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Original article

Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP

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Abstract

Background: Some patients with obstructive sleep apnea/hypopnea syndrome (OSA/HS) who are regular users of nasal continuous positive airway pressure (nCPAP) therapy continue to experience daytime sleepiness that impairs performance and quality of life. A randomized, double-blind, placebo-controlled, parallel-group study was conducted to determine the effect of modafinil on sustained attention performance and functional quality of life in OSA/HS patients with residual daytime sleepiness, who were regular users of nCPAP therapy.

Methods: Seventy-seven patients received modafinil (200 mg/day, week 1; 400 mg/day, weeks 2–4) and 80 patients received matching placebo once daily for 4 weeks. Sustained attention performance on the psychomotor vigilance task (PVT) and functional status and quality of life using the Functional Outcomes of Sleep Questionnaire (FOSQ) were measured.

Results: The frequency of lapses of attention during PVT performance was significantly decreased, and both the median and slowest reaction times were significantly improved in patients receiving nCPAP plus modafinil compared with those receiving nCPAP plus placebo ($P = 0.010$ for the number of lapses [transformed], $P = 0.023$ for the median reaction time, and $P = 0.014$ for the reciprocal of the 10% slowest reaction times). Treatment with nCPAP plus modafinil significantly improved the FOSQ total score (weeks 1 and 4), the vigilance subscale score (weeks 1 and 4), and the activity level subscale score (week 4) compared with treatment with nCPAP plus placebo (all $P < 0.05$).

Conclusions: Consistent with previous results for objective and subjective measures of sleepiness, modafinil used adjunctively improved performance on a test of behavioral alertness and reduced functional impairments in patients with OSA/HS who were regular users of nCPAP therapy but still experiencing sleepiness.

Keywords: Modafinil; nCPAP; Obstructive sleep apnea; PVT performance; Sustained attention; Functional status; Quality of life

1. Introduction

Daytime sleepiness is a serious and debilitating symptom of many sleep disorders, including narcolepsy and obstructive sleep apnea/hypopnea syndrome (OSA/HS). Deficits in intellectual function, attention or vigilance, memory, executive and motor function, and motivation also have been demonstrated in patients with OSA/HS [1–10]. Moreover, untreated OSA/HS is associated with an increased risk for cardiovascular disease [11,12], increased rates of accidents [13–22], and increased mortality [23–26].

The impairments in neuropsychological function experienced by individuals with OSA/HS contribute to decreased quality of life. The results of various studies [27–33] have demonstrated that patients with OSA/HS have significantly poorer health status compared with that of healthy control subjects, as measured with both generic (i.e. the Medical Outcomes Study short-form health survey (SF-36) [34] and the Nottingham Health Profile) [35] and disease-specific instruments (i.e. the FOSQ) [33]. Moreover, SF-36 scores were significantly related in a dose–response manner to the apnea–hypopnea index (AHI) after adjusting for age, sex, body-mass index, smoking status, alcohol use, and cardiovascular history [36]. These AHI-related decreases in SF-36 scores were comparable to

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those reported in arthritis, angina, hypertension, and diabetes [37].

Nasal continuous positive airway pressure (nCPAP) therapy is the standard non-surgical treatment for the management of clinically significant OSA/HS [38,39]. Proper use of nCPAP manages apneas and hypopneas, eliminates hypoxia, restores normal sleep architecture, and significantly improves subjective and objective measures of wakefulness [40–50]. Improvements in reaction times (RTs), driving skills, cognitive performance, and quality of life also have been reported with nCPAP therapy [23,31, 36,40–43,45,46,51–53]. Despite the proven efficacy of nCPAP in clinical trials, some patients who are regular users of nCPAP may experience inadequate or compromised sleep and residual daytime sleepiness [45–49]. The prevalence of and reasons for residual daytime sleepiness in some regular users of nCPAP therapy remain unknown. To manage persistent sleepiness in patients with OSA/HS who are regular users of nCPAP therapy, pharmacological treatment with central nervous system (CNS) stimulants has been described [54]. However, the benefit-to-risk ratio of CNS stimulants for the treatment of daytime sleepiness is not well documented in the medical literature. Cardiovascular side effects (i.e. tachycardia and hypertension) [55] of CNS stimulant treatment that have been reported in patients with daytime sleepiness associated with narcolepsy may be relevant because of the increased risk for cardiovascular disease in patients with OSA/HS [11,12].

