Modafinil as Adjunct Therapy for Daytime Sleepiness in Obstructive Sleep Apnea*

A 12-Week, Open-Label Study

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Study objectives: The purpose of this 12-week study was to evaluate the efficacy and safety of adjunct modafinil to treat excessive sleepiness in patients with obstructive sleep apnea (OSA) who experience residual sleepiness despite regular nasal continuous positive airway pressure (nCPAP) use.

Design: Twelve-week, open-label trial.

Setting: Twenty-two centers in the United States.

Patients: We studied 125 patients with moderate-to-severe OSA (i.e., respiratory disturbance index ≥ 15) before nCPAP therapy and residual daytime sleepiness (Epworth sleepiness scale [ESS] score ≥ 10) despite effective and regular nCPAP therapy. Patients were studied after completing a 4-week, double-blind, placebo-controlled trial of nCPAP plus modafinil for the treatment of residual daytime sleepiness.

Interventions and measurements: Patients received individually titrated doses of modafinil (200 to 400 mg qd). Sleepiness was assessed using the ESS, quality of life was evaluated using the Functional Outcomes of Sleep Questionnaire (FOSQ), and the overall clinical effect was indexed using the clinical global impression of change scale. Adverse events, nCPAP use, and vital sign measurements were also recorded.

Results: The significant improvements in daytime wakefulness and sleep-related functional status observed with modafinil treatment during the 4-week, double-blind study were maintained throughout 12 weeks of open-label treatment: week 12 ESS, 7.8 (4.7) vs 14.4 (3.1) at double-blind baseline; week 12 FOSQ, 3.3 (0.6) vs 14.4 (2.7) at double-blind baseline (mean [SD]). The percentage of patients rated as clinically improved increased from 83% after 1 week to ≥ 93% after 2 to 12 weeks of open-label treatment. Mean (SD) nCPAP use decreased from 6.3 (1.3) h/night at baseline to 5.9 (1.4) h/night (p = 0.004) during open-label treatment. The most common adverse events were headache (28%), anxiety (16%), and nervousness (14%).

Conclusions: Modafinil remained effective and well tolerated as an adjunct therapy for residual daytime sleepiness even after 12 weeks of daily dosing in patients with OSA receiving nCPAP therapy.

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Key words: continuous positive airway pressure; modafinil; obstructive sleep apnea; quality of life; sleepiness; wakefulness

Abbreviations: ESS = Epworth sleepiness scale; FOSQ = Functional Outcomes of Sleep Questionnaire; nCPAP = nasal continuous positive airway pressure; OSA = obstructive sleep apnea

Obstructive sleep apnea (OSA) affects an estimated 2 to 4% of middle-aged adults in the United States.1 Approximately 80% of cases of moderate-to-severe OSA in middle-aged adults may be undiagnosed.2 Pathophysiology entails upper airway collapse during sleep, which is associated with snoring, arousals, sleep fragmentation, daytime sleepiness,3,4 and diminished quality of life.5–7 Additionally, OSA is an independent risk factor for systemic hypertension3,4 and is linked to increased mortality.9–11

Nasal continuous positive airway pressure (nCPAP) is the preferred therapy for treating OSA.12,13 When used properly, nCPAP reduces apnea and hypopnea rate, often normalizes arterial blood oxygen saturation, decreases sleep fragmentation, and improves sleep quality.14,15 As a result, alertness, mood, cognitive function, and quality of life improve.15–17 nCPAP-related improvements in wakefulness depend largely on nightly use; however, some regular nCPAP users with adequate titration experience residual daytime sleepiness.16,18–23 Patient-specific etiology for residual sleepiness can be difficult to ascertain, but usually

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involve one or more of the following factors. First, patients who are regular users of nCPAP may have insufficient sleep syndrome, which leads to cumulative partial sleep loss and impaired alertness and performance. Second, sleep-disrupting abnormalities in the upper airway may persist even with nCPAP therapy. Third, years of sleep disturbances, hypoxemia, or both may have permanently altered the sleep-generating mechanisms. Finally, patients may have an undiagnosed coexisting sleep disorder, such as narcolepsy or CNS hypersomnia. Nonetheless, after psychoeducational and sleep hygiene attempts to maximize sleep are conducted and comorbid sleep pathologies are ruled out, some patients still experience residual daytime sleepiness that may benefit from adjunct pharmacologic treatment.

