

Efficacy and Safety of Adjunctive Modafinil Treatment on Residual Excessive Daytime Sleepiness among Nasal Continuous Positive Airway Pressure-Treated Japanese Patients with Obstructive Sleep Apnea Syndrome: A Double-Blind Placebo-Controlled Study

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SCIENTIFIC INVESTIGATIONS

Study Objectives: This double-blind study evaluated the efficacy and safety of modafinil for treating excessive daytime sleepiness in Japanese patients with obstructive sleep apnea syndrome (OSAS).

Methods: Patients with residual excessive sleepiness (Epworth Sleepiness Scale [ESS] ≥ 11) on optimal nasal continuous positive airway pressure (nCPAP) therapy (apnea-hypopnea index ≤ 10) were randomized to either 200 mg modafinil (n = 52) or placebo (n = 62) once daily for 4 weeks. Outcomes included baseline-week 4 changes in ESS total score, sleep latency on maintenance of wakefulness test (SL-MWT), nocturnal polysomnography, Pittsburgh Sleep Quality Index (PSQI), and safety.

Results: All 114 randomized patients completed the study. Mean change in ESS total score (-6.6 vs -2.4, $p < 0.001$) and SL-MWT (+2.8 vs -0.4 minutes, $p = 0.009$) were significantly greater with modafinil than with placebo. ESS total score decreased from > 11 to < 11 at the final assessment in 69.2% of modafinil-treated patients and 30.6% of placebo-treated patients ($p < 0.001$). Corresponding rates at week 1 were

57.7% and 33.9% ($p = 0.014$). Changes in nocturnal polysomnography, PSQI, and apnea-hypopnea index from baseline to the final assessment were similar in both groups. Adverse drug reactions occurred in 36.5% and 22.6% of patients in the modafinil and placebo groups, respectively ($p = 0.146$).

Conclusions: Once-daily modafinil was effective and well tolerated for managing residual daytime sleepiness in Japanese OSAS patients with residual excessive daytime sleepiness on optimal nCPAP therapy.

Clinical Trial Registration: JapicCTI-No.090777

Keywords: Randomized clinical trial, daytime sleepiness, Epworth Sleepiness Scale, modafinil, nasal continuous positive airway pressure, maintenance of wakefulness test, obstructive sleep apnea, safety

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Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by recurrent episodes of upper airway collapse that occur during sleep. OSAS frequently causes nocturnal intermittent hypoxemia, sympathetic activation and fragmented/disrupted sleep.¹ Studies of Caucasian and Asian populations have consistently estimated that the prevalence of OSAS associated with excessive daytime sleepiness ranges from 3% to 7% in adult men and from 2% to 5% in adult women.² In Japan, Nakaya-Ashida et al.³ reported that the prevalence of moderate to severe sleep disordered breathing (respiratory disturbance index ≥ 15) was 22.3% in male workers aged 23-59 years.

Factors predisposing to OSAS include obesity, advanced age, male sex, and craniofacial abnormalities.^{4,5} The diagnosis of OSAS generally requires objective measurement of obstructive respiratory events and the presence of characteristic symptoms, such as excessive daytime sleepiness and unrestored nocturnal

BRIEF SUMMARY
Current Knowledge/Study Rationale: Very few studies, and none in Asian patients, have examined the effects of modafinil on subjective or objective sleep measures in patients with residual sleepiness on optimal nCPAP.
Study Impact: Treatment with 200 mg modafinil once daily improved residual daytime sleepiness in Japanese patients with OSAS on optimal nCPAP compared with placebo.

sleep that could not be better explained by other factors.⁶ Severe OSAS is often associated with vascular morbidities,^{7,8} cognitive impairment, occupational and vehicular accidents attributable to excessive daytime sleepiness, and worse quality of life than unaffected individuals.⁹

Management of OSAS requires the use of nasal continuous positive airway pressure (nCPAP) therapy, a first-line treatment, which acts as a pneumatic splint to maintain patency of

the upper airway. nCPAP therapy is widely accepted to reduce excessive sleepiness and to improve daytime functioning and self-reported health status.¹⁰⁻¹² However, despite the reported improvements of respiratory events, clinically significant excessive sleepiness persists in some patients on optimal nCPAP. In some of these patients, the residual sleepiness may reflect the presence of other sleep disorders, including narcolepsy, behaviorally induced sleep insufficiency syndrome and periodic limb movement disorders.¹³ In other patients, this outcome may be caused by hypoxia-induced cerebral metabolic changes.¹⁴ In a recent study in France, 6.0% (95% confidence interval [CI] 3.9-8.0) of OSAS patients who were optimally treated with nCPAP had evidence of residual excessive sleepiness.¹⁵ Considering the potential adverse outcomes that may affect the health and safety of the patients, residual sleepiness requires prompt attention.