Modafinil, a novel wake-promoting agent that appears to be chemically and pharmacologically distinct from CNS stimulants, is effective for improving wakefulness in a variety of clinical models. Modafinil significantly improves wakefulness in patients with narcolepsy [56–58], and has been recommended by the American Academy of Sleep Medicine as a 'standard' treatment for this patient population [55]. In patients with excessive daytime sleepiness associated with narcolepsy, treatment with modafinil improves health-related quality of life, with significant improvements in the SF-36 domains of vitality, physical functioning, role limitations due to physical problems, role limitations due to emotional problems, and social functioning, and in the mental health summary scale [59]. Modafinil is well tolerated and its efficacy is maintained during long-term treatment [60,61]. Modafinil has negligible sympathomimetic activity, does not adversely affect nighttime sleep, and is associated with a low frequency of adverse cardiovascular events [56–58]. The abuse potential for modafinil is low, and there is no clinical evidence for the development of dependence or tolerance [60,62,63].

Its efficacy and safety profiles and preliminary clinical trial results suggest that modafinil may be a promising adjunct treatment for residual daytime sleepiness in patients with OSA/HS. Four preliminary double-blind studies of modafinil in OSA/HS patients have been reported [64–67]. The results of these studies suggest that modafinil (either with or without nCPAP therapy) may improve wakefulness, cognitive performance, and memory without affecting nighttime sleep parameters, blood pressure, or heart rate. The present randomized, placebo-controlled, parallel-group, multicenter study was conducted to evaluate the efficacy and safety of modafinil as an adjunct treatment for residual daytime sleepiness in a large cohort of OSA/HS patients who were effectively treated with and regular users of nCPAP therapy. The results of this study on the effects of adjunct modafinil treatment on objective and subjective measures of daytime sleepiness and on overall clinical condition have been reported previously [68]. Briefly, both subjective and objective measures of daytime wakefulness and physician-determined disease severity were significantly improved with nCPAP plus modafinil treatment. Importantly, modafinil did not have a clinically significant effect on nCPAP use or cardiovascular parameters. Presented here are additional results from this trial [68], involving assessment of the effects of nCPAP plus modafinil on sustained attention performance and sleep-related functional status and quality of life.

2. Methods

2.1. Study design and patients

A double-blind, randomized, placebo-controlled, parallel-group study was conducted at 22 centers in the United States, with the approval of the local institutional review boards. The study design and patient selection criteria have been described previously [68]. The study included a 1-day screening period; a 2-day period to confirm nCPAP effectiveness; a 3-week period to monitor nCPAP use; a 2-day period for baseline assessments; and a 4-week, double-blind treatment period (Fig. 1).

Inclusion criteria included moderate-to-severe OSA/HS (i.e. respiratory disturbance index (RDI) of ≥ 15 before or in

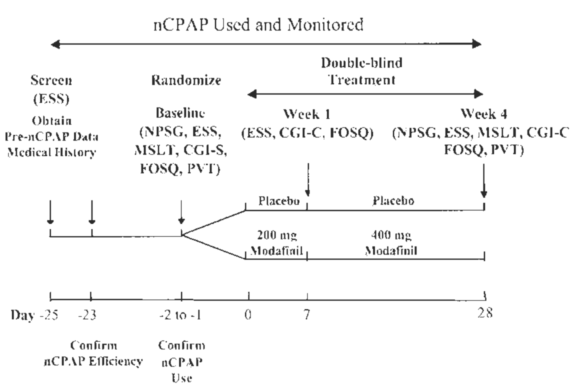

Fig. 1. Study design. CGI-C, Clinical Global Impression of Change; GGI-S, Clinical Global Impression of Severity; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; MSLT, Multiple Sleep Latency Test; nCPAP, nasal continuous positive airway pressure; NPSG, nocturnal polysomnography; PVT, Psychomotor Vigilance Test.

