Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy

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Proceedings Title: Neurology
Conference Name: 49th Annual Meeting of the American Academy of Neurology
Publisher: Lippincott Williams & Wilkins
Conference Place: Boston, Massachusetts
Volume/Issue: Volume 54 | Issue 5
Publication Date: 2000-03-14
Type of Work: Conference | Final Publisher PDF
Publisher DOI: 10.1212/WNL.54.5.1166
Permanent URL: https://pid.emory.edu/ark:/25593/rq5zk

Final published version: http://dx.doi.org/10.1212/WNL.54.5.1166

Neurology
Issue: Volume 54(5), 14 March 2000, pp 1166-1175

Publication Type: [Articles]
DOI: 10.1212/WNL.54.5.1166
ISSN: 0028-3878
Accession: 00006114-200003140-00031
Keywords: Narcolepsy, Modafinil, Sleepiness, Somnolence, Performance, Wakefulness, Withdrawal, Dependence.

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US Modafinil in Narcolepsy Multicenter Study Group

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*See the Appendix on page 1173 for a list of members of the US Modafinil in Narcolepsy Study Group.
%This study was funded in its entirety by a grant from Cephalon, Inc.
Presented in part at the annual meeting of the American Academy of Neurology; Boston, MA; April 16, 1997.
Received September 29, 1998. Accepted in final form November 1, 1999.
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Disclosure
Some individuals involved in the conduct of this study were paid consultants or were otherwise under contract to Cephalon, Inc.

Abstract

Objective: This is one of two separate clinical trials to evaluate the efficacy and safety of modafinil, a novel wake-promoting agent, in patients with excessive daytime sleepiness (EDS) associated with narcolepsy.

Methods: In this 9-week, randomized, placebo-controlled, double-blind, 21-center clinical trial, patients were randomized to receive fixed daily doses of modafinil 200 mg, modafinil 400 mg, or placebo. A placebo-controlled, 2-week treatment discontinuation phase was included to evaluate the effects of withdrawal on patients who had been receiving modafinil. A total of 271 patients who were naïve to modafinil received study medication in the 9-week trial and 240 patients received study medication in the discontinuation phase.

Results: Treatment with modafinil resulted in significant improvement in two objective measures of

EDS: the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. Additionally, patient self-assessment of sleepiness was significantly improved, as measured by the Epworth Sleepiness

Scale, and level of illness was significantly reduced on the independent clinician assessment, the Clinical Global Impression of Change. Nighttime sleep, monitored by nocturnal polysomnography, was not adversely effected with modafinil treatment compared with placebo treatment. The most frequent adverse experience was headache, which was not significantly greater for modafinil than placebo. During treatment discontinuation, individuals who had been receiving modafinil experienced a return of their EDS to baseline levels. During treatment discontinuation, patients did not experience symptoms associated with amphetamine withdrawal syndrome. For up to 9 weeks of daily use there was no evidence for the development of dependence at the dose levels studied.

Conclusion: The data indicate that modafinil has an excellent safety profile and is very well tolerated. Modafinil is an effective treatment for excessive daytime sleepiness in narcolepsy and shows continued efficacy with up to 9 weeks of daily use.

Narcolepsy is a disabling CNS disorder marked by excessive daytime sleepiness (EDS) and cataplexy. 1 This disorder is often inherited, 2,3 and is of unknown etiology. A form of narcolepsy occurs in dogs. This condition parallels the human form in terms of sleepiness, cataplexy, and therapeutic response to alerting drugs and anticataplectic drugs. 4,5 Canine narcolepsy has recently been linked to mutations in the hypocretin receptor 2 gene. 6 Studies are underway to assess the hypocretin system in human narcoleptic and normal individuals because it is likely that genetic abnormalities affecting this system may account for some familial and, perhaps, some non-human leukocyte antigen–associated human narcolepsy. 6

Treatment of narcolepsy-related sleepiness traditionally employs amphetamine and amphetamine-like stimulant drugs, such as methylphenidate. 1,7 Stimulants can cause CNS, cardiovascular, or gastrointestinal adverse experiences (e.g., anxiety, palpitations, and nausea). Additionally, amphetamine and methylphenidate are often associated with an increased liability for abuse. Another concern relates to the potential for dependence characterized by withdrawal symptoms on discontinuation. 7-9

Modafinil, 2-[(diphenylmethyl)sulfinyl] acetamide, is a pharmacologically unique wake-promoting agent used successfully to treat EDS associated with narcolepsy. Modafinil requires an intact [alpha]$_1$-adrenergic system but its exact mechanism of action is undetermined. 10,11 It does not appear to be a dopaminergic agonist 10,12 and has site-specific CNS activity. In studies evaluating the activation of sites in cat and rat brain (using increased expression of c-*fos* as a marker of activity), the regional effects of modafinil were distinct from those of amphetamine and methylphenidate. Equal wake-promoting doses of methylphenidate and amphetamine, but not modafinil, increased c-*fos* expression throughout the brain, including the cortex, basal ganglia, and nucleus accumbens. Modafinil, at an equivalent wake-promoting dose, selectively and prominently increased c-*fos* expression in subcortical areas such as the anterior hypothalamus and central nucleus of the amygdala, areas of the brain believed to regulate sleep and waking. Modafinil did not increase c-*fos* expression in cortex, basal ganglia, or nucleus accumbens. 13,14

A recent report showed that mice with a knockout of the hypocretin (orexin) gene had abnormalities of sleep that resembled narcolepsy, 15 further implicating the hypocretin neurons in the regulation of wakefulness and sleep. 16 This report also showed that modafinil activates orexin-containing neurons. 15 Orexin-A and orexin-B are neuropeptides of 33 and 28 amino acids, respectively, that are produced exclusively by a group of neurons in the lateral hypothalamus. 17 Acting at axon terminals, orexins can increase the release of the inhibitory transmitter gamma-aminobutyric acid (GABA) and the excitatory transmitter glutamate. 18 Whereas the activation by modafinil of orexin-containing neurons does not prove that this is modafinil's mechanism of action, it is consistent with other reports indicating that modafinil acts on the hypothalamus and in a manner distinct from methylphenidate and amphetamines.