Modafinil is a novel wake-promoting agent that is chemically dissimilar to and has a pharmacologic profile that differs from CNS stimulants. Modafinil is an effective and well-tolerated treatment for excessive daytime sleepiness associated with narcolepsy,27–29 and is now the “standard” therapy. In patients with OSA, the efficacy and safety of modafinil for treating residual daytime sleepiness were evaluated in placebo-controlled studies, including one large-scale, double-blind trial. In a crossover pilot study of 30 patients with OSA, treatment with nCPAP and modafinil for 2 weeks improved objective measures of wakefulness but not self-reported sleepiness, quality of life, or cognitive function, compared to the nCPAP and placebo control groups. In a 12-week crossover study, modafinil treatment (with or without nCPAP therapy) significantly improved objectively measured alertness, self-reported sleepiness, and memory. Finally, in a 4-week, multicenter, placebo-controlled trial in which 157 patients with OSA who regularly used nCPAP were assessed, adjunct modafinil treatment significantly improved objective and self-reported daytime wakefulness, overall quality of life, and psychomotor performance. Thus, short-term treatment with nCPAP plus modafinil can reduce residual daytime sleepiness in patients with OSA.25,32 The purpose of the present study was to extend these findings by evaluating wakefulness and tolerability for 12 weeks in modafinil-treated patients with OSA who receive nCPAP therapy regularly.

**Materials and Methods**

This 12-week, open-label study was conducted at 22 centers in the United States. All centers received study approval from their institutional review boards. Patients completing a 4-week, double-blind, placebo-controlled study of nCPAP plus modafinil for the treatment of residual daytime sleepiness were eligible. Inclusion and exclusion criteria and the methods for determining nCPAP therapy effectiveness and utilization are described elsewhere. Briefly, patients were eligible if they had OSA (apnea/hypopnea index ≥ 15) and if they reported residual daytime sleepiness (Epworth sleepiness scale [ESS] ≥ 10), notwithstanding effective and regular nCPAP therapy (≥ 4 h/night on ≥ 5 of 7 nights).

All patients (aged 25 to 76 years) received open-label treatment with 200 mg qd of modafinil during week 1, followed by 400 mg qd of modafinil during week 2. At the end of week 2, the investigator determined the most desirable dose of modafinil for each patient (200 mg, 300 mg, or 400 mg) based on efficacy and tolerability; patients received this dose of modafinil during weeks 3 to 12. Sleepiness was evaluated using the ESS, and the change in disease severity was assessed using the clinical global impression of change scale. The clinical global impression of change was scored relative to the clinical global impression of severity rating at double-blind baseline (ie, baseline before the start of double-blind treatment). Daytime functional status and quality of life were assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ). A 30-item, self-administered questionnaire designed to assess the impact of disorders of excessive sleepiness on five domains of everyday living: activity level, vigilance, intimacy, general productivity, and social outcome. The ESS and FOSQ were administered at open-label baseline (ie, the end of the 4-week, double-blind study) and after 1 week, 2 weeks, 6 weeks, and 12 weeks of open-label treatment. Nightly nCPAP use was objectively monitored with the ResMed Elite device (Sydney, Australia) based on the total time the mask was worn. The mean duration of use was calculated at open-label baseline, for each week of open-label treatment, and for the entire open-label study. Adverse events were recorded throughout the study, together with their severity and relationship to study medication. Complete physical examinations, ECGs, clinical laboratory tests, and vital signs were assessed at open-label baseline and at week 12 of the open-label study. Patients were advised that nCPAP was necessary for the treatment of their condition and instructed to use nCPAP therapy whenever they slept.

All patients who received at least one dose of modafinil during the study were included in the efficacy and safety analyses. Mean double-blind baseline values for all efficacy parameters were calculated using data for the 125 patients who received open-label treatment. Comparisons of mean changes from double-blind baseline in ESS scores, FOSQ total scores, FOSQ subscale scores, and nCPAP use at open-label baseline and weeks 1, 2, 6,
and 12 of treatment were evaluated using paired t tests. Because all patients in this open-label study had received treatment with nCPAP plus either modafinil or placebo during the previous double-blind study, between-group comparisons at the end of the double-blind study and at all visits of the open-label study were performed using an analysis-of-covariance model. This analysis of covariance model used treatment and site as factors and the double-blind baseline value as a covariate. Comparisons of mean changes from double-blind baseline in vital sign measurements were performed using the Wilcoxon signed-rank test.