the absence of regular nCPAP use), and residual daytime sleepiness (i.e. Epworth Sleepiness Scale [ESS] [69] score ≥ 10 at baseline) despite the use of nCPAP therapy for at least 2 months before screening. Patients meeting these and other previously published inclusion criteria [68] underwent a 21-day run-in period with a therapeutic level of nCPAP. nCPAP effectiveness was monitored at home on 2 consecutive nights with an AutoSet T device in the manual (constant pressure) mode that operated at each patient's prescribed therapeutic level. AutoSet T data recorded included median pressure, median leak, maximum leak, mask on time, time in apnea, apnea index, and hypopnea index. Effective use of nCPAP was defined as an AHI of < 10 and with a $> 50\%$ reduction versus the historical pre-nCPAP AHI as assessed with nocturnal polysomnography. Patients who were effectively treated with nCPAP at baseline and who were regular users of nCPAP, as defined by ≥ 4 h use per night on ≥ 5 of 7 nights [70], were randomized to treatment. All participants provided written informed consent and were compensated for their participation. As in usual clinical practice, the importance of regular nCPAP use was stressed and patients were instructed to always use nCPAP when sleeping. At baseline, patients randomized to modafinil (200 mg/day, week 1; 400 mg/day, weeks 2–4) plus nCPAP ($n = 77$) or matching placebo plus nCPAP ($n = 80$) were instructed to take a once-daily oral dose after breakfast.

2.2. Assessments

2.2.1. Psychomotor vigilance performance

Behavioral alertness was assessed using performance on the psychomotor vigilance task (PVT) [71]. For this test of sustained attention, patients were instructed to respond to the appearance of a visual stimulus by pushing a response button as quickly as possible. The stimulus was a red light-emitting diode display of a three-digit millisecond counter appearing in a window of the portable PVT-192 device (supplied by Ambulatory Monitoring, Inc., Ardsley, NY). During each 10-min session, visual stimuli appeared at variable intervals of 2–10 s. From each PVT trial, reaction times (RTs) were collected and 14 performance variables were extracted using a software program [71]. The performance variables included the number of lapses (i.e. RT ≥ 500 ms); number of lapses (x) transformed by $(\sqrt{x} + \sqrt{(x+1)})$; cumulative lapse time; shifts in the duration of responses in the lapse domain (i.e. mean reciprocal of the 10% slowest RTs); median RT; shifts in optimum RTs (i.e. mean of the 10% fastest RTs); y intercept of the least-squares regression line for 1/RT across 10 min; slope of the least-squares regression line for 1/RT across 10 min; and the coefficient of determination (R^2) for the least-squares regression line for 1/RT across 10 min. The transformations performed on the number of PVT lapses and the duration of PVT responses in the lapse domain were applied to normalize the distributions of responses in each of these areas, as per previous research [71–76]. This was done blind to treatment condition. A visual analog rating of sleepiness was obtained immediately before and after each 10-min PVT performance trial. At screening, patients completed a PVT trial for adaptation and practice purposes. On each study day (baseline and week 4), patients participated in four PVT test sessions that were conducted at 2-h intervals, with the first session beginning at approximately 08:30 h.

2.2.2. Sleep-related functional status

A component of quality of life, sleep-related functional status was assessed at baseline, week 1, and week 4 using the Functional Outcomes of Sleep Questionnaire (FOSQ), a self-administered, 30-item validated instrument that assesses the impact of disorders of excessive sleepiness on five domains of everyday living and quality of life (i.e. activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome) [33]. The range of scores for each subscale was 1–4, with lower scores indicating greater dysfunction. FOSQ total scores, calculated by summing the five subscale scores, could range from 5 to 20.

2.2.3. Sleepiness and polysomnography

Daytime sleepiness was measured subjectively using the ESS (baseline, week 1, and week 4) [69] and objectively using the Multiple Sleep Latency Test (MSLT) (baseline and week 4) [77]. Polysomnography was performed on the evening before administration of the MSLT (baseline and week 4). The level of illness at baseline was established using the Clinical Global Impression of Severity (CGI-S) [78]. nCPAP use was monitored during double-blind treatment as described previously [68]. Treatment-emergent adverse events were recorded throughout the study.