Results of previously published controlled clinical trials indicate that modafinil has an excellent safety profile, is well tolerated, and is effective for up to 9 weeks. 19,20 Moreover, modafinil use has neither the incidence rate or severity of side effects associated with the use of traditional stimulant drugs. Although modafinil appears to have less abuse potential than amphetamine and methylphenidate, the physiologic response to withdrawal has not been previously investigated.

The aims of this 21-center controlled study were threefold: 1) to replicate and extend information on the safety and efficacy of modafinil in maintaining wakefulness in patients with narcolepsy 19,20; 2) to investigate the response to withdrawal after 9 weeks of daily medication; and 3) to evaluate the tolerability of a dose step-up routine that included a 1-week initiation of modafinil at 100 mg/day before administration of the 400 mg/day modafinil dose.

Patients and methods.

Patients. Study patients were 17- to 67-year-old men and women diagnosed with narcolepsy according to International Classification of Sleep Disorders criteria. 21 These criteria include specifications for a history of EDS and rules regarding the presence or absence of cataplexy. For this study, inclusion criteria also required objective documentation of sleepiness with the Multiple Sleep Latency Test (MSLT; mean latency of 8 minutes or less), and two or more sleep-onset REM periods. Exclusion criteria included prior treatment with modafinil, any medical or psychiatric disorder that could account for narcolepsy symptoms, the inability to continue daily activities safely without the use of anticataplectic medication, a prior adverse reaction to CNS stimulants, or any other active, uncontrolled medical disorder. Other exclusions included use of any medication with stimulating or sedating properties and use of any psychoactive agents (e.g., marijuana) within 3 weeks of participation in this study. All patients were informed of the potential benefits and risks of study medication and provided institutional review board–approved informed consent.

Randomization and blinding.

For the double-blind treatment phase, each patient was individually randomized to receive modafinil 200 mg, modafinil 400 mg, or placebo by use of a computerized randomization schedule. The randomization list was generated by an individual who was geographically and operationally independent from the study personnel responsible for executing the randomization assignment and conducting the study. Each investigator was supplied with an individual blinded patient card corresponding to each double-blind medication package in the event unblinding would become necessary in a medical emergency. Each patient card included the patient randomization number, identity of the medication, and dosage of the medication. When a patient qualified for the double-blind phase of the study, the patient was assigned a four-digit patient number.

Each patient was identified only by his or her assigned number, initials, date of birth, and gender. The investigator maintained a list of patient names and identifying information. In the event of a medical emergency requiring unblinding of the patient code, the investigator was to call the medical monitor for concurrence and authorization. Upon concurrence, an independent party responsible for study drug packaging provided the code breaks. The investigator was permitted to open a patient's card and reveal the blinded treatment without authorization only in the event of an extreme medical emergency. If this occurred, the medical monitor was notified as soon as possible. The event was to be recorded on the study termination record and the patient was to be discontinued from the study. All cards were to be returned at the completion of the study. The investigator was responsible for monitoring patient compliance with study medication and keeping drug accountability records.

Study drug administration.

Study medication was provided in blister packs consisting of a daily dose of four tablets (100 mg of modafinil and/or matching placebo). The tablets were identical in appearance to ensure that neither the patient, the investigator, nor the clinical staff knew the identity of the study medication.

Following the completion of screening procedures, patients were randomized to one of three treatment groups for the 9-week, double-blind phase: modafinil 200 mg/day, modafinil 400 mg/day, or placebo. All patients randomized to modafinil treatment received modafinil 100 mg for the first 7 days of therapy and 200 mg on the eighth day. Starting on day 9, patients received either modafinil 400 mg/day or modafinil 200 mg/day for the next 8 weeks. For the blinded discontinuation phase (weeks 10 and 11), 80% of the patients initially randomized to the modafinil treatment groups were randomly crossed over to placebo. All other patients remained on modafinil at their previous dosage. Those who had received placebo during the first 9 study weeks remained on placebo during the discontinuation phase. Modafinil was discontinued in only 80% of patients in order to assess the differences in effect of discontinuation versus continuation of medication among patients who entered a subsequent open-label extension phase. Study drug was administered once daily in the morning, approximately 1 hour after awakening.

Study design.

This was a randomized, placebo-controlled, double-blind, parallel-group, 21-center study of two fixed doses of modafinil. Study assessments were conducted at baseline and at the week 1, 3, 6, and 9 visits of the double-blind treatment phase and at week 2 of the discontinuation phase (week 11 of the study). A flow diagram of the progress through the trial that includes a schedule of study assessments is shown in figure 1.

