

ORIGINAL ARTICLE

Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder

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ABSTRACT

BACKGROUND

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Patients with shift-work sleep disorder chronically have excessive sleepiness during night work and insomnia when attempting to sleep during the day. We evaluated the use of modafinil for treating sleepiness in patients with this disorder.

METHODS

In a three-month, double-blind trial, we randomly assigned 209 patients with shift-work sleep disorder to receive either 200 mg of modafinil or placebo before the start of each shift. Assessments were performed with the use of the nighttime Multiple Sleep Latency Test, the Clinical Global Impression of Change, the Psychomotor Vigilance Test, diaries of patients, and daytime polysomnography. After randomization, we conducted monthly assessments.

RESULTS

Treatment with modafinil, as compared with placebo, resulted in a modest improvement from baseline in mean (\pm SEM) nighttime sleep latency (the interval between the time a person attempts to fall asleep and the onset of sleep) (1.7 ± 0.4 vs. 0.3 ± 0.3 minutes, respectively; $P=0.002$), and more patients had improvement in their clinical symptoms (74 percent vs. 36 percent, respectively; $P<0.001$). Patients who were receiving modafinil also had a reduction in the frequency and duration of lapses of attention during nighttime testing of their performance on the Psychomotor Vigilance Test (change from baseline, a reduction in lapse frequency of 2.6 vs. an increase of 3.8, respectively; $P<0.001$), and proportionally fewer patients reported having had accidents or near accidents while commuting home (29 percent vs. 54 percent, respectively; $P<0.001$). Despite these benefits, patients treated with modafinil continued to have excessive sleepiness and impaired performance at night. Modafinil did not adversely affect daytime sleep as compared with placebo. Headache was the most common adverse event.

CONCLUSIONS

Treatment with 200 mg of modafinil reduced the extreme sleepiness that we observed in patients with shift-work sleep disorder and resulted in a small but significant improvement in performance as compared with placebo. However, the residual sleepiness that was observed in the treated patients underscores the need for the development of interventions that are even more effective.

NEARLY 6 MILLION AMERICANS WORK at night on a permanent or rotating basis.¹ Night-shift work disrupts both sleep and waking because of the misalignment of circadian regulation and sleep-wake behavior.^{2,3} In about 5 to 10 percent of night-shift workers, the sleep-wake disturbance is severe enough to warrant diagnosis as shift-work sleep disorder,⁴⁻⁶ which is characterized by a level of excessive sleepiness during night work and insomnia when attempting to sleep in the daytime that is judged to be clinically significant.^{4,5} Persons with shift-work sleep disorder miss family and social activities more frequently and have higher rates of ulcers, sleepiness-related accidents, absenteeism, and depression than do night-shift workers without the disorder⁶ — conditions long known to affect a subgroup of shift workers.⁷ We conducted a study to evaluate the efficacy and safety of 200 mg of modafinil in patients with excessive sleepiness associated with chronic shift-work sleep disorder. This agent has shown efficacy in the treatment of narcolepsy and the residual excessive sleepiness in patients with obstructive sleep apnea.⁸⁻¹¹

METHODS

PATIENTS

Adults between the ages of 18 and 60 years were eligible if they worked each month at least five night shifts for 12 hours or less, with 6 hours or more worked between 10 p.m. and 8 a.m. and at least three shifts occurring consecutively. Patients were diagnosed with shift-work sleep disorder in accordance with criteria stipulated in the *International Classification of Sleep Disorders*.⁵ Our diagnostic criteria included a primary symptom of excessive sleepiness on the night shift and insomnia during opportunities for daytime sleep and the absence of other primary sleep disorders, other medical conditions, and medications that might cause sleepiness. Patients had to have reported chronic excessive sleepiness (≥ 3 months) during night shifts; a Clinical Global Impression of Severity¹² rating of moderately ill or worse for sleepiness on work nights, including the commute home from work; an average latency to sleep onset of 6 minutes or less during 20-minute nap opportunities at 2-hour intervals during the night, as measured by the Multiple Sleep Latency Test^{13,14}; and a sleep efficiency of 87.5 percent or less as determined by daytime polysomnography. Participants provided written informed consent.

STUDY DESIGN AND CONDUCT

The three-month randomized, double-blind, placebo-controlled study was conducted in the United States between December 2001 and September 2002. At each of 28 centers, an institutional review board approved the informed-consent statement and protocol. The study included a screening visit to assess eligibility; a baseline visit on the night after the patient had worked three or more consecutive night shifts in order to establish pretreatment levels of alertness and performance, the severity of sleepiness, and results of daytime polysomnography; and a randomization visit for the administration of the study drug. Thereafter, patients were evaluated monthly during an overnight laboratory shift after having worked for three or more consecutive nights.

Patients were randomly assigned (in a 1:1 ratio) to receive 200 mg of modafinil (Provigil, Cephalon), formulated as 100-mg tablets, or an identical-appearing placebo, taken 30 to 60 minutes before the start of each night shift. Assessment of treatment adherence was performed at visits after the initial baseline visit.