**RESULTS**

**Patients and Dosing**

In the 4-week, double-blind study that preceded this open-label study, 157 patients received treatment and 143 patients completed the study (91%). Of those patients completing the double-blind study, 125 patients entered the 12-week, open-label study (58 patients from the nCPAP plus modafinil treatment group and 67 patients from the nCPAP plus placebo group). Eighteen patients completed double-blind treatment but did not continue with open-label modafinil treatment; of these, 8 patients were from the nCPAP plus modafinil group and 10 patients were from the nCPAP plus placebo group. Patients did not provide reasons for declining open-label treatment continuation. One hundred five patients (84%) completed 12 weeks of open-label treatment.

The baseline characteristics of patients enrolled in the open-label study are listed in Table 1. On entry into the double-blind study, 80% of patients were rated as moderately to markedly ill, and all patients were receiving effective and regular nCPAP therapy, as indicated by a mean (SD) apnea/hypopnea index of 2.2 (2.3) events per hour and a mean duration of nCPAP use of 6.3 (1.3) h/night.

In accordance with the study protocol, the vast majority of patients enrolled in the open-label phase of the study received nCPAP plus modafinil 200 mg qd during week 1 (91%) and nCPAP plus modafinil 400 mg qd during week 2 (83%). At week 12, 17% of the patients were receiving 200 mg, 19% were receiving 300 mg, and 64% were receiving 400 mg of modafinil.

**Daytime Sleepiness**

At weeks 1, 2, 6, and 12 of open-label treatment with nCPAP plus modafinil, patients achieved significant improvements in wakefulness compared with double-blind baseline ratings (all p < 0.001; Fig 1). As early as week 1 of open-label treatment with nCPAP plus modafinil, mean ESS scores for patients previously treated with nCPAP plus placebo during the double-blind study (9.1 [4.9]) became comparable to scores for patients treated with nCPAP plus modafinil (9.3 [4.8]). Throughout the 12 weeks of open-label treatment with nCPAP plus modafinil, the significantly improved wakefulness observed during double-blind treatment with nCPAP plus modafinil was maintained.

**Overall Clinical Condition**

At the end of the 4-week, double-blind study, the percentage of the 125 patients enrolled in the open-label study who were rated as clinically improved was significantly greater in the nCPAP plus modafinil group than in the nCPAP plus placebo group (73% vs 31%, p < 0.001; Fig 2). After 1 week of open-label treatment with nCPAP plus modafinil, 83% of the patients were rated as clinically improved (84% of the patients who had previously received treatment with nCPAP plus placebo during the double-blind study and 81% of patients who had received nCPAP and modafinil during the double-blind study). For the remainder of the 12-week, open-label study, ≥ 93% of the patients were rated as clinically improved. The percentage of patients rated as “much improved” or “very much improved” was 47% at week 1, 72% at week 2, 74% at week 6, and 71% at week 12.

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### Table 1—Baseline Characteristics of the Patients Entering the 12-Week, Open-Label Study*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), yr</td>
<td>50 (28–76)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>99 (79)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Mean weight (range), lb</td>
<td>241 (114–401)</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>35 (7)</td>
</tr>
<tr>
<td>Mean heart rate (SD), beats/min</td>
<td>73 (11)</td>
</tr>
<tr>
<td>Mean systolic BP/diastolic BP</td>
<td></td>
</tr>
<tr>
<td>(SD), mm Hg</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>128/81 (10/8)</td>
</tr>
<tr>
<td>Standing</td>
<td>127/81 (12/8)</td>
</tr>
<tr>
<td>Disease severity (CGI-S)†</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Borderline ill</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Slightly ill</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Moderately ill</td>
<td>53 (57)</td>
</tr>
<tr>
<td>Markedly ill</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Mean respiratory disturbance</td>
<td></td>
</tr>
<tr>
<td>index (SD), events/h</td>
<td>2.2 (2.3)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.†CGI-S (clinical global impression of severity) ratings, obtained at baseline of the double-blind, placebo-controlled study, were available for 92 of the 125 patients.
**Sleep-Related Functional Status and Quality of Life**

Significant improvements ($p < 0.001$) from double-blind baseline were observed in the FOSQ total score and in the FOSQ subscale scores for activity level, vigilance, intimacy, general productivity, and social outcome (Fig 3). These improvements were noted as early as week 1 of open-label treatment and were maintained throughout 12 weeks of open-label treatment. The mean changes from double-blind baseline in FOSQ scores at any week of the open-label study did not differ significantly as a function of treatment group in the previous double-blind study.

