Modafinil for Treatment of Residual Excessive Sleepiness in Nasal Continuous Positive Airway Pressure-Treated Obstructive Sleep Apnea/Hypopnea Syndrome

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Study Objectives: Nasal continuous positive airway pressure (nCPAP) usually reduces sleepiness in patients with obstructive sleep apnea/hypopnea syndrome. However, even with regular use of nCPAP, some patients experience residual excessive sleepiness. We evaluated the efficacy and safety of the wake-promoting agent modafinil for treating residual excessive sleepiness in nCPAP-treated patients.

Design: 12-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial.

Patients: Patients aged 18 to 70 years diagnosed with obstructive sleep apnea/hypopnea syndrome and having residual excessive sleepiness during nCPAP therapy were eligible.

Interventions: Once-daily modafinil, 200 mg or 400 mg, or placebo.

Measurements and Results: Assessments included the Maintenance of Wakefulness Test, Epworth Sleepiness Scale, Clinical Global Impression of Change, and Functional Outcomes of Sleep Questionnaire. Both doses of modafinil significantly improved mean (SD) sleep latency on the Maintenance of Wakefulness Test at weeks 4, 8, and 12 compared with placebo (week 12: modafinil 400 mg, 15.0 [5.3] minutes; 200 mg, 14.8 [5.3] minutes; placebo, 12.6 [5.8] minutes; $P < .0001$). The Epworth Sleepiness Scale score decreased more in patients taking modafinil compared with those in the placebo group (week 12: modafinil 400 mg, -4.5 [4.3]; 200 mg, -4.5 [4.7]; placebo, -1.8 [3.5]; $P < .0001$). At week 12, overall clinical condition improved for 61% and 68% of patients treated with modafinil 200 mg and 400 mg, respectively, versus 37% of placebo-treated patients ($P < .001$). Modafinil was generally well tolerated and did not adversely affect nighttime sleep or nCPAP use.

Conclusions: These results confirm previous shorter-term controlled trials, indicating modafinil is a useful adjunct therapy for improving wakefulness in patients with residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome who were treated with nCPAP.

Key Words: Modafinil, obstructive sleep apnea/hypopnea syndrome, sleepiness, wakefulness

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME IS CHARACTERIZED BY REPEATED EPISODES OF COMPLETE OR PARTIAL UPPER-AIRWAY OBSTRUCTION during sleep. Obstructive sleep apnea/hypopnea syndrome is also commonly associated with snoring, arterial oxygen desaturation, sleep fragmentation, excessive sleepiness, and decreased functional status and daytime functioning.[1-4] As the standard treatment for obstructive sleep apnea/hypopnea syndrome, nasal continuous positive airway pressure (nCPAP) therapy effectively improves airway patency, objectively and subjectively measured daytime wakefulness, performance, and functional status.[3,5] Nasal CPAP also reduces blood pressure.[6,7] In nCPAP-treated patients who continue to experience excessive sleepiness, improving nCPAP adherence should be the first-line treatment strategy; average durations of use range from 3.2 to 4.7 hours per night.[8-10] Enhanced nCPAP use or nCPAP optimization frequently improves this sleepiness; however, some patients continue to experience excessive sleepiness.[11,12]

Modafinil, 2-[(diphenylmethyl)sulfinyl]acetamide, is a unique wake-promoting agent previously shown in placebo-controlled trials to significantly improve wakefulness in patients with excessive sleepiness associated with narcolepsy.[13,14] Short-term studies of modafinil treatment demonstrate improved wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome.[15-18] The aim of the present longer-term controlled study was to assess the efficacy and safety of 2 doses of modafinil for the treatment of excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome who were users of nCPAP therapy. This 12-week, placebo-controlled study essentially addresses 2 important questions: (1) Do the effects of modafinil continue over time? and (2) Does nCPAP adherence remain stable over a longer period under strictly controlled conditions (ie, does modafinil affect nCPAP adherence)?

Disclosure Statement

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PATIENTS AND METHODS

Patients

Patients (aged 18 to 70 years) diagnosed with obstructive sleep apnea/hypopnea syndrome, with excessive sleepiness (Epworth Sleepiness Scale [ESS] score of $\geq$ 10 at screening) despite nCPAP therapy, and with documented prior nCPAP education and intervention efforts were eligible.