MEASURES OF EFFICACY

Sleep latency during laboratory night shifts was measured by polysomnography at two-hour intervals, starting at 2 a.m., with the use of the Multiple Sleep Latency Test (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).^{13,14} To assess alertness with the use of a performance measure, a 20-minute Psychomotor Vigilance Test¹⁵ was administered every two hours, starting at 1 a.m. The level of sleepiness as reported by patients was assessed hourly using the Karolinska Sleepiness Scale,¹⁶ which ranges from 1 (very alert) to 9 (very sleepy). The investigator-rated Clinical Global Impression of Change,¹² the scoring of which ranges from 1 (very much improved) to 7 (very much worse), was used to assess changes from baseline in the severity of sleepiness during night shifts, including the commute to and from work. Patients also completed electronic diaries containing questions about sleepiness, sleep, and caffeine use during the night shift and the commute home.

There were two prespecified primary efficacy variables. The first was the rating on the Clinical Global Impression of Change test for sleepiness during the night shift, including the commute to and from work, at the final visit. This test assessed the extent to which treatment effects could be rec-

ognized by patients and physicians. The second prespecified primary efficacy variable was the change between baseline and the final visit (i.e., at the third month or at withdrawal from the study) in overall mean sleep latency on the basis of results of the nighttime Multiple Sleep Latency Test. This test has been validated as a measure of sleepiness during the day but not at night, so questions remain regarding which results on this test indicate pathological sleepiness during the night and what level of improvement at night is clinically meaningful. Therefore, as recommended,¹⁷ one of our secondary outcome measures — the frequency and duration of lapses of attention during performance on the Psychomotor Vigilance Test¹⁵ — served as a validated and objective measure of alertness at night.

SAFETY ASSESSMENTS

Adverse events were monitored throughout the study. Blood pressure and heart rate were monitored, and clinical laboratory tests (including chemical and hematologic studies) were conducted at each visit. Physical examination and electrocardiography were performed at the screening visit and the final visit.

OTHER ASSESSMENTS

Polysomnography was conducted for eight hours, starting at 10 a.m. after baseline and after final laboratory night shifts. Melatonin concentrations were measured from saliva samples.¹⁸

STATISTICAL ANALYSIS

A total of 204 patients were selected for enrollment in the study (see the Supplementary Appendix for calculations regarding the sample size). Randomization was performed with the use of a central randomization process and stratified by center with the use of permuted blocks of two. On the basis of the sample that was available for efficacy analysis, there was at least 80 percent power (with the use of post hoc power calculations) for the statistical inference on both prespecified primary end points (assuming an alpha level of 0.05).

Comparisons of continuous demographic variables between groups were conducted with the use of analysis of variance, with treatment as a factor. Discrete categorical demographic variables were compared with the use of the chi-square test or Fisher's exact test. Included in efficacy analyses were patients who had been randomly assigned to treatment and received at least one dose of study drug and who had had a baseline assessment and

at least one assessment after baseline on either the Multiple Sleep Latency Test or the Clinical Global Impression of Change. For the final-visit efficacy analysis, data from the patients' last visit on or before the third month were used.

Comparisons between the groups were conducted on the change between the baseline visit and the final visit with regard to variables on the Multiple Sleep Latency Test, scores on the Karolinska Sleepiness Scale, polysomnographic measures, and data from patients' diaries related to sleepiness ratings, unintentional and intentional sleep episodes during the night shift, the consumption of caffeinated drinks, and sleep efficiencies. All of these variables were analyzed with the use of analysis of variance, with treatment and site as factors. Data from the Clinical Global Impression of Change test were evaluated with the use of a Cochran–Mantel–Haenszel chi-square test, with adjustment made for site and modified ridit scores used to account for ordered categories.

Comparisons were made with the use of a chi-square test or Fisher's exact test on data from diaries that were related to the percentage of patients reporting mistakes, near accidents, or accidents during the night shift; unintentional sleep episodes, accidents, or near accidents during the commute home; and rates of adverse events. Comparisons of performance on the Psychomotor Vigilance Test and of melatonin phase were performed with the use of the Wilcoxon nonparametric rank test. There were no interim analyses of the data. All reported P values are two-sided and not adjusted for multiple testing.

Six academic investigators and four representatives of the sponsor designed the study and analyzed the data. Drs. Czeisler, Walsh, Roth, and Dinges conceived of and designed the study in collaboration with representatives of the corporate sponsors, Drs. Hughes, Niebler, Arora, and Kingsbury. Data were fully accessible to all group members, with the study sponsor placing no limits on interpretation or publication. The study designers vouch for the completeness and accuracy of the analyses. All authors were involved with the preparation of the manuscript.