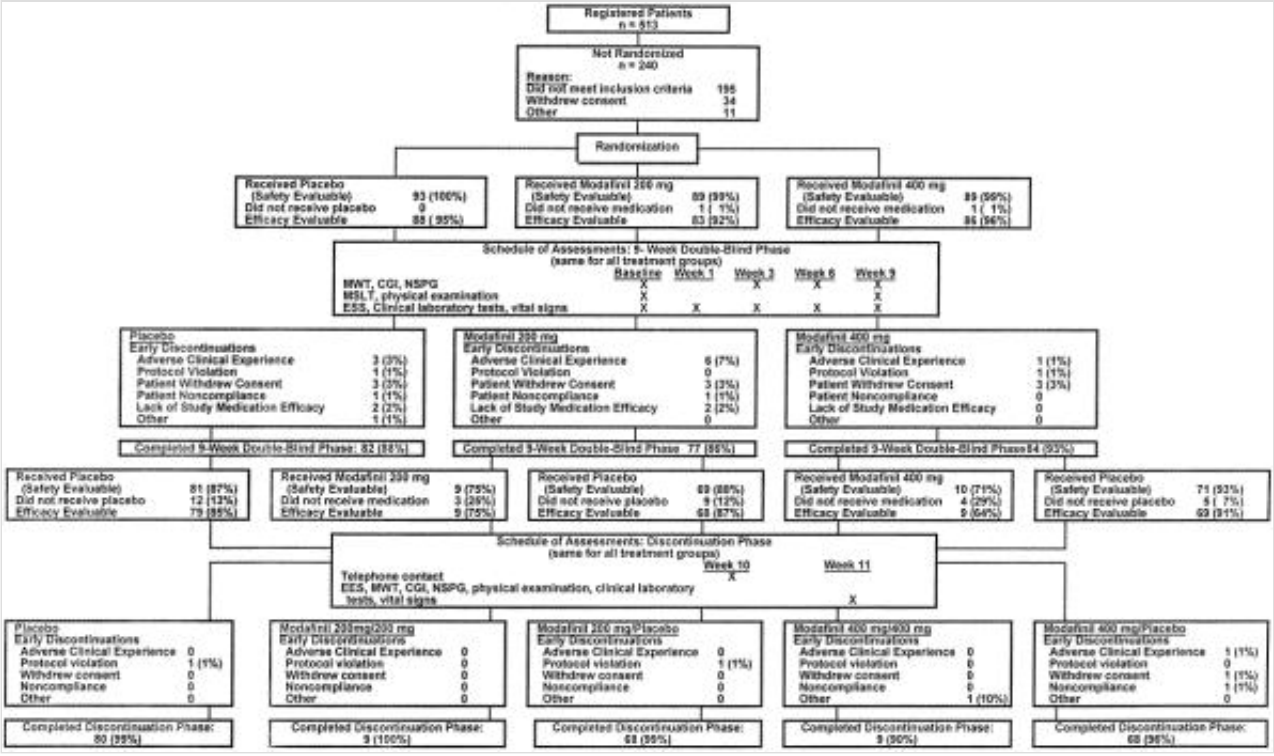

Figure 1. Flow diagram of progress through the trial, including patient registration, randomization, timing of outcome measures, and patient disposition. AE = adverse event; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; CGI = Clinical Global Impression; NPSG = nocturnal polysomnography; MSLT = Multiple Sleep Latency Test.

Study assessments.

Multiple Sleep Latency Test.

The MSLT is an objective measure of physiologic sleepiness. 22 For this study there were four 20-minute nap opportunities at 2-hour intervals during the assessment day, with the first session beginning 2 hours after awakening from the previous night's sleep and 1 hour after study drug administration. Patients were instructed to lie quietly in the dark and not resist falling asleep. Polysomnographic (PSG) measures that included EEG, electrooculogram (EOG), and electromyogram (EMG) were used to determine sleep onset. The nap opportunity was terminated after 20 minutes if sleep onset did not occur, or after 15 minutes of sleep. The MSLT was conducted at baseline and week 9, on the second day of a 48-hour laboratory visit.

Maintenance of Wakefulness Test (MWT).

The MWT, using four 20-minute tests, 23,24 was used to measure objectively the ability to maintain wakefulness and was one of two primary outcome measures. For this test, patients were instructed to sit semirecumbent in a darkened room and try to remain awake. The four wakefulness tests were separated by 2-hour intervals throughout the day. PSG measures were used to determine sleep onset. The MWT was assessed at all visits except week 1 and was conducted on the first day of the 48-hour visit.

Epworth Sleepiness Scale (ESS).

Subjective sleepiness was measured using the ESS 25 at each study visit. Study patients estimated their likelihood of falling asleep during eight normal daily situations (e.g., while watching TV), on a four-point scale ranging from "would *never* doze" to "a *high* chance of dozing."

Clinical Global Impression (CGI).

Severity of illness was measured by an independent clinician using the CGI, the second primary outcome measure. 26 The CGI of Severity (CGI-S) was used to rate patients at baseline on a scale ranging from "Normal" to "Markedly ill." The patients' change in illness at subsequent visits (in weeks 3, 6, and 9) was rated by the same clinicians on a scale ranging from "Very much improved" to "Very much worse," using the Clinical Global Impression of Change (CGI-C).

Nocturnal polysomnography (NPSG).

Sleep was monitored with NPSG on the night before each MWT and MSLT assessment day. NPSG recording included EEG (central and occipital leads), EOG, EMG (submentalis and tibialis), electrocardiogram (ECG), oxygen saturation (oximetry), and measures of respiratory flow (nasal and oral) and effort (thoracic and abdominal). Sleep stages were scored using standard criteria. 27

Adverse experiences and drug safety.

Adverse experience reports were collected throughout the study, independent of study visits. Investigators rated the severity and the relationship of each adverse experience to study medication. Additional safety measures included clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs (including body weight), 12-lead ECG, and physical examinations conducted at study visits.

Statistical analyses.

The sample size in this study was based on the projected change in the two primary efficacy measures (MWT and CGI-C) at the end of 9 weeks of treatment. Assuming a 15% dropout rate by the end of treatment and a standard deviation of 8.0 minutes for MWT sleep latency, a sample size of 95 patients in each treatment group would provide at least 80% power to detect a 4.0 minute difference in mean MWT scores between treatment groups (two-tailed test at [alpha] = 0.050). For the dichotomous variable CGI-C, the same sample size was sufficient to provide at least 80% power to detect a one point difference in mean CGI-C scores (two-tailed test at [alpha] = 0.050). Efficacy analyses were performed on the intent-to-treat population. Specifically, intent to treat was defined as all randomized patients who received study medication and had at least one postbaseline measure from both primary endpoints (MWT and CGI-C).

For the purpose of analysis, baseline was defined as the last assessment before the first day of study drug administration. Demographic and baseline characteristics were tested to ensure the groups were comparable at baseline. Continuous variables were analyzed using an analysis of variance (ANOVA) model with factors for treatment and site. Categorical variables were analyzed using a Cochran-Mantel-Haenszel test stratified by site.

Each test of treatment effect was two-tailed at the $p < 0.05$ level of significance. The MWT was analyzed at baseline with an adjusted means ANOVA model for treatment including effects for site and treatment by site interaction. At other visits, analyses were based on adjusted means from an analysis of covariance (ANCOVA) model for treatment, including effects for site, and baseline measurement. (Unadjusted means are shown in data presentations.) Changes from baseline in efficacy parameters within each treatment group were analyzed by paired *t*-test. The MSLT and ESS were analyzed in a similar manner.