All patients were using nCPAP according to a stable regimen for at least 4 weeks and were required to meet nCPAP effectiveness criteria during the pre-enrollment period. Patients qualified if their apnea-hypopnea index was less than 10. Nasal CPAP effectiveness

was monitored at home on 2 consecutive nights using a ResMed AutoSet T™ device (ResMed Corporation, San Diego, Calif) set to constant-pressure mode at the patient's prescribed pressure.

Patients were excluded if they had clinically significant hypoxemia (O_2 saturation < 80% for ≥ 5% of total sleep time during the pre-enrollment period); comorbid sleep disorder other than obstructive sleep apnea/hypopnea syndrome; active clinically significant disease; prior experience with modafinil; history of alcohol, narcotic, or other drug abuse within the past 2 years or a positive urine drug screen result; 900 mg or more of caffeine per day; or a requirement for excluded concurrent medications (eg, methylphenidate, amphetamines, pemoline, or tricyclic antidepressants).

Methods

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 42 centers (38 in the United States and 4 in the United Kingdom), with institutional review board or independent ethics committee approval at each center. The primary recruitment method was print advertisements; investigators also approached patients who met inclusion criteria to determine interest in participation. Written informed consent was obtained from each patient. This study was conducted in compliance with Good Clinical Practice, according to the International Conference on Harmonisation Tripartite Guideline.

The study included a 12-week double-blind treatment period. Based on the results of a 2-week pre-enrollment period to monitor nCPAP use, patients were stratified into regular nCPAP (≥ 4 hours per night on ≥ 70% of nights) and partial nCPAP (any use < 4 hours per night on > 30% of nights) use groups. A previous study[19] found that application of nCPAP in the first 4 hours of sleep resulted in a significant reduction in the severity of obstructive sleep apnea/hypopnea syndrome over the remainder of the night, during which treatment was not applied. The term "regular users" and the cutoff value of effective nCPAP treatment (ie, ≥ 4 hours use per night on at least 5 of 7 nights) have been defined previously in the literature (eg, Kribbs et al[8]). This terminology and cutoff value have also been used in a previous study of the effects of modafinil in residual excessive sleepiness.[18] Thus, we felt that the cutoff value of 4 hours per night constituted a reasonable dividing line between the regular-user and partial-user groups.

Eligible patients in each subgroup were randomly assigned on a 1:1:1 basis to receive modafinil 200 mg, modafinil 400 mg, or placebo once daily in the morning. The modafinil doses were titrated as follows: 100 mg on days 1 and 2 (200 mg for the remainder of the 12-week double-blind treatment period—200-mg group), 200 mg on days 3 and 4, and 300 mg on days 5 and 6 (400 mg for the remainder of the 12-week double-blind treatment period—400-mg group). A centralized, stratified, randomization process was used. The randomization list and study medication labels were generated using ClinPro software.

Mean sleep latency was calculated from sleep-onset latencies during four 20-minute sessions of the Maintenance of Wakefulness Test (MWT),[14,20] providing an objective assessment of sleepiness. The MWT sessions were performed at 2-hour intervals, beginning at approximately 10:00 AM. Changes in self-reported sleepiness were measured using the ESS.[21] Overall clinical condition was assessed with the Clinical Global Impression of Severity and the Clinical Global Impression of Change scales.[22] Other efficacy outcome measures included sleep-related functional status, assessed by the Functional Outcomes of Sleep Questionnaire.[23] To evaluate the effects of a morning dose of modafinil on subsequent nighttime sleep, nocturnal polysomnographic recordings were conducted.[24,25] A standard polysomnographic montage was employed, consisting of central and occipital electroencephalogram, digastric electromyogram, eye movement electrodes, a nonquantitative index of respiratory airflow, and electromyogram for both anterior tibialis muscles. Nasal CPAP use was objectively monitored using the ResMed Elite 5 device each night of the treatment period. Adverse events were monitored throughout the study, with severity (mild, moderate, or severe) and relationship to study medication rated by the investigator. Concomitant medications were recorded. Physical examinations (screening and week 12 or final visit), vital-sign measurements (screening, baseline, week 4, week 8, and week 12 or final visit), and standard hematologic laboratory tests and chemistries (screening, baseline, week 4, and week 12 or final visit) were performed.

Statistical Analysis

The study was powered at 90% to detect a 2-minute difference in mean sleep latency on the MWT between the modafinil and placebo treatment groups (assuming a pooled SD of 4.5 minutes).