RESULTS

DISPOSITION AND BASELINE CHARACTERISTICS OF PATIENTS

A total of 4533 shift workers were prescreened through telephone calls placed to a central agency;

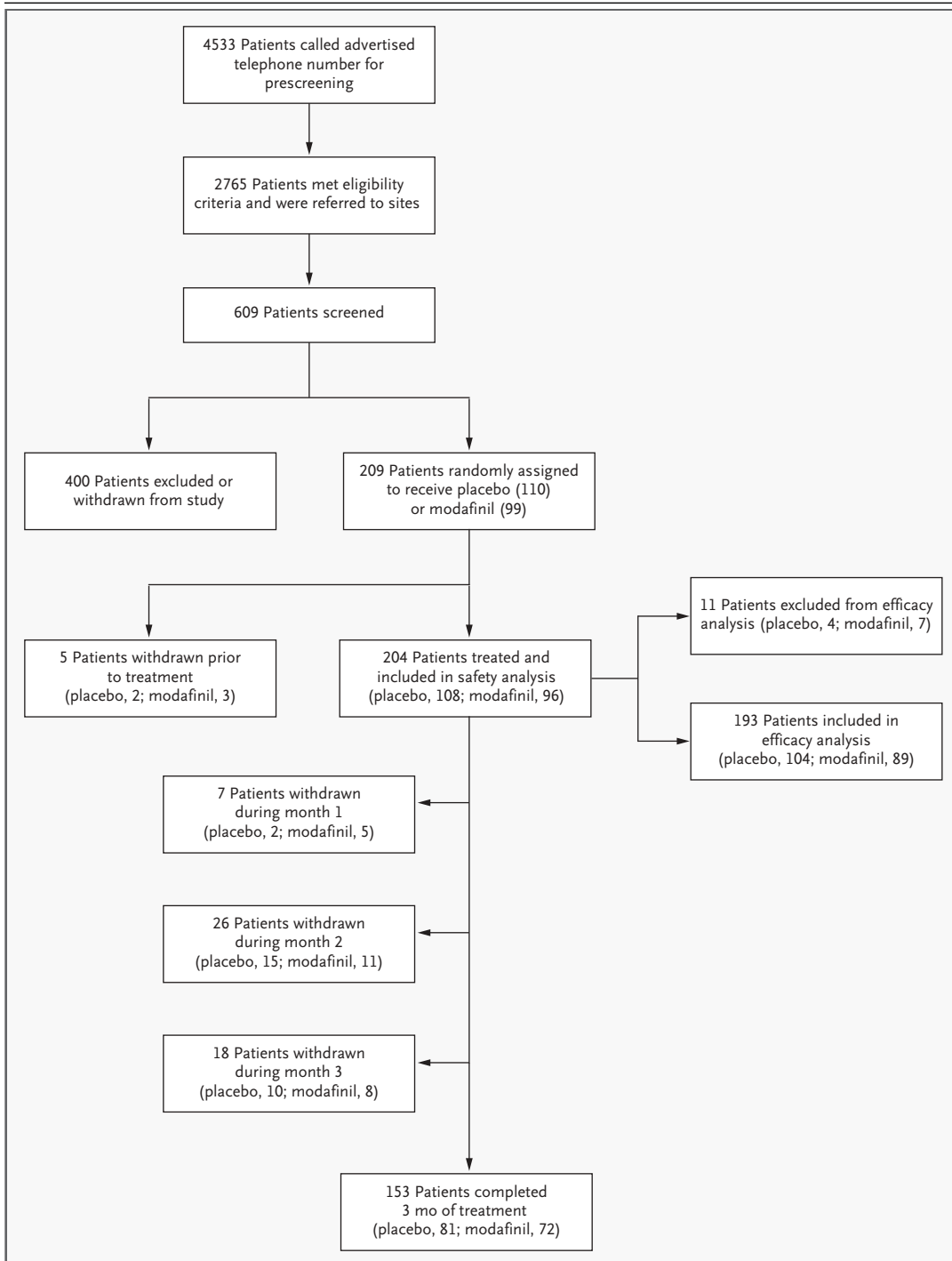


Figure 1. Enrollment and Status of Patients in the Study.

Patients who were initially screened to participate in the study were recruited by advertisements or were referred by investigators. Patients who were randomly assigned to treatment and received at least one dose of study drug and who had a baseline assessment and at least one assessment after baseline for any given variable were included in the efficacy analysis (see the Supplementary Appendix for more details).

2765 workers were referred to study sites. Of 609 patients undergoing laboratory testing, 400 were judged ineligible or withdrew (Fig. 1 and Supplementary Appendix). Most commonly, ineligible patients did not meet inclusion criteria for polysomnography (107 patients) or sleep latency (53) or either withdrew their consent or were lost to follow-up (118). Of 209 patients who were randomly assigned to receive the study drug, 204 patients received the drug, and 153 patients completed the study. At baseline, there were no significant differences in demographic variables, shift-work type, sleepiness, performance, and results on polysomnography between the group that received modafinil and the one that received placebo (Table 1). The patients who completed the trial and those who did not had similar baseline values for the primary outcome variables (as measured by the Multiple Sleep Latency Test and the Clinical Global Impression of Severity test) and similar results on polysomnography. Patients were severely sleepy at baseline, with overall mean (\pm SD) sleep latencies of 2.0 ± 1.8 minutes and 2.1 ± 1.5 minutes for the placebo and modafinil groups, respectively.

