean (SD) QIDS-SR-16 scores were reported at final visit in both treatment groups: –2.2 (4.6) following armodafinil and –1.8 (4.2) following placebo. No patients reported suicidal ideation, mania, or hypomania. Two patients in the armodafinil group discontinued because of psychiatric adverse events—1 due to nervousness and the other due to anxiety.

One patient (1%) in the armodafinil group reported a serious adverse event (atypical chest pain, considered by the investigator not to be related to study drug), and 3 patients (2%) in the placebo group reported serious adverse events (unstable angina, cholelithiasis, and cervical spinal stenosis with intravertebral disc protrusion). No deaths were reported. Adverse event–related discontinuations occurred in 12 patients (10%) in the armodafinil group and 7 patients (6%) in the placebo group. Adverse events leading to study discontinuation in > 1 patient were headache (n = 3), dyspnea (n = 3), dry mouth (n = 2), and disturbance of attention (n = 2) in the armodafinil group; no events were associated with > 1 discontinuation in the placebo group.

Mean changes from baseline to final visit in clinical laboratory values, ECG parameters, and body weight were not considered clinically meaningful. Small increases from baseline to final visit were noted for heart rate and systolic blood pressure but were also not considered clinically important. Use of CPAP throughout the study was high: mean use was 6.9 h/night for the armodafinil group and 7.0 h/night for the placebo group at baseline, and mean change from baseline to final visit was similar for those in the armodafinil group (–0.7 h/night) and placebo group (–0.5 h/night).

Mean changes from baseline to final visit for nocturnal PSG variables were small and comparable between treatment groups. Mean changes from baseline in subjective measures of sleep, as documented in the patient diaries, did not suggest any meaningful differences between the armodafinil and placebo groups.

DISCUSSION

In patients with OSA and comorbid mood disorders, the etiology of excessive sleepiness and depression may be multifactorial. Somnolence occurring as an adverse effect of antidepressants[14–17] and the sleepiness that is commonly reported as a symptom of depression[11] may contribute to the excessive sleepiness associated with OSA and negatively affect treatment outcomes. Conversely, some of the depressive symptoms reported in the study might have been associated with mild OSA. Regardless of the etiology of the depression, patients in this study had to have been diagnosed with both depression and OSA as defined by the *DSM-IV-TR* and *ICSD*, respectively. Because all patients were treated for both conditions and remained depressed, the complexity of treating these patients remains the same irrespective of the cause of depression. It is important to determine the effects of armodafinil in patients with OSA and mood disorders because of the high incidence of these comorbidities[5] and the potential for treatment resistance in this group.

In this study, the proportion of patients with at least minimal improvement in overall clinical condition as related

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to excessive sleepiness (CGI-C) was significantly higher in the armodafinil group than in the placebo group ($P = .012$). Improvement in ESS mean score and ESS responder rate were also greater in the armodafinil group than in the placebo group (nominal P values = .003 and .006, respectively), but these differences could not be considered statistically significant because, as stipulated by the hierarchical testing procedure, the coprimary outcome (change from baseline in MWT mean sleep latency) did not achieve statistical significance.

In 2 previous, similarly designed studies in a general population of patients with treated OSA, significant improvements in MWT mean sleep latency were detected for armodafinil compared with placebo. In addition, improvements over placebo were also detected for ESS score changes and the proportion of patients with at least minimal improvement on CGI-C.[21,22] The MWT mean increase in sleep latency with armodafinil compared with placebo was 2.6 minutes in the current study. Mean increases of 2.3 minutes following armodafinil 150 mg,[22] 1.7 minutes following armodafinil 150 mg,[21] and 2.2 minutes following armodafinil 250 mg[22] have been reported in previous studies in OSA compared with placebo. The placebo response on MWT was higher in the current study than in these previous studies and appeared to account for the inability to detect significant differences in this study. Placebo response was also higher for ESS mean changes in the current study than reported in the earlier studies[21,22] and was high for CGI-C, as has been previously reported.[21] High rates of placebo response are commonly reported in studies of antidepressant efficacy for MDD, and the placebo response rate has been increasing over recent years.[39] The findings from our study suggest that the increase in placebo response seen on assessments of depressive symptoms in patients with MDD may extend to objective and subjective assessments of sleepiness.