Efficacy analyses included all patients who received at least 1 dose of double-blind study medication and had at least 1 post-baseline evaluation of at least 1 efficacy parameter; safety analyses included all patients who received at least 1 dose of double-blind study medication. Separate analyses were performed for the week-4, week-8, week-12, and final visits. The last-observation-carried-forward algorithm was used to impute missing values, which in no case were more than 13% of the values. In addition, analyses of efficacy and safety data by regular nCPAP use and partial nCPAP use were conducted.

Continuous demographic variables were compared using an analysis of variance method with treatment and strata as factors; categorical variables were compared using Fisher exact test or a χ^2 test. Between treatment group and pairwise comparisons of mean changes from baseline in MWT, ESS, and Functional Outcomes of Sleep Questionnaire scores were made using an analysis of covariance method, with baseline score as a covariate and treatment and strata as effects. Clinical Global Impression data were analyzed using the Cochran-Mantel-Haenszel χ^2 test adjusted for strata. Between treatment group comparisons of adverse-event incidences were made using Fisher exact test. All tests of treatment effect were 2-tailed, and significance was determined at $P \leq .05$. Mean changes from baseline in MWT and ESS in the subset of partial nCPAP users were made using the nonparametric test of Wilcoxon rank test and the CGI by Fisher exact test.

RESULTS

Of the 515 patients who were screened, 309 were randomly assigned to treatment, and 305 received treatment (Figure 1). The most common reasons for not randomly assigning subjects were failure to meet inclusion criteria and withdrawn consent.

Patient characteristics at baseline were similar between the combined modafinil groups and the placebo group, with the exception of patient age and sex ($P < .05$; Table 1), which had no impact on the efficacy analyses. Two hundred sixty-four patients were regular nCPAP users, and 41 were partial users. Baseline apnea-hypop-

nea indexes (SD) for patients prior to and during nCPAP use were 49.6 (31.7) and 5.8 (8.1) for placebo-treated patients, respectively; 46.8 (26.5) and 4.2 (5.6) for modafinil-treated (200 mg); and 46.9 (28.9) and 4.2 (5.6) for modafinil-treated (400 mg).

Wakefulness

Modafinil significantly improved wakefulness on the MWT compared with placebo at weeks 4, 8, and 12 of treatment (all $P \leq .0001$; Figure 2). For modafinil-treated patients, mean MWT sleep latency increased by 1.6 minutes (200 mg) and 1.5 minutes (400 mg) at week 12 from baseline, in contrast to being shorter by 1.1 minutes for patients receiving placebo ($P < .0001$).

Treatment with modafinil significantly reduced the extent to which excessive sleepiness interfered with daily activities (as shown by a 4.5-point decrease in ESS score for both the modafinil 200-mg and 400-mg groups at week 12, versus a 1.8-point decrease for placebo; $P < .0001$ for overall and pairwise comparisons; Figure 3). Similar reductions were observed at weeks 4 and 8 ($P < .0001$). The percentage of patients with an ESS score < 10 at endpoint was 38% for modafinil 200 mg, 45% for modafinil 400 mg, and 17% for placebo.

There were no significant differences in mean MWT sleep latency or mean ESS scores between the 200-mg and 400-mg groups at weeks 4, 8, and 12, and at final visit (each $P > .15$).

Overall Clinical Condition

Treatment with modafinil significantly improved overall clinical condition as assessed by the Clinical Global Impression of Change compared with placebo at weeks 4, 8, and 12 (Figure 4). At week 12, 61% and 68% of patients receiving modafinil 200 mg and 400 mg, respectively, had improvement in overall clinical condition on the Clinical Global Impression of Change, compared with 37% of patients receiving placebo ($P < .001$). The percentages of patients who improved were similar at weeks 4 and 8.