EFFICACY MEASURES

Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the Clinical Global Impression of Change test at the final visit, as compared with 36 percent in the placebo group ($P<0.001$) (Fig. 2A, and Table 2 in the Supplementary Appendix). Overall mean (\pm SEM) sleep latency, as measured by the Multiple Sleep Latency Test, increased from 2.1 minutes at baseline to 3.8 minutes at the final visit with modafinil (change, 1.7 ± 0.4 minutes; $P<0.001$) but not with placebo (2.04 at baseline vs. 2.37 at the final visit; change, 0.3 ± 0.3 ; $P=0.24$) (Fig. 2B). Sleep latency was significantly greater in the modafinil group than in the placebo group ($P=0.002$). This improvement in sleep latency with modafinil versus placebo was found at 2 a.m. ($P=0.02$) and 4 a.m. ($P<0.001$) (Fig. 2C), but not at 6 a.m. ($P=0.45$) or 8 a.m. ($P=0.17$) (Fig. 2D). A higher proportion of patients receiving modafinil had a positive change in the sleep-latency score from pretreatment to the final visit (Fig. 1 in the Supplementary Appendix). Notwithstanding this improvement, sleep latencies during the night shift averaged less than six minutes, which is below the level considered normal during the daytime.

Significant differences between the modafinil

group and the placebo group were also found for performance on the Psychomotor Vigilance Test. The median number of lapses of attention in 20-minute tests during the night was 12.50 at baseline and 10.25 at the final visit for the modafinil group (median change from baseline, -2.6 ; $P=0.012$). In the placebo group, the median number of lapses per test bout was 16.13 at baseline and 23.75 at the final visit (median change from baseline, 3.8 ; $P=0.008$). The groups did not differ significantly at baseline ($P=0.797$), but they did differ significantly at the final visit ($P=0.005$), and the change in lapses of attention during performance of the Psychomotor Vigilance Test from baseline to the final visit was significant for modafinil versus placebo ($P<0.001$) (Fig. 2E).

The duration of lapses showed a similar result, decreasing from baseline (780 msec) to the final visit (669 msec) for patients receiving modafinil and increasing from baseline (852 msec) to the final visit (1235 msec) for those receiving placebo. This resulted in a significant difference at the final visit ($P=0.004$) and in the change from baseline to the final visit in favor of modafinil versus placebo ($P=0.019$). Sleepiness levels on the Karolinska Sleepiness Scale were also significantly reduced for patients receiving modafinil (baseline mean, 7.3; final visit mean, 5.8; change, -1.5 ± 0.2), as compared with placebo (baseline, 7.1; final visit, 6.7; change, -0.4 ± 0.2) ($P<0.001$) (Fig. 2F). In general, the results of efficacy measures at the final visit were observed at the first visit after baseline and sustained throughout subsequent visits (see the Supplementary Appendix).

DATA DERIVED FROM ELECTRONIC DIARIES

There were significant effects for three of the seven efficacy variables in the patients' diaries (Table 2). As compared with placebo, 200 mg of modafinil reduced the maximum level of sleepiness during night-shift work ($P<0.001$ for the change from baseline vs. placebo) and the level of sleepiness during the commute home ($P=0.01$), and 25 percent fewer patients receiving modafinil reported having had accidents or near accidents during the commute home ($P<0.001$). Modafinil treatment during night shifts had no statistically significant effects on unintentional or intentional sleep episodes, mistakes, accidents or near accidents, or caffeine consumption (Table 2). During days following nights off, there were no significant differences in caffeine use and sleep efficiency between the modafinil

Table 1. Baseline Characteristics, Test Scores, and Severity of Sleepiness among Patients with Shift-Work Sleep Disorder Treated with Modafinil or Placebo.*

Characteristic	Placebo (N=108)	Modafinil (N=96)	P Value
Mean age — yr	38.8±9.1	37.5±9.2	0.31
Sex — no. (%)			0.81
Male	67 (62)	58 (60)	
Female	41 (38)	38 (40)	
Race or ethnic background — no. (%)†			0.63
White	75 (69)	62 (65)	
Black	27 (25)	25 (26)	
Asian	0	1 (1)	
Other	6 (6)	8 (8)	
Type of shift work — no. (%)			0.35
Permanent night shift	95 (88)	89 (93)	
Rotating shift	13 (12)	7 (7)	
Night shifts worked per mo — no. (%)			0.02
5–10	11 (10)	2 (2)	
>10	97 (90)	94 (98)	
Mean sleep latency — min‡	2.0±1.8	2.1±1.5	0.89
No. of lapses of attention§	24.3±26.4	22.5±23.0	0.69
Patient-estimated sleepiness¶	7.1±1.2	7.3±1.0	0.43
Sleepiness severity — no. (%)			0.91
Moderately ill	53 (49)	49 (51)	
Markedly ill	34 (31)	29 (30)	
Severely ill	17 (16)	16 (17)	
Among the most extremely ill	4 (4)	2 (2)	
Daytime polysomnographic measures			
Sleep latency — min	8.0±10.9	7.8±10.4	0.91
Sleep efficiency — %**	74.1±12.6	73.7±11.7	0.83

* Plus-minus values are means ±SD.