2.3. Statistical analyses

Treatment group comparisons of continuous demographic variables were conducted using two-way analysis of variance (ANOVA), with treatment and center as main effects. Between-group differences in categorical demographic variables were determined using Fisher's exact test. Based on published studies, three of the 14 PVT variables analyzed were specified a priori for testing the hypothesis that adjunct modafinil treatment would improve sustained attention performance relative to placebo treatment. These were the number of lapses (transformed); the duration of lapses (i.e. reciprocal of the 10% slowest RTs); and the median RT. The mean value of the second, third, and fourth PVT trials within each assessment day was calculated, and the mean changes from baseline for patients receiving nCPAP plus modafinil and for those receiving nCPAP plus placebo were compared using a paired t-test and a Mann–Whitney test. The first PVT trial (at baseline and after treatment) was not included in the analyses because it showed a marked learning effect at baseline, and it was conducted at approximately 08:30 h, in close temporal proximity to the ingestion of placebo or modafinil, when active medication effects would not be expected to be evident.

PVT data collected at baseline and week 4 were available for 124 patients; however, data files for 20 patients were determined to be electronically corrupted and unreliable (e.g. RTs were equal to 0 ms). The corrupted data for all but one of these patients were acquired at only two of the 22 study sites. Discovery of the corrupted data and exclusion of the affected PVT trials from analyses occurred prior to unblinding. Thus, analyses of PVT data were based on 104 patients (nCPAP plus placebo, $n = 58$; nCPAP plus modafinil, $n = 46$).

The mean change from baseline in the total FOSQ score and in each of the five subscale scores was analyzed at weeks 1 and 4 and comparisons between treatment groups were made using an analysis of covariance (ANCOVA) model, with treatment and center as factors and baseline value as a covariate. Between-group comparisons of the incidence rates of treatment-emergent adverse events and discontinuation rates were performed using a chi-square or two-tailed Fisher's exact test.

Table 1
Patient characteristics: baseline (with therapeutic nCPAP therapy) and historical (pre-nCPAP) data

Characteristic	Placebo ($n = 80$)	Modafinil ($n = 77$)
Baseline (with nCPAP therapy) data		
Mean age, years (range)[a]	50 (28–72)	50 (32–76)
Sex; n (%)		
Male	59 (74)	61 (79)
Female	21 (26)	16 (21)
Mean weight, lb (range)	239 (114–380)	245 (162–401)
Mean BMI, kg/m^2 (SD)	35.0 (7.4)	35.9 (7.3)
CGI-S, n (%)[b]		
Normal	4 (7)	5 (9)
Borderline ill	2 (3)	3 (5)
Slightly ill	5 (9)	4 (7)
Moderately ill	38 (66)	31 (54)
Markedly ill	9 (16)	14 (25)
RDI, events/h (S.D.)	2.1 (2.3)	2.5 (2.6)
Mean ESS (S.D.)	14.4 (3.2)	14.2 (2.9)
Mean MSLT, min (S.D.)	7.5 (4.6)	7.4 (4.8)
Historical (pre-nCPAP) data[c]		
Mean RDI, events/h (S.D.)	46.8 (33.7)	53.7 (30.0)
Mean minimum % O_2 saturation (S.D.)	79.2 (10.7)	77.6 (13.8)

BMI, body-mass index; CGI-S, clinical global impression of severity; ESS, Epworth Sleepiness Scale; MSLT, mean sleep latency test; NSPG, nocturnal polysomnography; RDI, respiratory disturbance index.

[a] Six patients were >65 years of age at study entry; patients with this minor protocol violation were included in the intention-to-treat analysis.

[b] CGI-S scores were available for 115 of 157 patients.

[c] Pre-nCPAP data were provided at screening and included historical data from patient medical records obtained at diagnostic work-up for OSA/HS.