The Standards of Practice Committee of the American Academy of Sleep Medicine recommends use of the wake-promoting agent modafinil in nCPAP-treated patients without other identifiable causes for their residual sleepiness.¹⁶ Modafinil differs from other amphetamine-like wake-promoting agents, such as methamphetamine and methylphenidate, in its chemical structure and mechanisms of action.¹⁷⁻²⁰ Modafinil mainly interacts with the dopamine transporter,^{21,22} and affects the γ -amino butyric acid (GABA)-ergic, serotonergic, glutaminergic, noradrenergic, and histaminergic neurotransmitter systems,²²⁻²⁶ which may contribute to its wake-promoting activity. Double-blind placebo-controlled clinical studies on nCPAP-treated patients with residual sleepiness associated with OSAS have revealed that modafinil significantly improved objectively determined sleep latency, overall subjective severity of sleepiness, health-related quality of life, and functional status, and that it was well tolerated.²⁷⁻²⁹ To date, however, no studies have examined the effects of modafinil on residual excessive sleepiness in Japanese patients with OSAS on optimal nCPAP treatment. Furthermore, although central nervous system stimulants may theoretically disturb nocturnal sleep,³⁰ previous studies have not documented the effects of modafinil on subjective or objective nocturnal sleep measures.

Therefore, in the present study, we evaluated the effects of modafinil on the efficacy and safety of modafinil in Japanese patients with OSAS and excessive daytime sleepiness despite optimal therapeutic use of nCPAP. We also examined the effects of modafinil on subjective and objective measures of nocturnal sleep in these patients.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 37 sites specialized in sleep disorders in Japan between May 2009 and December 2009. The study included a screening visit, an observation period ≥ 15 days, and a 4-week double-blind treatment period. The protocol and the informed consent form were reviewed and approved by the internal review board at each institution. All patients provided written informed consent to participate in this study.

Patients

Patients evaluated in this study were required to be receiving effective nCPAP therapy to rule out inadequate or incorrect nCPAP use as a cause of their residual sleepiness. Patients with sleep disorders other than OSAS were excluded from the study. The main inclusion criteria for eligible patients in this study were as follows: men and women aged 20-70 years; confirmed diagnosis of OSAS; and the presence of subjective excessive sleepiness (i.e., Epworth Sleepiness Scale [ESS] total score ≥ 11)³¹ despite optimal use of nCPAP; having received nCPAP therapy for ≥ 3 months and being willing and able to continue its use during the study period; the use of nCPAP for $\geq 70\%$ of nights for ≥ 4 h/night³² for 14 days before the baseline visit; and an apnea-hypopnea index (AHI) ≤ 10 determined by nocturnal polysomnography (PSG) during the observation period. Definitive diagnosis of OSAS or other sleep disorders was made using PSG data obtained before randomization based on Rechtschaffen and Kales criteria³³ and American Sleep Disorders Association arousal criteria.³⁴ The data were scored according to American Association of Sleep Medicine criteria.³⁵ Patients who met any of the following criteria were excluded from this study: diagnosis of other sleep disorders (e.g., narcolepsy, periodic limb movement disorders, and central sleep apnea); pregnant, potentially pregnant, or lactating women; presence of arrhythmias, angina, and clinically significant cardiac, respiratory, cardiovascular diseases, psychiatric disorders (e.g., depression³⁶), or hypertension with systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg,³⁷ as specified in the exclusion criteria of the U.S. OSAS study.²⁹ Patients who were concomitantly administered prohibited drugs, such as central nervous system stimulants, sedative medications, antidepressants, antiepileptic drugs, acetazolamide, warfarin, monoamine oxidase inhibitors, or antimigraine drugs, within 2 weeks before the start of the study, were also excluded. Patients fulfilling these criteria were identified by the physicians and invited to participate in the study at the physician's request.