† Race or ethnic background was self-reported.

‡ A mean sleep latency of less than 5 minutes indicates a pathological level of daytime sleepiness. In control groups, sleep latencies for adult volunteers without sleepiness occur in the range of 10 to 20 minutes.¹³ Multiple Sleep Latency Test data were available for 96 patients receiving placebo and for 86 patients receiving modafinil at baseline.

§ For the Psychomotor Vigilance Test, patients were instructed to respond to randomly occurring visual stimuli appearing in the window of a portable Psychomotor Vigilance Test-192 device (Ambulatory Monitoring) by pushing a button as quickly as possible. Reaction times were collected from four 20-minute sessions conducted at 2-hour intervals. Psychomotor Vigilance Test data were available for 64 patients receiving placebo and for 60 patients receiving modafinil at baseline.

¶ Ratings on the Karolinska Sleepiness Scale range from 1 (very alert) to 9 (very sleepy, great effort to keep awake, fighting sleep). Patients rated their level of sleepiness at the time of testing, not retrospectively. Karolinska Sleepiness Scale data were available for 95 patients receiving placebo and for 85 patients receiving modafinil at baseline.

|| Polysomnographic data were available for 78 patients receiving placebo and for 72 patients receiving modafinil at baseline.

** Sleep efficiency was calculated as the sleep duration divided by the time spent in bed multiplied by 100.

group and the placebo group (Table 2). The use of sleeping pills was not specifically monitored, although concomitant use of medications was queried at each visit. One of 96 patients in the modafinil group reported the use of a prescription hypnotic

agent, whereas none of the 108 patients in the placebo group did. Five of the 96 patients in the modafinil group reported the use of over-the-counter sleep aids versus 1 of the 108 patients in the placebo group (P=0.102).

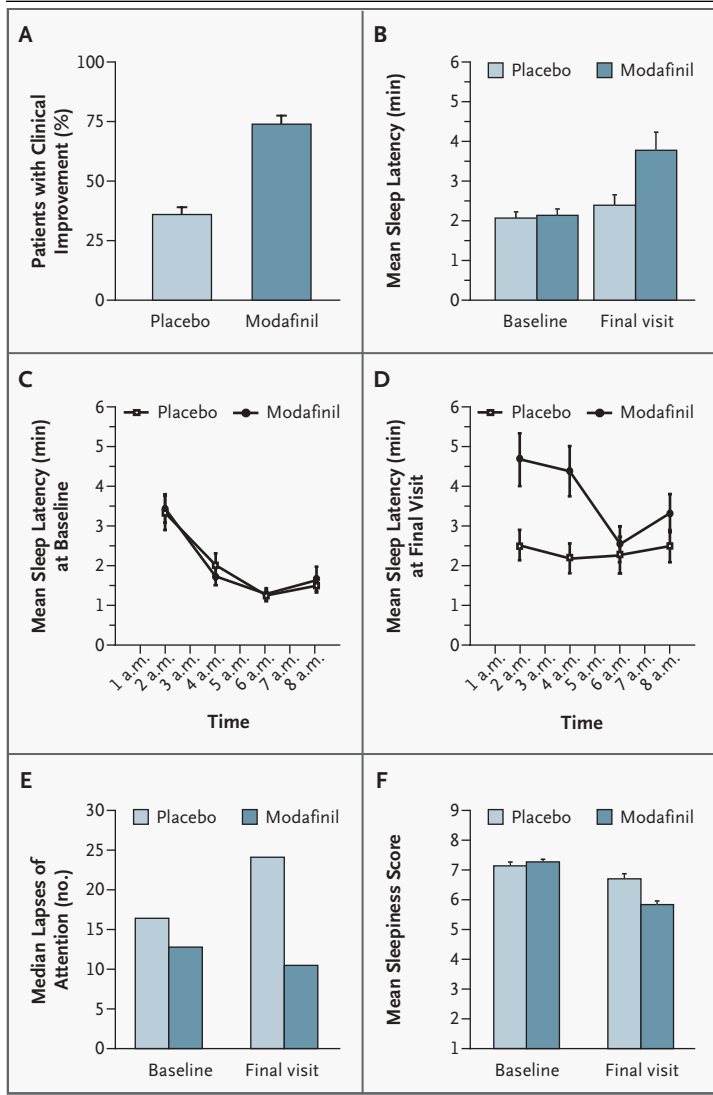


Figure 2. Efficacy Measures Used to Assess the Effects of Modafinil versus Placebo in Patients with Shift-Work Sleep Disorder.