Functional Outcomes

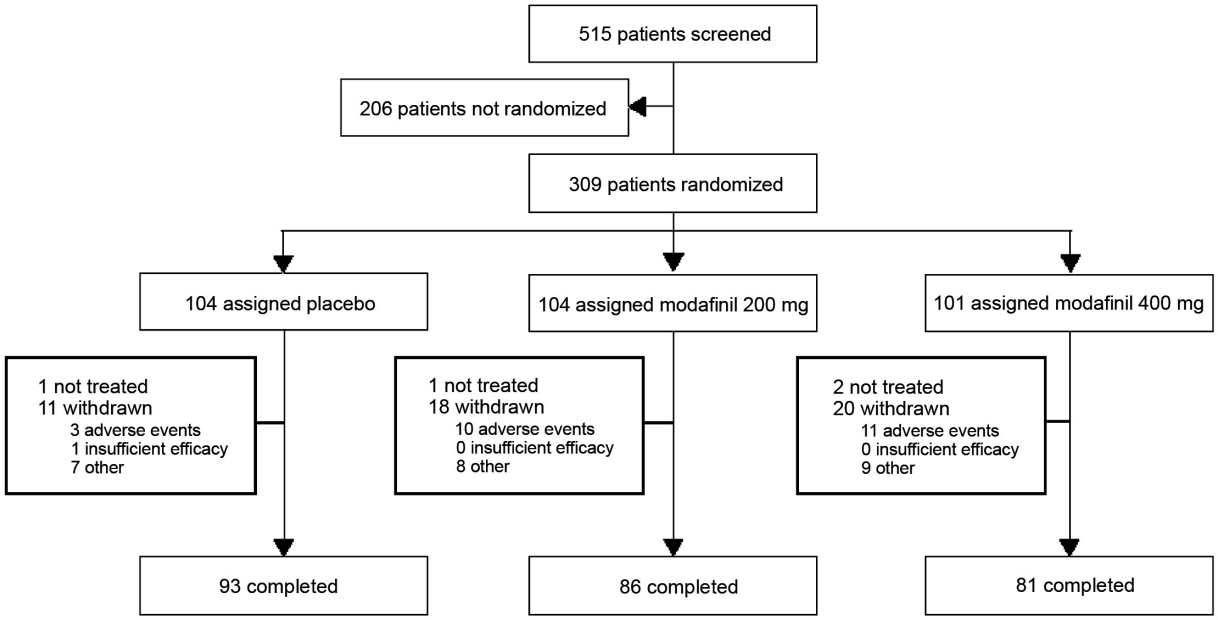

Figure 1—Patient disposition.

Table 1—Baseline Characteristics of Randomly Assigned Patients

Characteristic	Placebo (n = 104)	Modafinil 200 mg (n = 104)	Modafinil 400 mg (n = 101)
Sex, no. (%)			
Male	75 (72)*	90 (87)	69 (68)
Female	29 (28)*	14 (13)	32 (32)
Age, y	51.2 (9.4)*	48.1 (10.0)	48.7 (8.9)
Range	28-68	24-68	28-70
Weight, kg†	111.1 (24.8)	110.3 (23.4)	111.1 (26.0)
BMI, kg/m²†	37.3 (8.5)	36.2 (7.6)	36.9 (8.0)
AHI prior to nCPAP‡	49.6 (31.7)	46.8 (26.5)	46.9 (28.9)
AHI at baseline during nCPAP	5.8 (8.1)	4.2 (5.6)	4.2 (5.6)

Data are mean (SD) unless otherwise specified.
*$P \leq .05$ versus combined modafinil treatment groups.
†Weight and BMI were available for 103 patients in the placebo group.
‡AHI was available for 314 patients.
BMI refers to body-mass index, AHI, apnea-hypopnea index; nCPAP, nasal continuous positive airway pressure.

Modafinil treatment significantly improved functional status at weeks 8 (both modafinil groups combined versus placebo, $P < .01$) and 12 (both modafinil groups combined versus placebo, $P < .001$; Table 2), indicated by mean increases from baseline in Functional Outcomes of Sleep Questionnaire total scores compared with placebo. At week 12, modafinil treatment (both groups combined) significantly improved mean scores versus baseline scores for vigilance, general productivity, and activity level ($P \leq .02$). Intimacy and social outcome domains showed improvements that did not achieve statistical significance.

Evaluation of Nighttime Sleep and nCPAP Use

Modafinil did not adversely affect nighttime sleep, as assessed by nocturnal polysomnography (Table 3). Total sleep time, sleep efficiency, and duration of rapid-eye-movement and non-rapid eye movement sleep (stage 1, 2, 3, and 4) were unchanged from baseline. Modafinil did not adversely affect sleep-consolidation measures, including wake time after sleep onset, number of arousals, and arousal index.

nCPAP Use

Modafinil treatment did not significantly alter nCPAP use. During 12 weeks of treatment, the mean (SD) duration of nCPAP use was 5.9 (1.6) hours per night for the 200-mg group (baseline, 6.0 [1.7] hours per night), 6.0 (1.6) hours per night for the 400-mg group (baseline, 6.0 [1.7] hours per night), and 6.0 (1.7) hours per night for the placebo group (baseline, 5.9 [1.7] hours per night).