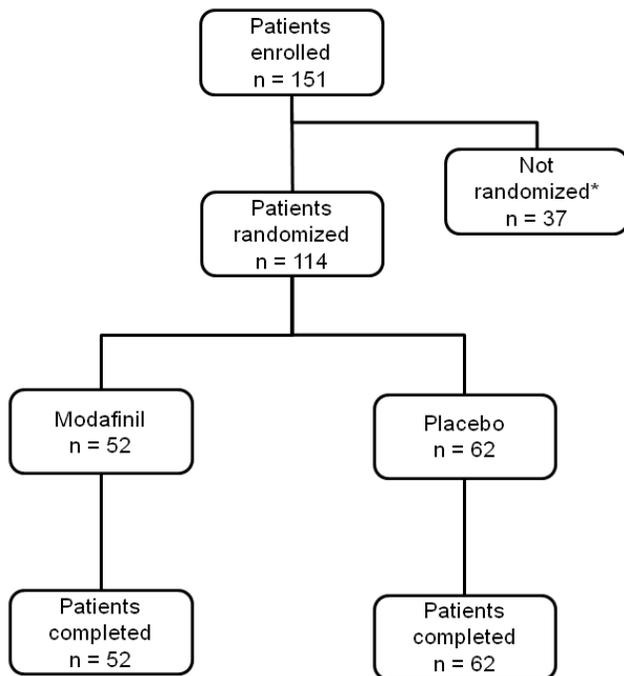
Randomization and Dosing

Patients were randomly assigned in a blocked randomization manner to receive 2 tablets of 100 mg modafinil (total dose, 200 mg/day) or placebo once daily in the morning, to be administered before or after meals. Randomization was performed using a computer-generated random number list prepared by an independent contract research organization. Clinicians contacted the organization via telephone to obtain the randomization sequence for each patient.

Efficacy Measures

Efficacy assessments were conducted at the start (i.e., baseline) and at Weeks 1 and 4 of the double-blind treatment period. The primary efficacy measure was ESS score at Week 4 of treatment. The secondary efficacy measure was mean sleep latency on the maintenance of wakefulness test (MWT).^{38,39} The MWT was conducted in a subset of patients (modafinil, $n = 22$; placebo, $n = 28$) at baseline and at Week 4 of the double-blind period on the days immediately after nocturnal PSG. Each MWT session lasted 20 min. Because of the methodology, the MWT was only performed at study sites with the facilities required to conduct the test. Some patients at these facilities were unable

Figure 1—Patient disposition



*37 patients were not randomized to the study for the following reasons: 35 patients did not meet the eligibility criteria, one patient withdrew consent, and one patient gave up on the starting dose because of changes in work schedule.

to do the MWT because of the burden associated with the test. Other secondary variables were ESS score at each visit, and the total score of Japanese version of Pittsburgh Sleep Quality Index (PSQI),⁴⁰ which represents the severity of subjective sleep disturbance, and sleep parameters measured by nocturnal PSG at baseline and Week 4. PSG and MWT were conducted in an inpatient setting.

Safety

Safety was assessed by evaluating adverse drug reactions (ADRs) as well as the results of general laboratory tests (blood and urine), physiological variables (blood pressure and pulse rate), 12-lead electrocardiograms, and physical examinations. ADRs were defined as any unfavorable or unintended symptom or disease that was considered to be associated with the study drug during the study period.

Statistical Analysis

Continuous demographic variables were compared using the 2-sample *t*-test. Categorical variables were compared using the Fisher exact test. The efficacy population ($n = 114$) was defined as patients who received ≥ 1 dose of modafinil and underwent ≥ 1 post-baseline evaluation for any efficacy or safety variable during the treatment period. The changes in efficacy variables (ESS and MWT) from baseline to the final assessment (Week 4) were compared between the modafinil and placebo groups using analysis of covariance with the baseline value as a covariate. To verify the efficacy of modafinil administration, the point estimate and 2-sided 95% (CI) of the difference