**nCPAP Use**

Mean (SD) nCPAP use during the 12-week open-label study was 5.9 (1.4) h/night compared with 6.3 (1.3) h/night at double-blind baseline; the mean change from double-blind baseline was statistically significant ($p = 0.004$). Values for the mean duration of nCPAP use during week 1 and throughout the entire open-label treatment period were similar for patients who received treatment with nCPAP plus modafinil and those receiving nCPAP plus placebo during the double-blind study.

**Safety Outcomes**

During 12 weeks of open-label treatment with nCPAP plus modafinil, the most common adverse events of all causes were headache (28%), anxiety (16%), nervousness (14%), insomnia (11%), and nausea (11%) [Table 2]. The vast majority (98%) of adverse events were mild or moderate. Twenty patients (16%) discontinued treatment during the 12-week, open-label study; only 1 patient discontinued (< 1%) because of insufficient efficacy. Thirteen patients (10%) discontinued because of adverse events of all causes; 8 patients (6%) discontinued treatment because of adverse events judged to be related to treatment. Two patients withdrew because of severe adverse events (anxiety and palpitation, headache). Eight patients (6%) reported cardiovascular adverse events (hypertension, $n = 4$; palpitation, $n = 2$; tachycardia, $n = 2$), with one case of palpitation rated as severe. Small increases from double-blind baseline were found for heart rate at week 1 (2.1 beats/min) and for standing diastolic BP at week 6 (1.9 mm Hg) and week 12 (1.9 mm Hg) of open-label treatment (all $p \leq 0.03$). However, these changes were not judged to be clinically significant. No differences were observed in laboratory param-

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*Figure 1. Mean (SD) ESS scores at double-blind (DB) baseline (BL), at the end of the double-blind study, and during 12 weeks of open-label (OL) treatment with nCPAP and modafinil according to treatment during double-blind study. Closed and open circles represent the mean scores for those patients who received modafinil and nCPAP and those who received placebo and nCPAP, respectively, during the double-blind study. $^{*} p < 0.001$ for the mean change from double-blind baseline. $^{†} p < 0.001$ for the mean change from double-blind baseline nCPAP plus modafinil vs double-blind baseline nCPAP plus placebo.*
eters, ECGs, or physical examinations between double-blind baseline and week 12 of open-label treatment.

Discussion

This open-label study, conducted as an immediate follow-up to a double-blind study, demonstrated the continued efficacy and safety of adjunct modafinil in patients with OSA and residual sleepiness despite regular nCPAP therapy. The improved wakefulness demonstrated during 4 weeks of double-blind treatment with nCPAP plus modafinil was maintained throughout 12 weeks of open-label treatment. Mean ESS scores remained below 10, the upper limit of normal. This sustained effect of modafinil over 16 weeks of treatment indicates the lack of the development of tachyphylaxis. Patients who had received nCPAP with placebo in the double-blind study experienced improved wakefulness within 1 week of modafinil dosing. This improvement was maintained throughout the 12-week study. The vast majority of patients (≥93%) demonstrated overall clinical improvement. The percentage of patients rated as much improved or very much improved was somewhat higher (71 to 74%) than that found in an open-label study of patients with narcolepsy (49 to 59%). Thus, modafinil clearly provided clinical benefit as adjunct to nCPAP. Furthermore, the modafinil-related FOSQ improvements in this 12-week trial indicated possible productivity improvements in patients with OSA.

During the 12-week open-label study, the mean (SD) duration of nCPAP use remained relatively high (5.9 [1.4] h/night); however, declines were noted. This differs from prior results of no differences in nCPAP utilization between patients receiving modafinil vs placebo, but replicates the crossover study of 30 patients, where a small (approximately 12 min) but significant reduction in nCPAP use occurred after 2 weeks of modafinil treatment compared with placebo. Generally, nCPAP should be used throughout each sleep period to increase the likelihood of recovery of sleep loss from untreated sleep-disordered breathing and to prevent sleep debt. Additionally, modafinil does not treat the underlying pathophysiology of airway collapse in OSA, so it is not expected that modafinil would have a therapeutic role in patients who are not receiving adequate prophylactic treatment for apneas and hypopneas.