In addition, a time-to-event analysis using Kaplan-Meier estimation was conducted on the MWT mean sleep latency to provide an estimate of the probability of patients remaining awake over the 20-minute test for all three treatment groups. The log-rank test was used to test the significance of the differences among the three treatment groups.

The CGI-C was analyzed with the Cochran-Mantel-Haenszel statistic, adjusting effects for site and baseline value. Adverse experiences were analyzed using chi-square tests to make paired comparisons between treatment groups.

Statistically significant differences ($p < 0.05$) between the modafinil 400 mg group and the placebo group at endpoint for the MWT and CGI-C were the primary study endpoints defined a priori. All other measures and statistical comparisons were considered secondary endpoints. Independent data-entry personnel entered all trial data into a database, and the database was locked at the time of the randomized code break. Prospectively defined stopping rules were not warranted in this trial, although the blinded monitor could have halted the study at any time if safety was cause for concern.

Results.

Patients. A total of 273 patients were enrolled in this study. There were no significant differences between groups in baseline demographic characteristics or current narcolepsy symptoms. Treatment group values for demographic characteristics are shown in table 1 and narcolepsy history and current symptomatology are shown in table 2.

Table 1 *Baseline demographic characteristics of patients who received study medication*

Characteristic	Treatment group		
	Placebo	Modafinil 200 mg	Modafinil 400 mg
n	93	89	89
Age, y, mean (range)	41 (17–66)	42 (18–67)	42 (18–66)
Male/female	43/50	37/52	44/45
Race, n (%)			
White	81 (87)	79 (89)	75 (84)
African American	9 (10)	9 (10)	6 (7)
Hispanic	3 (3)	1 (1)	7 (8)
Other	0	0	1 (1)
Weight, kg, mean (SD)	81.2 (17.4)	79.2 (20.1)	82.5 (17.8)
Height, cm, mean (SD)	172.6 (9.2)	171.3 (10.8)	172.6 (11.0)

Table 1. Baseline demographic characteristics of patients who received study medication

Table 2 *Narcolepsy history and current symptomatology of patients who received study medication*

Characteristic	Treatment group		
	Placebo	Modafinil 200 mg	Modafinil 400 mg
n	93	89	89
Years (SD) since first narcolepsy symptoms	24.8 (15.7)	21.8 (14.5)	22.0 (14.8)
Years (SD) since first narcolepsy diagnosis	8.1 (11.4)	7.6 (10.8)	6.6 (9.2)
Narcolepsy symptoms, n (%)			
Daytime sleep attacks	85 (91)	83 (93)	87 (98)
Cataplexy	70 (75)	63 (71)	63 (71)
Hypnagogic hallucinations	66 (71)	49 (55)	50 (56)
Sleep paralysis	56 (60)	43 (48)	49 (55)
Disturbed nighttime sleep	69 (74)	63 (71)	61 (69)
Clinical Global Impression–Severity, n (%)			
Borderline ill	5 (6)	4 (5)	1 (1)
Slightly ill	12 (14)	18 (22)	11 (13)
Moderately ill	38 (43)	38 (46)	39 (45)
Markedly ill	26 (30)	19 (23)	30 (35)
Among the most extremely ill	7 (8)	4 (5)	5 (6)

Table 2. Narcolepsy history and current symptomatology of patients who received study medication

Of the 273 patients enrolled in the study, 271 received modafinil or placebo and were analyzed for safety (i.e., adverse experiences and clinical laboratory values). Owing to positive results on the initial drug screen, two patients were terminated from the study before administration of study medication. A total of 257 patients had at least one postbaseline MWT and CGI-C evaluation, the requirement for inclusion in efficacy analyses. A total of 240 patients received study medication in the discontinuation phase. Patient disposition and information regarding patient withdrawal are shown in figure 1.

One patient did not have a baseline CGI-S score and was excluded from the efficacy analysis. Other violations in entrance criteria or efficacy assessments occurred, but were not thought to affect efficacy evaluations or conclusions, and therefore did not result in patient discontinuation.

At baseline, treatment groups did not differ on the primary efficacy outcome measures (level of illness measured by the CGI-S, and sleepiness measured by the MWT) and ESS. However, baseline MSLT was higher for the modafinil 200 mg group compared with placebo ($p < 0.03$). Mean baseline values for MSLT, MWT, and ESS are shown in table 3. CGI-S scores indicated that over 70% of patients were moderately ill, markedly ill, or among the most extremely ill patients. For each treatment group, the mean baseline MSLT sleep latency was less than 3.0 minutes, the mean MWT sleep latency was 6.0 minutes or less, and the mean ESS score was 17.0 or greater.

Table 3 *Comparison of sleepiness measures between treatment groups for efficacy evaluable patients at baseline and week 9*

	Placebo		Modafinil 200 mg		Modafinil 400 mg	
Measure	Baseline	Week 9	Baseline	Week 9	Baseline	Week 9
MSLT sleep latency						
Number of patients	88	82	83	77	85	84
Mean min (SD)	2.2 (1.8)	3.5 (3.4)[a]	3.0 (2.2)[b]	4.9 (4.3)[a]	2.7 (2.0)	5.1 (4.0)[a,c]
MWT sleep latency						
Number of patients	88	83	83	78	86	84
Mean min (SD)	6.0 (5.0)	5.5 (4.5)	6.1 (4.9)	8.2 (5.9)[a,c]	5.9 (4.4)	7.8 (5.3)[a,c]
Epworth Sleepiness Scale						
Number of patients	86	85	83	79	85	82
Mean score (SD)	17.6 (4.0)	15.8 (4.8)[a]	17.4 (3.8)	13.0 (5.1)[a,c]	18.0 (3.4)	12.3 (5.1)[a,c]

[a] Significantly different from baseline ($p < 0.001$).
[b] Significantly different from placebo ($p < 0.03$).
[c] Significantly different from placebo ($p < 0.001$).

MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test.

Table 3. Comparison of sleepiness measures between treatment groups for efficacy evaluable patients at baseline and week 9[a] Significantly different from baseline ($p < 0.001$).[b] Significantly different from placebo ($p < 0.03$).[c] Significantly different from placebo ($p < 0.001$).MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test.

MSLT.

Mean MSLT sleep latency at week 9 was greater (5.1 minutes, $p < 0.001$) in the modafinil 400 mg treatment group, but not in the modafinil 200 mg treatment group (4.9 minutes), compared with placebo (3.5 minutes). However, MSLT sleep latency was greater in both modafinil treatment groups compared with baseline ($p < 0.001$). There was also a significant improvement from baseline in the placebo group at week 9 (see table 3).

MWT.

MWT mean sleep latency improved for each modafinil treatment group (200 mg and 400 mg) compared with placebo at every follow-up visit (weeks 3, 6, and 9; all p values < 0.001). The two modafinil treatment groups did not differ significantly from one another. Similarly, mean sleep latency was significantly increased compared with baseline. The change from baseline to weeks 3, 6, and 9 for both modafinil 200 mg and 400 mg treatment groups, but not the placebo group, was significant. Week 9 MWT means are shown in table 3.

At baseline, the probability of remaining awake was similar among the three treatments (modafinil 200 mg, modafinil 400 mg, and placebo; see figure 2). The median time to sleep onset at baseline was approximately 5 minutes (i.e., 50% of the patients had a probability of sleep onset at 5 minutes). At the end of 9 weeks, the probability of staying awake was higher ($p < 0.05$) with both modafinil treatment groups compared with placebo (50% of the patients receiving modafinil 200 mg and modafinil 400 mg were able to remain awake for approximately 7 minutes).

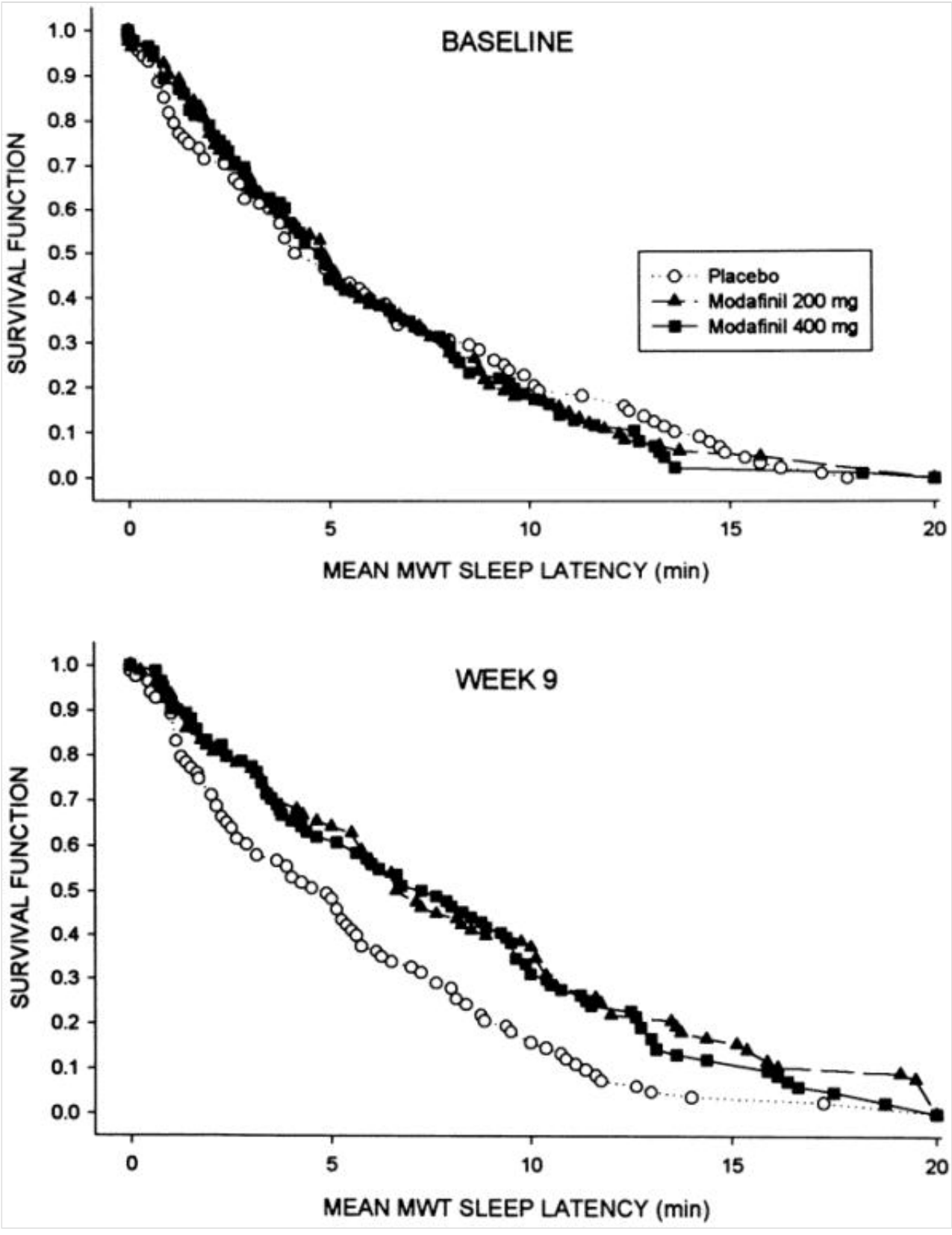

Figure 2. Ability to remain awake determined by Kaplan-Meier analysis for the Maintenance of Wakefulness Test (MWT) at baseline and after 9 weeks of treatment with modafinil 200 mg, modafinil 400 mg, or placebo.