No prior studies of modafinil for excessive sleepiness in OSA patients with comorbid depression have been reported. However, 3 placebo-controlled studies of modafinil in patients with sleepiness and MDD[40–42] did not show consistent effects of modafinil on excessive sleepiness. In the 2 studies that required patients to have excessive sleepiness at baseline (ESS score ≥ 10),[41,42] changes from baseline to final visit in ESS score did not differ significantly between groups. The percentage of patients with at least minimal improvement on CGI-C was significantly higher in the modafinil group at final visit in 1 of these studies ($P = .02$ versus placebo); however, CGI-C was a measure of overall clinical condition (not specific to sleepiness) in that study.[42] For the 1 study in which excessive sleepiness was not an entry criterion, 51% of patients nonetheless had baseline ESS scores ≥ 10.[40] In that study, ESS scores declined significantly in the modafinil group at week 1, but at weeks 2 and 6, no benefit of modafinil over placebo was shown. Examination of the ESS data from these 3 studies suggests that a high placebo response rate played a role in the inability to detect significant differences.[40–42] MWT sleep latency was not assessed in any of these studies.[40–42]

The tolerability profile of armodafinil in this study was largely similar to its tolerability in the general populations of patients from previous studies in treated OSA, shift work disorder, and narcolepsy (references 21, 22, and 24 and data on file, Cephalon, Inc., Frazer, Pennsylvania). Headache, insomnia, and nausea were among the most commonly reported events. Armodafinil was generally well tolerated, as shown by the rate of adverse event–related discontinuations, which was not substantially different between armodafinil (10%) and placebo (6%) or as compared with previously published studies.[21,22,24]

Given the nature of the study population, a higher incidence of psychiatric adverse events might be expected. Insomnia (including middle insomnia, early morning awakening, and dyssomnia) and anxiety occurred in a higher proportion of the armodafinil group than the placebo group. The increase in incidence of insomnia following armodafinil compared with placebo (9% vs 2%) was slightly higher than that seen in the previously published studies (5% vs 1%), but the difference in incidence of anxiety (5% vs 1%) was similar to those studies (4% vs 1%).[21,22,24] The incidence of depression (or worsening of depression in this study) was 2% in the armodafinil group versus 1% in the placebo group. In the previously published studies, the incidence of depression was similar to that reported here (2% for armodafinil and none for placebo).[21,22,24]

Objective measures of sleep from PSG studies did not show clinically meaningful differences between treatment groups, nor did subjective variables reported in the sleep diary. On the whole, PSG data, sleep diary data, and adverse event reports of insomnia suggest that significant sleep disturbance is likely to be relatively uncommon among patients with excessive sleepiness associated with OSA and comorbid depression treated with armodafinil, although a small proportion of patients may experience insomnia as an adverse effect.

The limitations of this study include its relatively short duration (12 weeks), which does not permit generalization of the findings to treatment over a longer time period. In addition, there were limited objective data on patients' history of CPAP use, which was based on a 1-week assessment of data collected from the patient's CPAP device as well as the patients' self-reports on CPAP use for 4 weeks prior to the study. All patients, though, were educated on the use of CPAP at screening, and intervention efforts to encourage compliance were documented throughout the study. Findings are also not generalizable to patients who are not receiving adequate CPAP therapy, have not responded to antidepressant therapy, require multiple antidepressants, or have severely depressed mood. The ability of the study to detect significant differences in MWT sleep latency was limited by the overestimate of the mean difference in MWT

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sleep latency and underestimate of the necessary patient sample size in the setting of a greater than expected observed placebo effect. This estimate was based on previous studies[21,22] of armodafinil in populations of patients with treated OSA, the majority of whom did not have a history of depression and were not taking antidepressants.

CONCLUSIONS

In this population of patients with CPAP-treated OSA and comorbid MDD or dysthymic disorder, armodafinil significantly improved overall clinical condition as related to excessive sleepiness compared with placebo. The improvement in objective wakefulness, as reflected by MWT mean sleep latency, did not achieve statistical significance when compared with placebo. Coadministration of armodafinil with stable SSRI or SNRI monotherapy in patients with depression appeared to be generally well tolerated. Psychiatric adverse event rates and adverse-event–related discontinuation rates were low and consistent with previous studies in nondepressed, sleep-disordered populations. The results of this study suggest that armodafinil provides a clinically important benefit for the treatment of residual excessive sleepiness in patients with treated OSA and comorbid depression.

Drug names: armodafinil (Nuvigil), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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