3. Results

3.1. Patient characteristics

Of 232 patients screened, 157 qualified patients with residual daytime sleepiness were randomized to double-blind treatment at baseline. Seventy-five patients were excluded for reasons described elsewhere [68]. Of 157 patients randomized, 143 patients (91%) completed the study. In the nCPAP plus placebo group, 77 of 80 patients (96%) completed the study compared with 66 of 77 patients (86%) in the nCPAP plus modafinil group ($P = 0.015$). Baseline characteristics, including age, sex, weight, and body-mass index, were not significantly different between the two groups (Table 1). Most patients in the two treatment groups were categorized as moderately or markedly ill, with the percentage of patients in each severity category of the CGI-S scale similar between the treatment groups. Mean baseline ESS scores and MSLT sleep latency times also were similar between the two treatment groups. The mean RDI decreased from approximately 50 events/h before nCPAP therapy (determined from medical histories) to approximately two to three events per hour at baseline after 3 weeks of regular nCPAP use.

3.2. Sustained-attention PVT performance

At baseline, there were no significant differences in PVT variables between the two treatment groups. Treatment with nCPAP plus modafinil significantly improved sustained attention performance on the PVT, as shown by significant decreases in the number of PVT performance lapses and the median RT and a significant increase (improvement) in the reciprocal of the 10% slowest RTs compared with the corresponding values for those receiving nCPAP plus placebo (Table 2). After 4 weeks of double-blind treatment, the statistical significance for the between-group difference in the mean change from baseline was $P = 0.010$ for the number of lapses (transformed); $P = 0.023$ for the reciprocal of the 10% slowest RTs; and $P = 0.010$ for the median RT. Among the remaining PVT variables, the y-intercept of the time-on-task regression line also discriminated between patients receiving nCPAP plus modafinil and those receiving nCPAP plus placebo ($P = 0.005$). Trends toward improvement with nCPAP plus modafinil were also observed for the 10% fastest RTs ($P = 0.051$) and cumulative lapse time ($P = 0.08$).

3.3. Sleep-related functional status

After 1 week and 4 weeks of double-blind treatment, nCPAP plus modafinil significantly improved FOSQ total scores compared with treatment with nCPAP plus placebo ($P < 0.05$; Fig. 2). The mean change from baseline in the FOSQ vigilance subscale score showed significant

Table 2
Psychomotor vigilance task (PVT) performance variables

Variable	Mean change from baseline[a] (SEM)		P value
	nCPAP + placebo	nCPAP + modafinil	
Number of lapses	0.346 (0.550)	−0.814 (0.426)	0.112
Number of lapses (transformed)[b]	0.118 (0.171)	−0.532 (0.177)	0.010
1/10% Slowest RTs[b], 1/ms	0.004 (0.042)	0.181 (0.059)	0.023
Median RT[b], ms	4.936 (4.777)	−10.343 (4.424)	0.010
10% Fastest RTs, ms	2.536 (1.827)	−3.500 (2.564)	0.051
Cumulative lapse time, ms	0.280 (0.697)	−1.964 (1.122)	0.080
Y-intercept, 1/ms	−0.077 (−0.046)	0.119 (0.051)	0.005
Regression slope[c]	0.005 (0.005)	0.005 (0.006)	0.948
Regression R^{2}[d]	−0.012 (0.025)	−0.063 (0.025)	0.167
Change over 10 min (%)	0.783 (2.149)	3.084 (2.028)	0.447
Distribution skew	−0.006 (0.006)	0.002 (0.009)	0.430
Number of false starts	−0.061(0.254)	0.408 (0.468)	0.355
VAS pretest	0.120 (0.250)	0.018 (0.305)	0.793
VAS posttest	−0.017 (0.234)	−0.166 (0.365)	0.721

RT, reaction time; VAS, visual analog rating of sleepiness.
[a] Mean for post-treatment trials 2–4 minus the mean of pre-treatment trials 2–4.
[b] Designated a priori as key PVT variable to test the hypothesis that performance would be significantly improved by treatment with modafinil compared with placebo.
[c] Regression slope = slope of the least-squares regression line for 1/RT across 10 min.
[d] Regression R^2 = coefficient of determination for the least-squares regression line for 1/RT across 10 min.

improvement at week 1 for patients receiving nCPAP plus modafinil treatment relative to those receiving nCPAP plus placebo treatment ($P = 0.032$). After 4 weeks of treatment with nCPAP plus modafinil, the mean change from baseline in the scores for the activity level and vigilance subscales of the FOSQ also demonstrated significant improvement when compared with those for patients receiving nCPAP plus placebo ($P < 0.05$) (Fig. 3). For the FOSQ subscales assessing general productivity, social outcome, and intimacy/sexual relations, the mean changes from baseline in scores were not significantly different between the two treatment groups at weeks 1 or 4; however, the mean changes from baseline in these subscale scores were consistently greater for the nCPAP plus modafinil group.