A comparison of individual MWT trials at baseline, week 3, week 6, week 9, and week 11 study days was conducted. At week 3, modafinil 400 mg, but not modafinil 200 mg, significantly improved patients' ability to remain awake on the first MWT trial compared with placebo. Significant improvement was observed at week 3 MWT trials 2, 3, and 4 for both modafinil groups compared with placebo. At weeks 6, 9, and 11, MWT did not improve with modafinil treatment on the first trial for either modafinil group; however, MWT trials 2, 3, and 4 showed significant improvement. The MWT means for each nap session from baseline to week 11 are illustrated in figure 3.

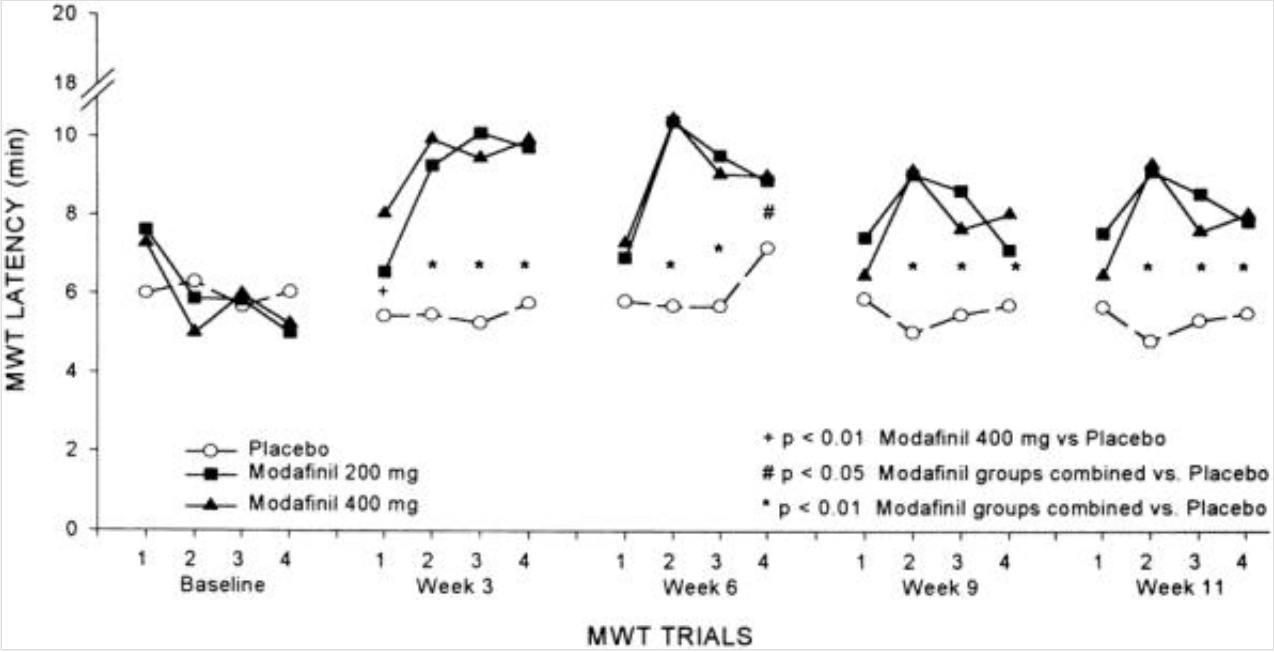

Figure 3. Maintenance of Wakefulness Test (MWT) mean sleep latency for each of the four 20-minute tests in patients with narcolepsy at baseline and after 3, 6, 9, and 11 weeks of treatment with modafinil 200 mg, modafinil 400 mg, or placebo.

During the discontinuation phase, patients who had been receiving modafinil, either 200 mg or 400 mg, experienced a return of sleepiness as measured by the MWT (figure 4). Patients discontinued from modafinil 200 mg regressed to baseline; patients discontinued from 400 mg modafinil had a rebound in sleepiness that appeared to exceed baseline level. There was a decrease ($p < 0.002$) in the change from baseline for this group after 2 weeks' discontinuation from medication. However, patients in the placebo group also had a decrease in change from baseline ($p < 0.03$).

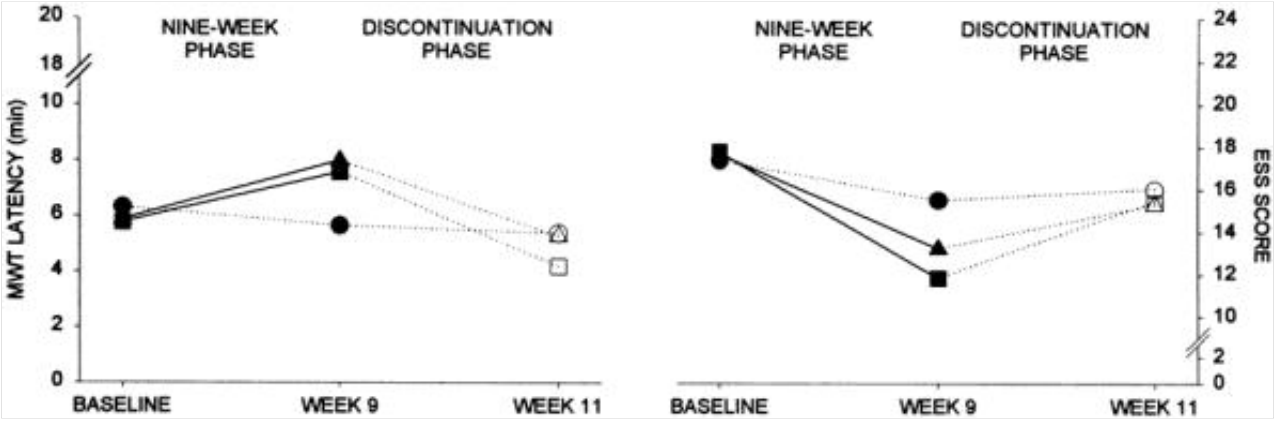

Figure 4. Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS) during the treatment and discontinuation phases in patients discontinued from modafinil 200 mg or modafinil 400 mg, or who remained on placebo. Nine-week: placebo = •, 200 mg modafinil = [black up pointing small triangle], 400 mg modafinil = [black small square]; Discontinuation: placebo = [white circle], 200 mg = [white up pointing small triangle], 400 mg = [white square]; dotted line, placebo; solid line, modafinil.