Panel A shows the percentage of patients receiving placebo (104 patients) and modafinil (89 patients) whose symptoms were rated as clinically improved during night shifts (including the commute to and from work) on the basis of the results of the Clinical Global Impression of Change test at the final visit ($P < 0.001$). Patients had to have undergone a baseline assessment and at least one assessment after baseline in order to be included in the analysis. T bars represent 1 SEM. In Panel B, the mean (\pm SEM) sleep latency, as measured by the Multiple Sleep Latency Test, during the night shift for the placebo group (96 patients at both the baseline visit and the final visit) was 2.04 ± 0.2 minutes at baseline and 2.37 ± 0.3 minutes at the final visit ($P = 0.24$ for the within-treatment comparison). For the modafinil group (86 patients at both the baseline visit and the final visit), the overall mean sleep latency was 2.07 ± 0.2 at baseline and 3.77 ± 0.5 at the final visit ($P < 0.001$ for the within-treatment comparison). The difference in the change in score on the Multiple Sleep Latency Test from baseline to the final visit for modafinil versus placebo was statistically significant ($P = 0.002$). Panel C and Panel D show the mean sleep latency values at each Multiple Sleep Latency Test from 2 a.m. to 8 a.m. for 96 patients receiving placebo and 86 patients receiving modafinil during the baseline and final laboratory night shift, respectively. Patients had to have undergone a baseline assessment and at least one assessment after baseline in order to be included in the analysis. The difference in change from baseline to the final visit for modafinil versus placebo was statistically significant at 2 a.m. ($P = 0.02$) and at 4 a.m. ($P < 0.001$). In Panel E, the median number of lapses of attention in performance of the Psychomotor Vigilance Test for the placebo group (baseline, 64 patients; final visit, 69 patients) per 20-minute test bout was 16.13 at baseline and 23.75 at the final visit (median change from baseline, $+3.75$; $P = 0.008$). For the modafinil group (baseline, 60 patients; final visit, 66 patients), the median number of lapses of attention was 12.50 at baseline and 10.25 at the final visit (median change from baseline, -2.63 ; $P = 0.012$). The modafinil group and placebo group did not differ significantly at baseline ($P = 0.8$) but did at the final visit ($P = 0.005$). The difference in change from baseline to the final visit for modafinil versus placebo was statistically significant ($P < 0.001$). In Panel F, the mean sleepiness rating on the Karolinska Sleepiness Scale for the placebo group (baseline, 95 patients; final visit, 97 patients) was 7.1 ± 0.1 at baseline and 6.7 ± 0.2 at the final visit ($P = 0.01$ for the within-treatment comparison). For the modafinil group (baseline, 85 patients; final visit, 86 patients), the overall mean sleepiness score was 7.3 ± 0.1 at baseline and 5.8 ± 0.2 at the final visit ($P < 0.001$ for the within-treatment comparison). The difference in change from baseline to the final visit for modafinil versus placebo was statistically significant ($P < 0.001$).

SAFETY OUTCOMES

Headache was the most common adverse event associated with treatment in both groups (Table 3). No serious adverse events were reported for patients in the modafinil group. More patients in the modafinil group than in the placebo group had insomnia (6 percent vs. 0 percent, respectively; $P = 0.01$). Adverse events that were not serious but resulted in the inability to carry out usual activities were defined as severe. Eleven patients reported such events (six in the modafinil group and five in the placebo group) (see Table 3 of the Supplementary Appendix). No clinically meaningful differences in vital signs, clinical laboratory measures, phys-

Table 2. Variables for Patients with Shift-Work Sleep Disorder Treated with Modafinil or Placebo, as Derived from Diaries.*

Variable	Placebo (N=108)			Modafinil (N=96)			P Value
	Baseline	After Baseline	Change	Baseline	After Baseline	Change	
During night shift							
Maximum level of sleepiness — score†	7.4±1.0	6.6±1.3	-0.9±1.0	7.3±0.9	5.4±1.5	-1.9±1.4	<0.001‡
No. of unintentional sleep episodes†	1.2±1.3	0.6±0.7	-0.6±1.0	1.0±1.1	0.2±0.4	-0.8±0.9	0.20
No. of intentional sleep episodes†	0.5±0.8	0.4±0.5	-0.1±0.5	0.4±0.5	0.2±0.4	-0.2±0.4	0.13
No. of caffeinated drinks consumed†	1.3±1.1	1.1±0.9		1.3±1.2	1.0±1.0		0.10
Patients reporting mistakes, accidents, or near accidents — no. (%)§		59 (55)			46 (48)		0.34
During the commute home							
Level of sleepiness — score†	5.9±1.8	5.4±1.7	-0.6±1.2	5.5±1.8	4.4±1.6	-1.1±1.5	0.012‡
Patients reporting unintentional sleep episodes — no. (%)§		47 (44)			34 (35)		0.24
Patients reporting accidents or near accidents — no. (%)§		58 (54)			28 (29)		<0.001¶
During days after night shift							
No. of caffeinated drinks consumed **	1.0±1.3	0.6±0.7	-0.4±1.0	0.9±1.1	0.7±0.8	-0.2±1.0	0.61
Sleep efficiency — %**††	78.0±20.7	87.5±14.1	9.5±18.3	80.3±19.9	87.5±14.4	7.3±18.5	0.55

* Plus-minus values are means ±SD. Patients recorded responses in electronic diaries on actual work nights. Sleepiness scores were obtained with the use of the Karolinska Sleepiness Scale. Analysis includes patients with baseline values and values after baseline. For each patient, baseline values and values after baseline are average values calculated before and after the start of double-blind treatment.