Regular and Partial Users of nCPAP

Eighty-seven percent (n = 268) of patients in the overall sample were defined as regular nCPAP users by protocol criteria. Although there was insufficient power to reliably compare treatment in partial users of nCPAP, no differences in efficacy were found when the partial-user group was included in the overall sample. In the 41 partial users of nCPAP, modafinil did not significantly improve wakefulness as assessed by MWT ($P = .34$ for 200 mg versus placebo; $P = .77$ for 400 mg versus placebo) or overall clinical condition ($P = .12$ for 200 mg versus placebo; $P = .42$ for 400 mg versus placebo). Modafinil significantly improved ESS scores in the 200-mg group compared with placebo ($P = .03$) but not in the 400-mg group ($P = .22$). The mean (SD) durations of nCPAP use for the 41 partial users were 2.9 (1.2) hours per night in the 200-mg group compared with a baseline of 3.0 (1.8) hours per night; 3.9 (1.5) hours per night in the 400-mg group compared with a baseline of 3.0 (1.0) hours per night; and 3.3 (1.8) hours per night in the placebo group versus a baseline of 3.4 (1.3) hours per night.

Safety Assessments

Among the 305 randomly assigned and treated patients, the most common treatment-emergent adverse events occurring more frequently in the modafinil groups than in the placebo group were headache, nausea, and anxiety (Table 4). The majority of adverse events were mild or moderate in severity. Ten patients taking 200 mg of modafinil and 11 patients taking 400 mg of modafinil had adverse events leading to patient withdrawal compared with 3 patients in the placebo group ($P < .05$). The most common adverse events leading to withdrawal for patients receiving modafinil were headache (200 mg: n = 3; 400 mg: n = 3), chest pain (200 mg: n = 3; 400 mg: n = 2), and dizziness (200 mg: n = 2; 400 mg: n = 2). Two patients in each of the modafinil treatment groups had a serious adverse event (200 mg: cellulitis, n = 1; hernia, n = 1; 400 mg: accidental overdose with a methanol de-icer, n = 1; vomiting, n = 1). Of these, none was considered by the investigator to be related to modafinil treatment.

There were no clinically significant treatment-related abnormalities in mean changes from baseline in physical-examination findings, vital signs, and laboratory-test data. There was no change in mean systolic or diastolic blood pressure over the experimental period. A relatively small percentage of patients (200-mg group, 4.6%; 400-mg group, 7.6%; and placebo group, 1.9%) reported hypertension as an adverse event. In this study, 55% of the patients entered the study with a history of hypertension. The hypertension in 7 of the 13 patients in the modafinil treatment groups was considered related to the study drug.

DISCUSSION

Untreated obstructive sleep apnea/hypopnea syndrome is an established independent risk factor for systemic hypertension[26,27] and, possibly, coronary artery disease[1] and stroke.[28-30] Additionally, obstructive sleep apnea/hypopnea syndrome is

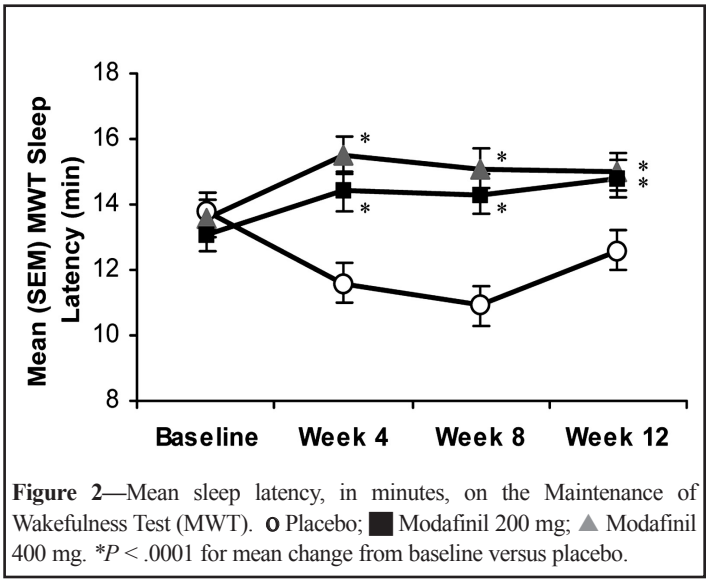

Figure 2—Mean sleep latency, in minutes, on the Maintenance of Wakefulness Test (MWT). o Placebo; ■ Modafinil 200 mg; ▲ Modafinil 400 mg. *$P < .0001$ for mean change from baseline versus placebo.