ESS.

Mean ESS score was reduced for both modafinil 200 mg and 400 mg treatment groups compared with placebo at week 9 (see table 3) and at weeks 3 and 6 (all p values < 0.001). The two modafinil groups did not differ at any assessment of self-reported sleepiness. All groups improved in subjective sleepiness from baseline at the week 3, 6, and 9 assessments (all p values < 0.001).

During the 2-week discontinuation phase, patients who were withdrawn from modafinil treatment experienced a regression in ESS to baseline (see figure 4).

CGI-C.

The percent of patients with improved clinician assessment of illness on the CGI-C was greater for modafinil 200 mg (46/80 patients, 58%) and 400 mg treatment groups (51/83 patients, 61%) compared with placebo (32/84 patients, 38%) at week 9 (both p values < 0.03;table 4). The percent of patients who improved was also greater in both modafinil groups at weeks 3 and 6 (all p values < 0.05). The percent of patients who improved in the modafinil 400 mg treatment group was not significantly greater than the percent of patients who improved in the 200 mg treatment group. The percent of patients who improved in the placebo treatment group was not significant at any postbaseline assessment.

Table 4 *Clinical Global Impression of Change (CGI-C) at week 9*

	Treatment group		
CGI-C	Placebo	Modafinil 200 mg	Modafinil 400 mg
Very much improved	0	7 (9)	5 (6)
Much improved	12 (14)	21 (26)	23 (27)
Minimally improved	20 (24)	18 (23)	23 (27)
No change	40 (47)	26 (33)	24 (29)
Minimally worse	9 (11)	7 (9)	5 (6)
Much worse	3 (4)	1 (1)	3 (4)
Very much worse	0	0	0

Values are n (%).

Table 4. Clinical Global Impression of Change (CGI-C) at week 9Values are n (%).

NPSG.

The modafinil treatment groups had slightly better sleep efficiency than the placebo group; this difference was only significant for the 200 mg group. There were no other statistically significant differences among treatment groups for NPSG variables, as shown in table 5.

Table 5 *Polysomnography measures during night 2 of week 9 study for patients evaluable for efficacy*

Measure	Treatment group		
	Placebo	Modafinil 200 mg	Modafinil 400 mg
Total sleep time, min	381.7 (69.6)	397.1 (64.6)	393.7 (59.3)
Sleep efficiency, % (sleep time/time in bed)	86.4 (11.2)	89.5 (7.7)*	88.9 (9.7)
Stage 1	14.9 (10.0)	13.2 (9.7)	12.4 (9.3)
Stage 2	47.9 (11.5)	48.6 (9.4)	48.8 (11.2)
Stage 3	6.3 (4.7)	7.0 (4.9)	7.9 (7.0)
Stage 4	8.6 (9.1)	8.3 (7.4)	7.2 (7.5)
REM	22.4 (6.5)	23.1 (6.7)	23.8 (5.8)
Sleep latency, min	5.6 (11.4)	4.6 (5.8)	5.2 (7.1)
REM latency, min	44.5 (45.1)	44.5 (44.9)	34.0 (32.4)
PLMS, n	85.0 (118.3)	97.1 (127.3)	63.2 (85.3)

Values are mean (SD).

* Significantly different from placebo ($p < 0.05$).

PLMS = periodic leg movements during sleep.

Table 5. Polysomnography measures during night 2 of week 9 study for patients evaluable for efficacyValues are mean (SD).* Significantly different from placebo ($p < 0.05$).PLMS = periodic leg movements during sleep.

Safety assessments.

During the 9-week treatment phase, there were no differences between the two modafinil treatment groups, or between the modafinil and placebo groups, in the percentage of patients who reported at least one adverse experience. Most adverse experiences were mild to moderate in severity (patient self report). All adverse experiences occurring in >=4% of patients in the 9-week treatment phase and 2-week discontinuation phase, regardless of relationship to study medication, are listed in table 6. During the 9-week treatment phase, there was a greater number of patients who had nausea in each of the modafinil groups (200 mg = 12/89 [13%]; 400 mg = 11/89 [12%], $p < 0.05$) compared with placebo (2/93 [2%]). There was also a greater number of patients with rhinitis in the 200 mg group (10/89 [11%];$p < 0.05$) compared with placebo (3/93 [3%]), but not for the 400 mg group (8/89 [9%]).

Table 6 *Most common adverse experiences (≥4% in any one treatment group), regardless of relationship to study medication*

	Treatment group		
9-Week treatment phase	Placebo, n = 93	Modafinil 200 mg, n = 89	Modafinil 400 mg, n = 89
Headache	41 (44)	37 (42)	48 (54)
Hypothermia	15 (16)	13 (15)	13 (15)
Back pain	13 (14)	9 (10)	10 (11)
Infection	11 (12)	10 (11)	14 (16)
Pain	10 (11)	9 (10)	5 (6)
Nausea	2 (2)	12 (13)*	11 (12)*
Dyspepsia	6 (6)	8 (9)	8 (9)
Rhinitis	3 (3)	10 (11)*	8 (9)
Diarrhea	4 (4)	7 (8)	9 (10)
Nervousness	7 (8)	8 (9)	4 (4)
2-Week discontinuation phase	Placebo/ placebo, n = 81	200 mg/ placebo, n = 69	400 mg/ placebo, n = 71
Headache	17 (21)	10 (14)	8 (11)
Rhinitis	6 (7)	4 (6)	1 (1)
Pain	4 (5)	3 (4)	1 (1)

Somnolence	1 (1)	7 (10)*	4 (6)
Infection	0	4 (6)*	3 (4)
Hypothermia	0	4 (6)*	2 (3)
Cataplexy	0	3 (4)	0
Dyspepsia	0	0	3 (4)

Values are n (%).

* Significantly different from placebo ($p < 0.05$).