† Data were available for 84 patients receiving placebo and for 79 patients receiving modafinil.

‡ P value is for the change from baseline for modafinil versus placebo.

§ Values are for the number of patients with a value after baseline. Patients were counted once.

¶ P value is for modafinil versus placebo.

|| Data were available for 85 patients receiving placebo and for 78 patients receiving modafinil.

** The time interval was from the end of the night shift until 60 minutes after waking up from the last sleep episode.

†† Data were available for 84 patients receiving placebo and for 78 patients receiving modafinil. Sleep efficiency was calculated as the sleep duration divided by the time spent in bed multiplied by 100 so that scores could range from 0 to 100 percent.

ical examinations, or electrocardiographic findings were observed between treatment groups.

OTHER ASSESSMENTS

There were no significant differences between modafinil and placebo with respect to any measurement of daytime sleep, including sleep duration, latency, and efficiency and the proportion and distribution of sleep stages (Table 4). Patients receiving modafinil did not differ significantly from those receiving placebo in the mean change in melatonin phase from baseline to the final visit (0.4 hour and -0.1 hour, respectively).

DISCUSSION

Circadian-rhythm sleep disorders have long been recognized as important disruptions of sleep-wake behaviors in a subgroup of people who are substantially more impaired than others with similar schedules.¹⁹⁻²¹ Such differential vulnerability regarding cognitive impairment that is induced by extended wakefulness at night is a stable characteristic of these persons.^{22,23} Estimates of the proportion of night-shift workers who meet the clinical criteria of both excessive sleepiness and daytime insomnia that we used to diagnose shift-work sleep

Table 3. Adverse Events in Patients Diagnosed with Shift-Work Sleep Disorder Treated with Modafinil or Placebo.*

Adverse Event	Placebo (N=108)	Modafinil (N=96)	no. (%)	
Headache	21 (19)	25 (26)		
Infection	11 (10)	6 (6)		
Nausea	3 (3)	9 (9)		
Rhinitis	7 (6)	3 (3)		
Accidental injury	9 (8)	6 (6)		
Abdominal pain	2 (2)	6 (6)		
Nervousness	1 (<1)	6 (6)		
Insomnia	0 (0)	6 (6)†		
Dry mouth	4 (4)	5 (5)		
Tooth disorder	1 (<1)	5 (5)		

* Patients could report more than one event. Adverse events that were associated with treatment included untoward medical occurrences of all causes that developed or worsened in severity during the course of double-blind treatment. The adverse events that are listed are those that occurred in 5 percent or more of patients in either the modafinil group or the placebo group.

† P=0.01 for the comparison between modafinil and placebo.

disorder range from 5 to 10 percent.^{4-6,24} The burden of illness in persons with shift-work sleep disorder is substantial, as compared with shift workers without the disorder.^{6,7,24,25} Thus, shift-work sleep disorder is more than simply being tired on the night shift.

In this randomized, placebo-controlled study — the first such trial in the investigation of shift-work sleep disorder — improvements in alertness and performance were found with 200 mg of modafinil in measures of sleep latency, clinical-impression rating, sustained-attention performance, and patient-estimated sleepiness. Consistent with this profile were reductions in patient-estimated sleepiness on work nights and during the morning commute home. Despite these benefits, patients treated with modafinil continued to have high levels of sleepiness and impaired performance at night.

Although patients receiving 200 mg of modafinil continued to have lapses in performance on the Psychomotor Vigilance Test,²⁶⁻²⁹ there were twice as many lapses per night at the final visit in the placebo group as there were in the modafinil group, and the mean duration of these lapses in the modafinil group was nearly twice as long as that in the placebo group. It is likely that the effects of modafinil on sustained-attention performance derive, at least in part, from its effects on reducing the instability of

wakefulness caused by brief episodes of sleep intruding into waking performance.^{15,30,31} Although lapses of attention were reduced, they remained at a high level in the treatment group. This suggests that although modafinil improves the measured levels of performance, it is far from what is needed for these patients to function at a normal level.

The results of this study also suggest that 200 mg of modafinil does not affect circadian adaptation to night-work schedules. Thus, the ability of modafinil to treat symptoms of excessive sleepiness in patients diagnosed with shift-work sleep disorder is a result of an improvement in wakefulness during the nocturnal work shift, similar to the improved alertness shown in other disorders of sleep and wakefulness,⁸⁻¹¹ and not an improvement in the alignment between internal circadian rhythms and the work-sleep schedule.