3.4. Adverse events

Treatment with modafinil was well tolerated. The most common treatment-emergent adverse events of all causes were headache (nCPAP plus modafinil, 23%; nCPAP plus placebo, 11%; $P = 0.044$) and nervousness (nCPAP plus modafinil, 12%; nCPAP plus placebo, 3%; $P = 0.024$). The adverse events for both groups were primarily mild or moderate in nature. One case of chest pain in the nCPAP

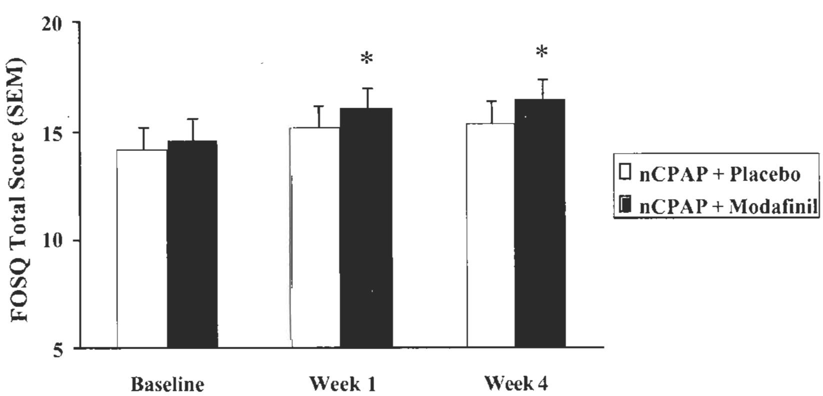

Fig. 2. FOSQ total scores at baseline (nCPAP therapy only) and after treatment with nCPAP plus modafinil or nCPAP plus placebo. *$P < 0.05$ for the mean change from baseline versus nCPAP plus placebo.

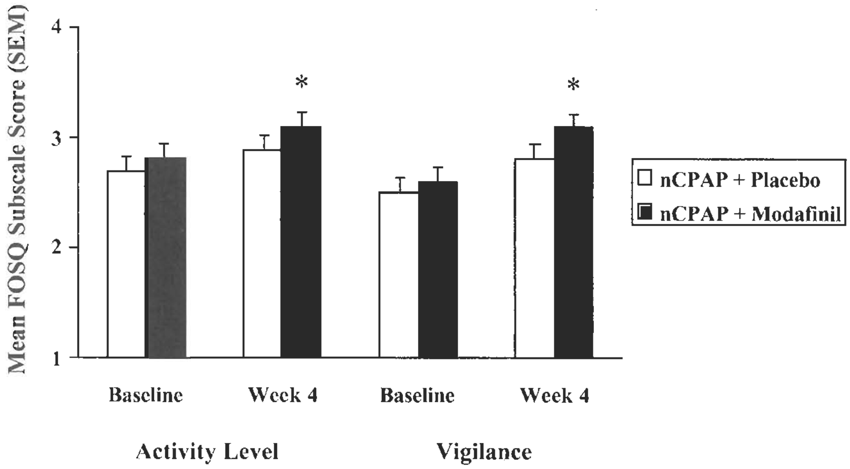

Fig. 3. FOSQ activity level and vigilance subscale scores at baseline (nCPAP therapy only) and after 4 weeks of treatment with nCPAP plus modafinil or nCPAP plus placebo. $^*P < 0.05$ for the mean change from baseline versus nCPAP plus placebo.

plus modafinil group was classified as a serious adverse event that was considered by the investigator to be not related to treatment. Eight of 77 (10%) discontinued treatment with modafinil and 1 of 80 (1%) discontinued treatment with placebo because of adverse events ($P = 0.016$).