Although it is difficult to ascertain the specific

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22001/)

**Figure 2.** Percentage of patients rated as clinically improved at the end of the double-blind study and during 12 weeks of open-label treatment with nCPAP plus modafinil according to treatment during the double-blind study. Closed and open circles represent the percentage of patients who received modafinil and nCPAP and those who received placebo and nCPAP, respectively, during the double-blind study. *p < 0.001 for the percentage of nCPAP plus modafinil patients who were improved vs those receiving nCPAP plus placebo at the end of the double-blind study. See Figure 1 legend for expansion of abbreviations.
cause of residual sleepiness for an individual patient, daytime sleepiness refractory to adherent use of nCPAP raises concern among patients and their physicians. Obvious contributors may be underutilization and/or misuse of nCPAP. Methodology to monitor nCPAP use should be an integral component of any regimen involving long-term nCPAP therapy in OSA patients because of the clinical consequences of hypoxemia potentially due to small reductions in nCPAP use. Simple educational and monitiorial interventions may also help to improve nCPAP use. Minor adjustments to the nCPAP system (ie, humidification, mask fit) and treatment of nasal congestion also may improve use, especially when initiated during early nCPAP therapy.

Another possible contributor for continuing residual sleepiness in patients who are adherent to nCPAP concerns the efficacy of nCPAP rather than its regular use. Results of three placebo-controlled, crossover studies evaluating nCPAP without adjunctive therapy in OSA patients are inconsistent regarding its effects on sleepiness, cognition, and health-related quality of life.

The most common adverse events reported here were similar in nature to those reported previously. The discontinuation rate related to adverse events was comparable to that reported in the double-blind OSA study. The lack of clinically meaningful changes in vital signs or ECG recordings is in agreement with results obtained in the 4-week, double-blind OSA study and a study of long-term

Table 2—Incidence of the Most Common Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n = 50)</th>
<th>Modafinil (n = 77)</th>
<th>12-Week Open Label (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9 (11)</td>
<td>18 (23)</td>
<td>35 (28)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1)</td>
<td>5 (6)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2 (3)</td>
<td>9 (12)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (4)</td>
<td>5 (6)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (3)</td>
<td>6 (8)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (3)</td>
<td>5 (6)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Pain</td>
<td>2 (3)</td>
<td>0</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

*Data are presented as No. of patients (%).
†Events that occurred in ≥ 5% of patients during open-label treatment.

Figure 3. Mean (SD) FOSQ subscale scores at double-blind baseline and after 12 weeks of open-label treatment with nCPAP plus modafinil. *p < 0.001 for the mean change from double-blind baseline. See Figure 1 legend for expansion of abbreviations.
modafinil treatment in patients with daytime sleepiness associated with narcolepsy,36

Safety and efficacy data obtained from this study and from clinical trials conducted in patients with narcolepsy28,29,36,47,48 indicate that modafinil is safe acutely and more chronically when used to treat sleepiness associated with primary sleep disorders. Data from short-term, double-blind studies28,29,36,47 of modafinil in patients with narcolepsy were highly predictive of subsequent 40-week, open-label data. Additionally, 40-week data were predictive of 58-week and 136-week data with regard to safety and continued efficacy.36,47,48 Furthermore, data from the 4-week, double-blind trial of adjunct modafinil in patients with OSA who regularly received nCPAP was highly predictive of the results of this current study,25 suggesting that efficacy can be sustained for at least 3 months. Controlled trials should be conducted to confirm and extend these findings in even more chronic models.

In conclusion, patients with OSA who received treatment with modafinil plus nCPAP maintained significant improvements in daytime wakefulness, overall clinical condition, and sleep-related functional status and quality of life for up to 4 months of combined double-blind and open-label treatment. Modafinil may be an effective and well-tolerated adjunct treatment for the chronic management of residual daytime sleepiness in patients with OSA who experience this sleepiness despite regular nCPAP use.

APPENDIX

Members of the United States Modafinil in Sleep Apnea Multicenter Study Group are Jed E. Black, Stanford, CA; Richard K. Bogan, Columbia, SC; Bruce Corser, Cincinnati, OH; William Devor, San Diego, CA; Russell Dodge, Tucson, AZ; Helene Emsellem, Washington, DC; Milton Erman, La Jolla, CA; Neil Feldman, St. Petersburg, FL; Stephen C. Hardy, Charlotte, NC; Max Hirshkowitz, Houston, TX; Daniel Loube, Washington, DC; Jean Matheson, Boston, MA (the use of the GRC facility is acknowledged and appreciated); Allan I. Pack, Philadelphia, PA; Ralph Pascualy, Seattle, WA; Russell Rosenberg, Atlanta, GA; R. Bart Sangal, Troy, MI; Helmut Schmidt, Dublin, OH; Wolfgang Schmidt-Nowara, Dallas, TX; Jonathan R. L. Schwartz, Oklahoma City, OK; Kingman P. Strohl, Cleveland, OH; Joyce A. Walden, New York, NY; Phillip Westbrook, Redlands, CA.

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