Several considerations limit the interpretation and applicability of the findings. There remains a need for validated criteria and clinical instruments for assessing excessive sleepiness in shift-work sleep disorder. Although the Multiple Sleep Latency Test is sensitive to changes in sleepiness during nighttime hours^{32,33} and is recommended for assessing sleepiness at night in this population,⁵ it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness, particularly in the absence of objectively monitored sleep in the laboratory on the day before testing. As recommended in the literature,¹⁷ we therefore used a validated performance measure — the Psychomotor Vigilance Test — to assess alertness at night, the results of which were consistent with the nighttime data from the Multiple Sleep Latency Test. Because patients worked in a variety of industries, actual work performance was not evaluated. We do not know how the laboratory sleep and performance variables that were used in the study may apply to actual on-the-job performance, although we do show concordance of results for measures of alertness, performance on the Psychomotor Vigilance Test, and diary data that collectively suggest a positive effect on personal and public safety. Although the study was open to both permanent and rotating night-shift workers with shift-work sleep disorder, the vast majority of study participants (90 percent) were permanent night-shift workers. Thus, it is not appropriate to generalize the findings of the study to patients who work on other types of shifts that include nighttime hours. The patients who met the criteria of having shift-work sleep dis-

Table 4. Daytime Polysomnographic Measures for Patients with Shift-Work Sleep Disorder Treated with Modafinil or Placebo.*

Polysomnographic Variable	Placebo (N=78)			Modafinil (N=72)			P Value
	Baseline	Final	Change	Baseline	Final	Change	
Time in bed (min)	479.7±2.3	478.0±9.1	-1.7±9.3	479.2±5.3	476.2±2.8	-3.0±27.4	0.38
Time awake (min)	118.9±59.9	110.1±75.0	-8.8±79.0	120.5±57.0	108.8±71.5	-11.7±75.0	0.60
Time asleep (min)	355.4±60.4	360.0±79.5	4.6±81.2	352.9±55.6	354.3±91.3	1.4±88.8	0.82
Sleep latency (min)	8.0±10.9	9.3±10.1	1.3±12.4	7.8±10.4	10.7±17.1	2.9±17.9	0.26
Sleep efficiency (%)	74.1±12.6	75.3±16.4	1.2±17.0	73.7±11.7	75.0±16.2	1.4±16.7	0.85
No. of patients who required >30 sec to awaken	19.1±10.4	16.9±10.9	-2.2±11.7	21.1±10.6	18.4±11.5	-2.7±12.1	0.85
No. of patients who required >2 attempts to awaken	7.2±4.1	6.1±3.8	-1.2±4.2	7.6±3.5	6.3±4.4	-1.3±4.2	0.70
Stage of sleep (%)							
Non-rapid-eye-movement sleep†							
Stage 1	11.9±6.4	11.5±5.7	-0.3±6.6	12.5±6.4	13.9±8.2	1.4±8.6	0.16
Stage 2	54.7±11.6	53.2±11.3	-1.5±11.2	53.1±10.0	52.7±11.0	-0.4±11.9	0.72
Stages 3 and 4	13.2±11.0	12.8±10.6	-0.4±9.6	14.2±9.6	12.7±10.9	-1.4±8.8	0.65
Rapid-eye-movement sleep	20.2±6.2	22.4±8.1	2.3±8.8	20.2±6.5	20.7±6.5	0.5±8.9	0.20

* Plus-minus values are means ±SD. Analysis includes patients with values for both baseline and final visits.

† Stage 1 is a transitional state between waking and sleeping (light sleep); stage 2 is an intermediate stage of sleep that normally accounts for half the total sleep time; and stages 3 and 4 are deep, slow-wave sleep characterized by high-amplitude delta waves on electroencephalography.

order are only a subgroup of shift workers,⁷ a fact that limits the applicability of the findings to the broader shift-work population in whom the safety and efficacy of modafinil have not been evaluated. Our study was 12 weeks in duration; the effects of long-term modafinil use in this population are unknown.

In summary, we found that patients with shift-work sleep disorder had excessive sleepiness during night work, similar to that seen during the day in patients with narcolepsy. Even after treatment with modafinil, these patients still showed evidence of excessive sleepiness during the night shift. Although modafinil did not restore sleepiness to normal daytime levels, treatment was associated with improvements in symptoms of sleepiness, as well as objective measures of sleep propensity and performance. Modafinil is of some value in the clin-

ical management of sleepiness associated with shift-work sleep disorder. Concern remains that even with treatment with 200 mg of modafinil, the excessive sleepiness observed in this underrecognized population requires the development of yet more effective therapies.

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APPENDIX

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CORRECTION

Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder

Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder . On page 484, in the left-hand column, lines 23 through 26 should have read, “. . . and the mean duration of these lapses in the placebo group was nearly twice as long as that in the modafinil group,” rather than “. . . and the mean duration of these lapses in the modafinil group was nearly twice as long as that in the placebo group,” as printed.