4. Discussion

When used as an adjunctive therapy for patients who have sleepiness refractory to nCPAP treatment, modafinil had beneficial effects on daytime functioning as assessed by the FOSQ, and on performance requiring sustained attention as measured by the PVT. These functional improvements were consistent with the previously reported reductions in objective sleepiness as measured by MSLT, and subjective sleepiness as assessed by ESS in these same patients with OSA/HS (e.g. mean [SD] ESS scores improved from 14.2 [2.9] at baseline to 9.6 [4.8] at study endpoint for patients receiving nCPAP plus modafinil [68]). Improvements in ESS scores are especially germane to a discussion of sustained attention performance, and functional status, as the ESS appears to be associated with quality-of-life outcomes [59,79], and a significant correlation between ESS scores and quality-of-life scores has been reported for generally healthy subjects [80], and for patients with OSAS/HS [81]. The improvements in sustained attention performance and quality of life demonstrated with nCPAP plus modafinil treatment in the present study also are generally consistent with the results of a crossover study of OSA/HS patients with nCPAP-resistant daytime sleepiness [66], and with results of three placebo-controlled pilot trials in which modafinil was used in the absence of nCPAP therapy in patients with OSA/HS [64,65,67]. However, since modafinil does not treat the underlying pathophysiology of airway collapse in OSA/HS disorder, it is doubtful that it has a therapeutic role in patients who are not being effectively treated with another therapy for prevention of apneas and hypopneas.

In terms of the effects observed in the nCPAP plus modafinil intervention in the present study, we believe that the improvements in PVT performance and in the FOSQ were the result of modafinil-related improvements in the stability of wakefulness [82]. The PVT has been shown to be highly sensitive to levels of behavioral alertness associated with excessive sleepiness in patients with sleep apnea [72,73,83,84], and in healthy adults undergoing either total or partial sleep deprivation [75,85,86]. Similarly, the FOSQ components specifically affected by modafinil intervention were the vigilance subscale, which consists of behaviors requiring sustained attention (e.g. driving, television); and the activity subscale, which consists of items asking about the extent to which sleepiness interferes with family, work and personal activities [33].

Daytime sleepiness refractory to adherent use of nCPAP is of concern to patients with OSA/HS and their physicians, as even modest levels of sleepiness may have a substantial negative effect on general health [80], quality of life [80], and safety [13,17]. Although it may be difficult to ascertain the cause of this sleepiness for a given patient, there are several potential factors that may contribute to residual daytime sleepiness. An obvious candidate is underutilization of nCPAP. Even patients who are regular users of nCPAP (with appropriate titration) may not obtain adequate amounts of nighttime sleep, which could lead to chronic partial sleep loss (i.e. sleep debt) and associated impairment in alertness and performance [75,85–87]. It is generally recognized that nCPAP should be used throughout each sleep period in order to increase the likelihood of recovery from sleep loss due to untreated sleep-disordered breathing and to prevent sleep debt [88,89]. Although the present study was not designed to evaluate the prevalence or etiology of patients' residual sleepiness, and the sleep durations of patients in this study were not directly measured with polysomnography, the objectively recorded nightly duration of nCPAP use at home averaged 6.2 h over the 4 weeks of the study [68], indicating that sleep duration with nCPAP was within a range that is currently regarded as effective clinical treatment. On the other hand, given that recent experiments in healthy adults show that chronic restriction of sleep to 6 h or less a night leads to cumulative daytime neurobehavioral impairments in PVT performance and other cognitive tasks [75,85–86], the criterion for adequate adherence to nCPAP treatment should be set above the conventional criteria of ≥4 h use per night on ≥5 of 7 nights [70], used in this and many other studies. If, for example, the nCPAP use thresholds for adherence were set to criteria needed for prevention of as much residual sleepiness attributable to inadequate quality sleep time as possible—for example, to criteria of at least ≥8 h use per night on 100% of nights, as suggested by the results of chronic sleep restriction studies—it is likely that fewer nCPAP-treated patients would be found who have residual sleepiness [90]. On the other hand, data are not yet available in OSA/HS patients on the dose–response relationship between degrees of nCPAP adherence and normalization of sleepiness and functional outcomes. There is also a dearth of evidence that nCPAP adherence can be increased and sustained at an increased level in many OSA/HS patients. Until such data become available in these two areas, the issue of the extent to which underutilization of nCPAP therapy contributes to the problem of residual daytime sleepiness and the functional risks it imposes in OSA/HS patients will be unresolved.