Table 6. Most common adverse experiences (>=4% in any one treatment group), regardless of relationship to study medicationValues are n (%).* Significantly different from placebo ($p < 0.05$).

During treatment discontinuation more patients among those withdrawn from modafinil experienced somnolence than did placebo patients. The modafinil 200 mg group had a greater number of patients (7/69 [10%];$p < 0.05$) with somnolence than the placebo group (1/81 [1%]). However, this difference was not significant for the 400 mg group (4/81 [6%]). In addition, the modafinil 200 mg treatment group had a greater number of patients with hypothermia and infection (4/69 [6%] each;$p < 0.05$]) compared with placebo (0/81).

There were no meaningful differences among treatment groups at week 9 in clinical laboratory test results, vital signs (including body weight), 12-lead ECG, or physical examinations.

Discussion.

During the 9-week treatment phase, patients in the modafinil 200 mg and 400 mg groups demonstrated a statistically significant increase in the ability to stay awake during inactivity as measured by the MWT. There was also a statistically significant decrease in the rate of falling asleep when given the opportunity, as measured by the MSLT. It is important to note, however, that the improvement in objective sleepiness did not occur until approximately 3 hours after dosing (second MWT nap session). This suggests that the individual requirements for peak alertness should be evaluated and the administration of therapy gauged accordingly. Furthermore, although modafinil was an effective therapeutic agent and improved alertness in a profoundly sleepy population, it did not completely resolve the symptoms of EDS.

As with other stimulants, discontinuation of modafinil resulted in a return of both objective and subjective sleepiness. However, there was not a pattern of amphetamine-like withdrawal symptoms. Amphetamine withdrawal syndrome is defined as dysphoria and two (or more) of the following: fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation. 28 During the discontinuation phase of this study, no patients reported such a set of withdrawal-emergent adverse experiences. Moreover, reports of adverse experiences during the discontinuation period were not qualitatively different from those during the 9-week treatment period. These findings suggest that dependence did not develop during 9 weeks of daily modafinil dosing at therapeutic levels. This is consistent with the results of preclinical 29 and clinical 30,31 studies of modafinil that support its low abuse liability.

The inclusion criteria for the participating patients did not permit the use of anticataplectic medication, presumably reducing in our sample the representation of patients who have severe cataplexy. This same criterion was employed in a previous 18-center study conducted in the United States 19 and was unavoidable as monotherapy is usually a property of initial pivotal studies conducted to determine therapeutic effects. However, to our knowledge, there are no reports of unexpected adverse events or higher incidence rates of adverse events in patients new to modafinil who require concomitant anticataplectic medication. In open-label extensions of both the current study and the previous 18-center study, patients with cataplexy were permitted to take anticataplectic medication. The data are currently being analyzed and will be the subject of a future report.

There was a statistically significant increase in mean MSLT sleep latency in the placebo group between baseline and week 9 (1.3 minutes). However, this difference was not judged to be clinically meaningful because it was unaccompanied by corresponding changes in MWT or CGI. The modafinil-related changes from baseline in mean ESS, MWT, and MSLT values were statistically significant and were also associated with corresponding changes in CGI. These measures of sleepiness did not completely normalize for all patients, although they were normalized in approximately 10% to 20% of patients. However, lack of normalization is not unexpected. In previous small-scale efficacy studies of other stimulants, methylphenidate, dextroamphetamine, pemoline, and methamphetamine did not completely normalize objective measures of sleepiness. 32,33

Overall, the adverse event profile of modafinil in this study was similar to that reported in a previous 18-center US study, 19 except in our study, the incidence of nausea and rhinitis were significantly higher in one or both modafinil treatment groups than in the placebo group, whereas the difference in incidence rates was not statistically significant in the 18-center study. Also, the incidence of headache was different between the two trials. Headaches are common in patients with narcolepsy. 34 In the previous 18-center US study, 19 which had a similar design to our study but did not include the initial 1-week initiation of modafinil at 100 mg before administration of the 400 mg dose, a significantly higher incidence of headache was reported with either 200 mg or 400 mg of modafinil than with placebo (~50% versus 36%). In the study reported here, 44% of patients receiving placebo reported headache compared with 42% and 54%, respectively, of patients receiving modafinil 200 mg and modafinil 400 mg, but the incidence of headache was not significantly greater with modafinil than with placebo. However, it also should be noted that the incidence of headache in the placebo group was somewhat higher in this study than in the placebo group in the 18-center study, which may account for the different findings. Although it is possible that the step-up dosing routine used in the 400 mg treatment arm of this trial reduced the incidence of headaches relative to that observed in the 400 mg treatment arm of the 18-center trial, a rigorous comparison of the adverse event profiles in these two trials cannot be made.

In the previous 18-center study, discontinuations due to adverse events were significantly greater in the modafinil 400 mg group than in the modafinil 200 mg or placebo groups. Most of the patients who withdrew from the 400-mg treatment group did so within the first 10 days of treatment. In the current study, discontinuations due to adverse events did not differ significantly between the modafinil and placebo treatment groups. Thus, using a dose step-up routine in which modafinil is administered at 100 mg/day for 1 week before administering a 400 mg dose may lead to a lower incidence of intolerable adverse events that lead to treatment discontinuation. However, it is not possible to make definitive comparisons between the two trials.

Preclinical 10-12 and clinical experience, including the lack of withdrawal-related abstinence syndrome in this study, indicate that modafinil is a mechanistically unique compound for improving daytime alertness. The major risks of withdrawal symptoms and abuse potential characterizing currently prescribed agents such as amphetamine and methylphenidate do not appear to be an issue with modafinil. Furthermore, nocturnal sleep is not adversely affected. Thus, modafinil is not only a well-tolerated and effective treatment for EDS associated with narcolepsy, its minimal side-effect profile during dosing and withdrawal represent clinical advantages over existing therapeutics.

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*Site for this 21-center study.

Key words: Narcolepsy; Modafinil; Sleepiness; Somnolence; Performance; Wakefulness; Withdrawal; Dependence.