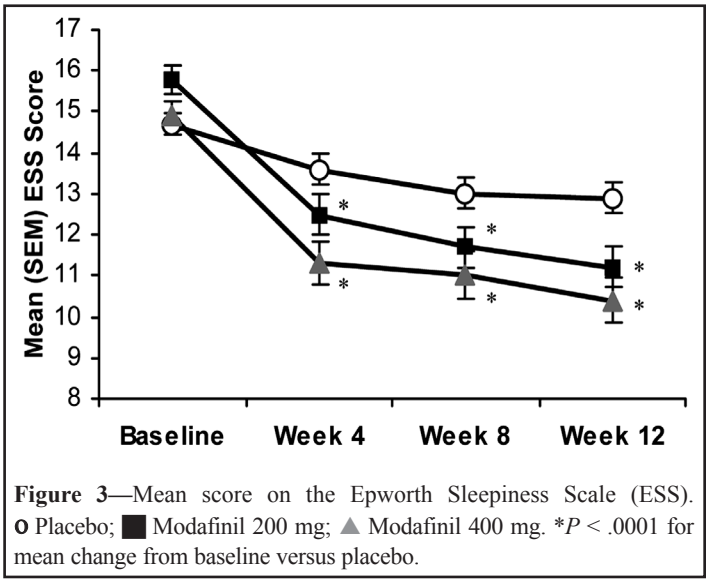

Figure 3—Mean score on the Epworth Sleepiness Scale (ESS). o Placebo; ■ Modafinil 200 mg; ▲ Modafinil 400 mg. *$P < .0001$ for mean change from baseline versus placebo.

often associated with excessive sleepiness.[11,12] Considering the documented benefit of nCPAP in lowering blood pressure and ameliorating excessive sleepiness, optimizing nCPAP use in patients with obstructive sleep apnea/hypopnea syndrome is a primary clinical goal, and appropriate steps should be initiated to this end. Some patients, however, may continue to experience excessive sleepiness (according to objective and subjective measures) notwithstanding adherence to nCPAP therapy.[11,12] Often, such individuals are under suboptimal treatment due to factors such as insufficient nCPAP pressure, insufficient sleep duration, or incomplete nCPAP use during sleep.[31] Others, however, demonstrate continued residual excessive sleepiness, by both subjective and objective measures, despite apparent nCPAP pressure optimization, adequate nightly sleep duration, and complete adherence to nCPAP use during sleep.[12,18,32]

Short-term clinical trials with modafinil show significant improvements in wakefulness in this population.[15-18] A recent 12-week open-label trial also reported significant improvements in wakefulness as a result of adjunct modafinil therapy.[32] However, the results of these long-term open-label efficacy data may be interpreted differently, since both the patients and investigators were unblinded, making it possible for a placebo effect to confound the results. An additional concern is continued nCPAP adherence in a patient population that has been suggested to experience motivation for adherence that correlates with the degree of subjective relief achieved with nCPAP.[33] It is important to note that modafinil therapy is neither shown nor theorized to improve airway patency or significantly lower blood pressure in patients with obstructive sleep apnea/hypopnea syndrome. This study used strictly controlled conditions to evaluate the longer-term efficacy of modafinil for reducing excessive sleepiness in patients with obstructive sleep apnea/hypopnea syndrome who use nCPAP therapy and to determine the stability of nCPAP adherence.

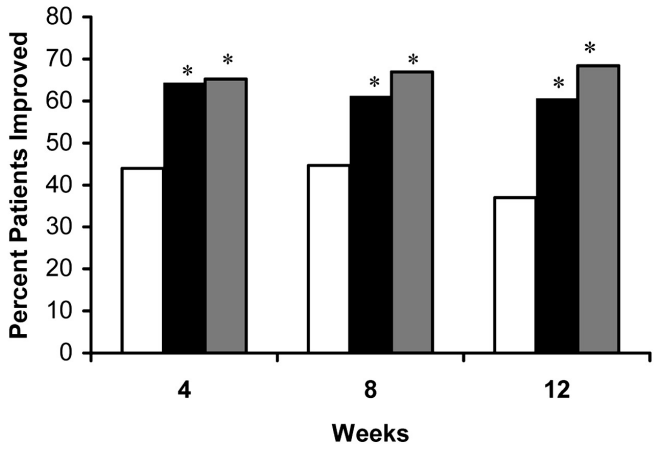

Figure 4—Percentage of patients with improved overall clinical condition. □ Placebo; ■ Modafinil 200 mg; ■ Modafinil 400 mg. *$P < .05$ versus placebo.