There are other possible reasons for residual sleepiness in patients who are regularly adherent to nCPAP therapy. (1) Foremost is the possibility the residual daytime sleepiness may be due to inadequate nCPAP pressure in OSA/HS patients who regularly use nCPAP. This may cause residual sleep-related breathing pathology, such as subthreshold hypopneas or upper airway resistance, and may be associated with more subtle sleep fragmentation. (2) There may also be some sleeping discomfort and impairment of sleep induced by nCPAP itself. In addition, residual sleepiness may be a result of some undiagnosed coexisting sleep pathology, such as narcoplesy or CNS hypersomnia [91]. (3) There is also the possibility that chronic sleep disruption before diagnosis and treatment of OSA/HS may result in permanent alteration of sleep-promoting mechanisms [68] or permanent change in the endogenous waking drive [92].

A final explanation for sleepiness and its neurobehavioral effects being refractory to nCPAP derives from the possibility that nCPAP does not reverse neurobehavioral deficits from OSA/HS to the same degree of efficacy that it splints the airway open. Although limited in number and study sample sizes, the few randomized, placebo-controlled, crossover studies [42,43,93] evaluating nCPAP in patients with OSA/HS have been equivocal. A recent report of 42 patients with mild OSA/HS found no benefit of nCPAP compared with placebo in objective or subjective measures of daytime sleepiness; sleep-specific quality of life questionnaire (FOSQ); or tests of cognition, memory, and vigilance [93]. An earlier study found that relative to placebo, nCPAP improved subjective but not objective daytime sleepiness in 34 patients with mild OSA/HS [43]. A similar study by this same group of 23 patients with moderate-to-severe OSA/HS found that objective and subjective sleepiness were significantly improved with nCPAP, but there were no significant improvements in tests of cognitive performance and psychosocial well being [42]. These placebo-controlled trials suggest nCPAP may not have as broad an effect on functioning, cognition, and quality of life in patients with OSA/HS as has been assumed. This is supported by a recent discourse analysis that identified several quality of life concerns (e.g. depression, memory loss, intimacy/sexual relations) outside the main symptoms of snoring, sleepiness, and fatigue of patients on or beginning nCPAP treatment [94]. Clearly, large scale, placebo-controlled trials of nCPAP need to be conducted to resolve the extent to which it results in improvements on a range of neurobehavioral and physiological (e.g. cardiovascular) functions. Thus, there are a number of potential etiologies for residual sleepiness or sleepiness-related neurobehavioral functioning that is refractory to nCPAP. Even after all attempts to rule out additional sleep pathology or to maximize sleep through optimal application of nCPAP technology, and through education about sleep hygiene, some patients may still experience performance-impairing daytime sleepiness that may require adjunctive treatment.

In conclusion, the results of this 4-week study suggest that adjunctive treatment with modafinil is well tolerated and may provide benefits with respect to daytime wakefulness, sustained attention, and quality of life beyond those afforded by regular nCPAP therapy to the subset of OSA/HS patients who experience daytime sleepiness that is refractory to nCPAP treatment. Importantly, modafinil did not have a clinically significant affect on nCPAP use or cardiovascular parameters [68]. Additional studies of modafinil in this patient population are needed to identify appropriate dosing regimens and to demonstrate whether the beneficial effects on wakefulness, cognitive performance, and quality of life are maintained during longer-term treatment, without a reduction in nCPAP use. Such data are also needed to help inform the debate [95–97] over the appropriate use of modafinil, or any wake-promoting medication, as an adjunctive therapy for residual sleepiness in OSA/HS patients being treated mechanically or with surgical therapies.

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