Table 1—Patient characteristics

Characteristic	Placebo (n = 62)	Modafinil (n = 52)	p-value*
Age, years	50.5 \pm 9.2	49.0 \pm 10.4	0.399
Sex, n (%)			0.330
Male	61 (98.4)	49 (94.2)	
Female	1 (1.6)	3 (5.8)	
BMI, kg/m ²	27.3 \pm 3.5	27.9 \pm 4.3	0.441
ESS, total score	14.6 \pm 3.1	14.3 \pm 2.7	0.553
AHI during nCPAP	2.6 \pm 2.6	2.8 \pm 2.7	0.740
Duration of nCPAP use per night, h	6.0 \pm 0.6	6.1 \pm 1.0	0.495

Data are means \pm SD or n (%). *The p-values were determined using the 2-sample *t*-test for continuous variables or the Fisher exact test for categorical variables. BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; nCPAP, nasal continuous positive pressure.

between the modafinil and placebo groups were calculated using the least squares mean (LS mean) method. Statistical tests were performed at a significance level of 5% using SAS System (Release 9.1.3, SAS Institute Inc., Cary, NC, USA). Changes in other secondary variables (PSQI and nocturnal PSG) from baseline were also compared between the modafinil- and placebo-treated groups. Safety data are summarized using descriptive statistics.

RESULTS

Subjects

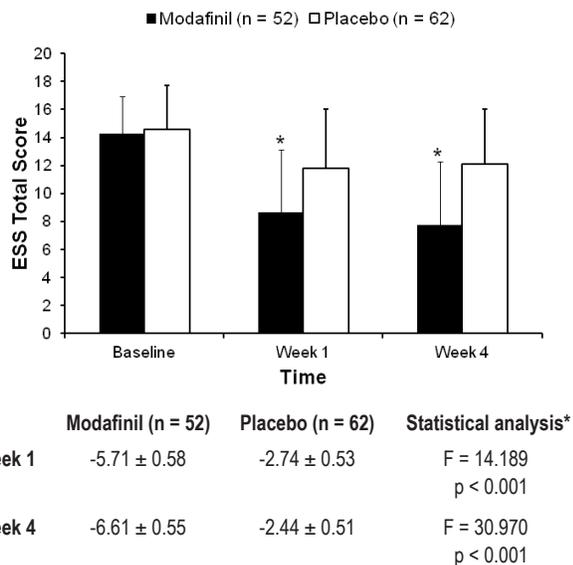
A total of 114 patients were randomized—52 patients to modafinil and 62 patients to placebo. All 114 patients completed the study (Figure 1). There were no differences between the 2 groups in terms of demographic and baseline characteristics (Table 1). Males accounted for > 94% of the patients in both groups. Before starting treatment with the study drug, the patients in both groups had moderate levels of residual sleepiness, with mean total ESS scores ≥ 14 despite effective nCPAP therapy; mean AHI was ≤ 10 in both groups. The mean duration of nCPAP use per night was 6.1 ± 1.0 and 6.0 ± 0.6 h in the modafinil and placebo groups, respectively (Table 1). Concomitant diseases included hypertension (modafinil, $n = 13$ [25%]; placebo, $n = 20$ [32%]) and hyperlipidemia (modafinil, $n = 4$ [8%]; placebo, $n = 14$ [23%]).

Subjective Sleepiness

Mean ESS total scores were determined at baseline and at the final assessment in both groups. The mean changes in ESS total score from baseline to the final assessment were -6.61 in the modafinil group and -2.44 in the placebo group (LS mean). The between-group difference of -4.17 (95% CI -5.66 to -2.69) was therefore significantly greater with modafinil than with placebo ($p < 0.001$). The change in mean ESS total score at 1 week after starting treatment was also significantly greater in the modafinil group than in the placebo group ($p < 0.001$; Figure 2).

The patients whose ESS total scores were ≥ 11 at baseline and decreased to < 11 at the final assessment were defined as

Figure 2—Mean Epworth Sleepiness Scale total score at baseline, and after 1 and 4 weeks of treatment with modafinil or placebo



The least significant mean change from baseline ± standard error is shown in the table. *The p-values were determined by analysis of covariance.

responders with normalization of ESS. Overall, 69.2% of patients (36/52) treated with modafinil and 30.6% of patients (19/62) treated with placebo were classified as responders. The Fisher exact test showed that a significantly higher percentage of patients treated with modafinil were classified as responders compared with patients treated with placebo ($p < 0.001$). The corresponding response rates at week 1 were 57.7% (30/52) and 33.9% (21/62) ($p = 0.014$).