In this study, the wake-promoting effect of modafinil persisted with longer-term treatment, thus expanding on evidence from short-term studies in this same patient population.[15-18] For both doses of modafinil, mean sleep latency, the objective measure of daytime sleepiness as assessed by the MWT, was significantly increased at week 12 versus baseline compared with placebo and showed no statistically significant difference between doses when both doses were compared. The magnitude of effect is consistent with results reported in methodologically similar studies of modafinil in patients with narcolepsy.[13,14] In addition, modafinil significantly reduced the extent to which sleepiness interfered with daily activities and significantly improved overall clinical condition, thus supporting the findings from the objective assessment. These results are similar to those previously reported in modafinil-treated patients with narcolepsy.[13,14]

Modafinil significantly improved functional status. These effects were most noticeable in those subscales related to wakefulness: vigilance, general productivity, and activity. These are comparable to the effect of modafinil on functioning in short-term modafinil treatment in patients with obstructive sleep apnea.[31]

The present study found no decline in nightly nCPAP usage during treatment with modafinil. Kingshott and colleagues, however, reported a small (12 minutes per night) but statistically significant reduction in nightly nCPAP use when modafinil 400 mg was administered in a 2-week placebo-controlled study of 30 patients with obstructive sleep apnea/hypopnea syndrome and excessive sleepiness.[16] This effect on nCPAP usage was not replicated in a larger study by Pack et al[18] or in the present 12-week study. Thus, it does not appear that nightly nCPAP usage is affected by adjunct modafinil therapy over a longer period of time. Nevertheless, nCPAP usage should be monitored carefully to ensure continued effectiveness and patient adherence.

In a 4-week study reported previously, a small but statistically significant increase in the number of arousals per hour of sleep (arousal index) was observed for patients receiving modafinil.[18] This effect was not replicated in this larger, more comprehensive, 12-week study, although a small number of individuals reported insomnia. The finding that modafinil can improve wakefulness without adversely affecting nighttime sleep is consistent with the results of studies in patients with narcolepsy.[13,14]

Table 2—Mean Change From Baseline to Week 12 in Functional Outcomes of Sleep Questionnaire Scores

Scores	Placebo (n = 100)	Modafinil 200 mg (n = 99)	Modafinil 400 mg (n = 91)	*P* for Modafinil (combined) vs Placebo
Total score	0.84 (1.89)	1.92 (2.47)	2.13 (2.61)	0.001
Subscale score				
Vigilance	0.25 (0.54)	0.48 (0.67)	0.55 (0.59)	0.0007
General productivity	0.08 (0.40)	0.30 (0.45)	0.33 (0.49)	0.0006
Activity	0.20 (0.49)	0.41 (0.59)	0.45 (0.65)	0.02
Social outcome	0.20 (0.58)	0.37 (0.76)	0.36 (0.77)	0.3
Intimacy	0.17 (0.61)	0.35 (0.65)	0.47 (0.76)	0.05

Data are mean (SD) changes in scores from baseline to week 12.

Modafinil treatment did not have an adverse effect on group mean blood pressure or mean heart rate; however, a small number of patients reported hypertension as an adverse event. Results from previous studies have shown that modafinil produces no changes in group mean blood pressure or mean heart rate in patients with narcolepsy or obstructive sleep apnea/hypopnea syndrome.[13,17,34-36] However, the finding that a small percentage of patients reported hypertension as an adverse event in this study and that the modafinil-treated patients reported this more often than did placebo-treated patients, and in a dose-response fashion, is noteworthy. Yet, 55% of study patients reported a prior history of hypertension before participating in the study.

The etiology of residual excessive sleepiness in nCPAP-treated patients with obstructive sleep apnea/hypopnea syndrome is not known, although it is likely multifactorial. Lack of adequate nighttime sleep (even with adherent use of nCPAP) is a leading candidate. Sleeping 7 hours or less a night produces cumulative sleep debt and is associated with impaired daytime wakefulness and performance.[37-39] Alternatively, residual excessive sleepiness may result from suboptimal nCPAP pressure, sleep fragmentation as a consequence of nCPAP therapy (eg, discomfort due to equipment), abnormal cytokine regulation, or damage to the sleep-wake mechanism due to chronic disease.[40] In the present study, great care was taken to select a patient sample that exhibited excessive sleepiness not related to inadequate or improper nCPAP use or other concomitant disorders (including sleep disorders). Modafinil might be considered among the treatment options for these conditions; however, it is important to note that this study does not address sleepiness in those who are inadequately treated with or noncompliant with nCPAP use. Our results do not support the notion that modafinil should be used in patients who are not fully adherent to nCPAP.