Objective Sleepiness

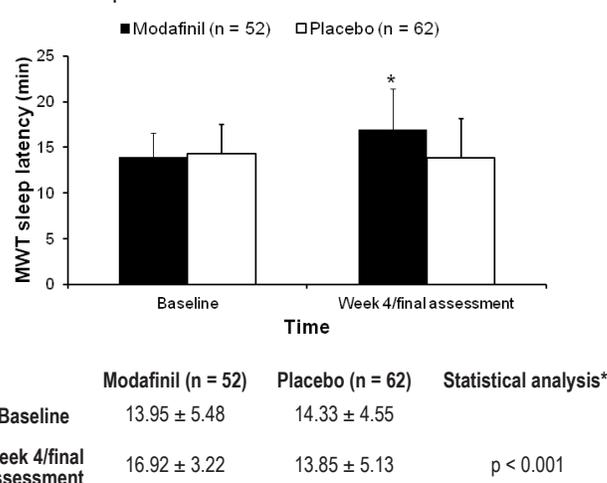
Fifty patients (modafinil, $n = 22$; placebo, $n = 28$) underwent the MWT. There were no differences in patient characteristics, including baseline ESS total score, between patients who did or did not undergo the MWT ($p = 0.292$). Mean sleep latencies determined by MWT at baseline and at the final assessment in both groups are shown in **Figure 3**. The LS mean change in MWT sleep latency from baseline to the final assessment was 2.8 min in the modafinil group and -0.40 min in the placebo group. The between-group difference of 3.2 min (95% CI 0.8 to 5.6) was statistically significant, showing greater effects of modafinil versus placebo ($p = 0.009$).

Objective and Subjective Measures of Nocturnal Sleep

Summary statistics for sleep parameters were determined in 101 patients who underwent nocturnal PSG at baseline and at the final assessment (modafinil, $n = 45$; placebo, $n = 56$). As shown in **Table 2**, there were no significant differences in the changes in any nocturnal PSG parameters between the 2 groups.

The total PSQI score decreased from 6.3 ± 2.7 at baseline to 4.8 ± 2.2 at the final assessment in the modafinil group, as compared with a change from 6.1 ± 2.3 to 5.4 ± 1.7 in the placebo group. The mean difference in total PSQI score between the 2 groups for the change from baseline to the final assess-

Figure 3—Mean maintenance of wakefulness test sleep latency at baseline and after 4 weeks of treatment with modafinil or placebo



*The p-value was determined by analysis of covariance.

ment was -0.7 points (95% CI: -1.5 to 0.0 points) and was not statistically significant.

Safety Outcomes

ADRs were reported by 19 patients (36.5%) in the modafinil group and 14 patients (22.6%) in the placebo group. There were no significant differences in the rate of ADRs between the 2 groups ($p = 0.146$; Fisher exact test). The most frequent ADRs in the modafinil group were headache ($n = 6$, 11.5%), insomnia ($n = 2$, 3.8%), and palpitation ($n = 2$, 3.8%). The most frequent ADRs in the placebo group were headache ($n = 4$, 6.5%) and upper abdominal pain ($n = 2$, 3.5%) (**Table 3**). All of these ADRs were mild or moderate in severity, and no deaths or other serious adverse events were reported. None of the patients withdrew from the study because of ADRs.

Regarding the time of onset of ADRs, the frequency of ADRs was greatest within 7 days after starting treatment in both the modafinil group (15/19 patients who experienced ADRs) and the placebo group (10/14 patients).

Laboratory test abnormalities included increased γ -glutamyl transpeptidase in one patient in each group; increased alkaline phosphatase in one patient in each group; increased alanine aminotransferase and increased thyroid stimulating hormone in one patient each in the modafinil group; the presence of urinary glucose and decreased white blood cell count in one patient each treated with placebo; and multiple liver enzyme abnormalities (increased aspartate aminotransferase, alanine aminotransferase, and γ -glutamyl transpeptidase) in one patient treated with placebo. Decreased body weight (from 77.0 kg at baseline to 73.0 kg at week 4 of the treatment period) was observed in one patient treated with modafinil. Sinus tachycardia (at Week 1 of the treatment period) and sinus bradycardia (at Week 4 of the treatment period) were observed in one patient each in the modafinil group. Ventricular extrasystole (at Week 1 of the treatment period) was observed in one patient treated with placebo. No clinically relevant abnormalities were ob-

Table 2—Comparison of nocturnal PSG indices at baseline and after 4 weeks of treatment with modafinil and placebo

Characteristic	Placebo (n = 56)		Modafinil (n = 45)		p-value*
	Baseline	Week 4	Baseline	Week 4	
Total sleep time (TST), min	425.2 ± 60.9	421.7 ± 61.4	417.4 ± 55.2	432.3 ± 65.0	0.054
Sleep efficiency (TST/TIB), %	85.0 ± 11.2	85.4 ± 11.2	84.4 ± 10.7	86.2 ± 9.7	0.377
Sleep latency, min	8.8 ± 12.4	11.4 ± 14.8	10.2 ± 16.8	9.3 ± 17.0	0.290
Stage 1, %TST	16.0 ± 6.7	13.7 ± 7.7	16.9 ± 10.7	15.7 ± 10.2	0.871
Stage 2, %TST	56.7 ± 8.4	58.0 ± 9.9	56.4 ± 12.3	58.3 ± 13.0	0.466
Stage 3, %TST	4.2 ± 5.5	5.6 ± 6.6	4.4 ± 5.7	3.6 ± 4.7	0.154
Stage 4, %TST	1.3 ± 3.7	1.3 ± 2.9	1.3 ± 3.1	1.7 ± 4.3	0.345
Stage 3-4, %TST	5.4 ± 7.1	7.0 ± 8.2	5.6 ± 7.7	5.3 ± 7.9	0.531
REM, %TST	21.9 ± 6.4	21.4 ± 5.8	21.1 ± 6.4	20.7 ± 5.5	0.505
Wake (WASO/SPT), %	12.28 ± 10.5	10.9 ± 9.0	12.1 ± 8.4	9.3 ± 6.8	0.264
AHI	2.6 ± 2.6	2.6 ± 2.8	2.8 ± 2.7	2.6 ± 2.7	0.500

Data are means ± SD. *Two-sample *t*-test to compare the change from baseline to Week 4 between the modafinil and placebo groups. TIB, time in bed; WASO, wake after sleep onset; SPT, sleep period time; AHI, apnea-hypopnea index.

served in the other variables, including laboratory tests, blood pressure, pulse rate, body weight, or electrocardiogram.

DISCUSSION

This study was the first Asian study to investigate the efficacy of modafinil for treating residual sleepiness in patients with nCPAP-treated OSAS using both subjective and objective measures. In this study, residual sleepiness was defined as excessive daytime sleepiness in patients who were compliant with OSAS treatment but had subjective sleepiness without any other identifiable cause of sleepiness, applying enrollment criteria identical to those in studies in the United States.^{27,29} The degree of residual sleepiness at baseline, as represented by the ESS total score, of the patients enrolled in this study, was also comparable to that in the US studies.^{27,29}

The use of the MWT was limited to a subgroup of patients in this study; hence, a subjective measure of sleepiness (the ESS) was used as the primary efficacy parameter. Consequently, in this 4-week study, the improvement in ESS total score was significantly greater in the modafinil group than in the placebo group. Four weeks of treatment with modafinil normalized the ESS total score in approximately two-thirds of the patients. In terms of ESS total score, significant improvements of excessive daytime sleepiness in the modafinil group were observed at the first post-treatment evaluation, i.e., one week after starting treatment, compared with the placebo group. Overall, the mean ESS total scores were normalized (to < 11) within 1 week of modafinil administration in 57.7% of patients, increasing to 69.2% at week 4. Modafinil also improved sleep latency determined by the MWT, representing the patient's ability to maintain wakefulness.