The use of adjunct modafinil therapy for residual sleepiness in patients with treated obstructive sleep apnea/hypopnea syndrome is controversial.[41-43] Concerns have been raised about the possibility that the use of modafinil will either supplant appropriate sleep-related airway management or negatively affect nCPAP

Table 3—Nighttime sleep parameters at baseline and final visit, assessed using nocturnal polysomnography

Parameter	Placebo (n = 85)		Modafinil 200 mg (n = 86)		Modafinil 400 mg (n = 80)	
	Baseline	End point	Baseline	End point	Baseline	End point
Total sleep time min (SD)	379 (63)	379 (66)	386 (51)	389 (61)	379 (63)	379 (66)
Stage 1	44 (36)	41 (36)	41 (35)	42 (43)	41 (35)	38 (36)
Stage 2	213 (54)	225 (50)	227 (54)	228 (49)	222 (53)	224 (59)
Stage 3	25 (24)	25 (27)	22 (21)	24 (39)	24 (25)	25 (26)
Stage 4	16 (23)	16 (22)	13 (21)	15 (20)	14 (24)	12 (24)
REM	74 (33)	77 (31)	78 (33)	83 (35)	77 (34)	80 (29)
Sleep efficiency (%)	82 (15)	86 (10)	87 (8)	87 (10)	86 (12)	87 (11)
WASO (min)	64 (52)	52 (43)	50 (37)	48 (39)	50 (39)	47 (51)
Number of arousals	19.3 (13.1)	18.7 (14.6)	21.8 (15.9)	20.9 (13.2)	19.6 (15.1)	21.0 (19.4)
Arousal index*	3.1 (2.3)	4.5 (12.4)	3.4 (2.7)	3.3 (2.2)	3.0 (2.3)	4.5 (12.4)
Number of awakenings	19.3 (13.1)	18.7 (14.6)	21.8 (15.9)	20.9 (13.2)	19.6 (15.1)	21.0 (19.4)
AHI	5.8 (8.1)	7.0 (10.0)	4.2 (5.6)	5.2 (11.5)	4.2 (5.6)	4.3 (7.9)

Data are mean (SD).
*Arousals per hour of sleep.
REM refers to rapid eye movement; AHI, apnea-hypopnea index; WASO, wake time after sleep onset; AHI, apnea-hypopnea index.

Table 4—The most frequently occurring adverse events (5% in any treatment group) for 305 randomized patients who received treatment

Adverse Event	Number (%) of Patients			
	Modafinil 200 mg (n = 103)	Modafinil 400 mg (n = 99)	Placebo (n = 103)	*P* for Modafinil vs Placebo
Headache	24 (23)	26 (26)	13 (13)	0.02
Infection	20 (19)	10 (10)	23 (22)	0.1
Nausea	10 (10)	10 (10)	2 (2)	0.01
Anxiety	6 (6)	8 (8)	2 (2)	0.1
Accidental injury	8 (8)	5 (5)	8 (8)	0.6
Diarrhea	8 (8)	5 (5)	8 (8)	0.6
Hypertension	4 (4)	8 (8)	2 (2)	0.2
Nervousness	6 (6)	6 (6)	2 (2)	0.2
Dizziness	6 (6)	5 (5)	3 (3)	0.4
Insomnia	7 (7)	4 (4)	1 (1)	0.07
Rhinitis	6 (6)	5 (5)	8 (8)	0.5

compliance, an outcome that, although not observed in this study, warrants close monitoring. Conversely, failing to treat residual sleepiness with adjunct wake-promoting therapy can be viewed as suboptimal management that inadequately addresses patients' functional impairments and, quite possibly, critical public health concerns revolving around excessive sleepiness.[44]

In conclusion, this 12-week controlled study demonstrated that modafinil significantly improved objective and subjective measures of wakefulness, overall clinical condition, and functional outcomes in patients with nCPAP-treated obstructive sleep apnea/hypopnea syndrome who had residual excessive sleepiness. Furthermore, modafinil was generally well tolerated and did not adversely affect nighttime sleep or nCPAP use. These results confirm those of a previous 4-week controlled trial and support the use of modafinil as adjunct therapy to optimized nCPAP in patients with obstructive sleep apnea/hypopnea syndrome who still experience excessive sleepiness.

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