As described above, modafinil exerts its wake-promoting activities by targeting several neurotransmitter systems, rather than a specific molecule or specific neurotransmitter system. Thus, the effects of modafinil on residual sleepiness in OSAS patients are at least partly attributable to its nonspecific pharmacological actions.

The present study evaluated adjunctive once-daily administration of 200 mg modafinil. Another placebo-controlled study

Table 3—Adverse events occurring in two or more patients in either treatment group

Adverse event	Placebo (n = 62)	Modafinil (n = 52)	p-value*
Headache	4 (6.5)	6 (11.5)	0.508
Upper abdominal pain	2 (3.2)	0 (0)	0.499
Insomnia	0 (0)	2 (3.8)	0.206
Palpitation	0 (0)	2 (3.8)	0.206

Values are number of patients (%). *Fisher exact test.

evaluated this dose and a higher dose (400 mg once daily) in a comparable patient population.²⁹ Interestingly, when the efficacy data for the 200 mg doses in both studies were compared, the changes in ESS score from baseline to Week 4 of treatment were -6.52 ± 5.04 (n = 52) and -3.20 ± 4.25 (n = 95) in our study and in the US study,²⁹ respectively. The respective changes in MWT sleep latency were 2.97 ± 5.25 (n = 22) and 1.20 ± 4.33 (n = 84). These data suggest that the response to 200 mg/day modafinil is greater in Japanese patients than in US patients, which may indicate slight differences in pharmacokinetic profiles among different ethnicities, as already reported among other ethnic groups.^{41,42} Differences in the pharmacokinetic profiles, including the absorption and distribution of modafinil, may also be attributable to the differences in body size between Japanese and US patients, as the mean BMI of patients treated with 200 mg modafinil was 27.9 ± 4.3 kg/m² in our study versus 36.2 ± 7.6 kg/m² in the US study.²⁹ Alternatively, excess obesity is known to exacerbate daytime sleepiness,^{43,44} possibly resulting in more severe symptoms or less apparent improvements in symptoms in US patients than in Japanese patients. Additionally, differences in the timing or content of the morning meal may partly explain the differences in clinical outcomes between these studies. Nevertheless, the precise reasons for this difference between Japanese and US patients are unclear, and this study was conducted to evaluate safety and efficacy in Japanese OSA patients and not to elucidate the difference between US and Japanese patients. However, the trends in posi-

tive outcomes for patient-reported sleepiness and objectively determined sleep latency in the present study were similar to those reported in the US study.²⁹

Of note, in this study of Japanese patients, treatment with modafinil did not significantly affect sleep parameters in terms of nocturnal PSG findings or total PSQI score. Therefore, the administration of modafinil in the morning did not seem to adversely affect the structure or quality of nocturnal sleep.

Generally, modafinil was well tolerated. The safety and tolerability findings of the current study are consistent with those of other double-blind placebo-controlled studies.^{27,29} Headache, insomnia, and palpitation were the most common ADRs in modafinil-treated patients. However, modafinil therapy was not associated with clinically significant changes in blood pressure or heart rate relative to placebo. Furthermore, there were no serious adverse events in either group in this study.

Some limitations of this study should be mentioned. First, most of the patients in this study were male, and there are some differences in the pharmacokinetics of modafinil between males and females.^{41,42,45} Second, we only included patients with OSAS on nCPAP. The efficacy of modafinil should therefore be evaluated in OSAS patients with residual sleepiness on other treatments.

In conclusion, residual daytime sleepiness was improved in Japanese patients with OSAS treated with 200 mg modafinil once daily. We found significant improvements in ESS total scores at 1 week after starting modafinil that were maintained until the end of the 4-week study. Modafinil may be an effective and well-tolerated adjunct treatment for the chronic management of residual daytime sleepiness in patients with OSAS who experience excessive daytime sleepiness despite regular nCPAP use.

ABBREVIATIONS

ADR, adverse drug reactions
 AHI, apnea-hypopnea index
 CI, confidence interval
 ESS, Epworth Sleepiness Scale
 GABA, γ -aminobutyric acid
 LS, least squares
 nCPAP, nasal continuous positive airway pressure
 OSAS, obstructive sleep apnea syndrome
 PSG, polysomnography
 PSQI, Pittsburgh Sleep Quality Index
 SL-MWT, sleep latency on maintenance of wakefulness test

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