Modafinil for Excessive Sleepiness Associated with Shift-Work Sleep Disorder

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BACKGROUND
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 (±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.
Early 6 million Americans work at night on a permanent or rotating basis. Night-shift work disrupts both sleep and waking because of the misalignment of circadian regulation and sleep–wake behavior. 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, 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. 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 disorder — conditions long known to affect a subgroup of shift workers. 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.

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. 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 (23 months) during night shifts; a Clinical Global Impression of Severity 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, 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 nighttime 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). To assess alertness with the use of a performance measure, a 20-minute Psychomotor Vigilance Test 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, which ranges from 1 (very alert) to 9 (very sleepy). The investigator-rated Clinical Global Impression of Change, 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 pre-
specified 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 regard-
ing which results on this test indicate pathological
sleepiness during the night and what level of im-
provement at night is clinically meaningful. There-
fore, as recommended, one of our secondary out-
come measures — the frequency and duration of
lapses of attention during performance on the
Psychomotor Vigilance Test — served as a vali-
dated and objective measure of alertness at night.

SAFETY ASSESSMENTS
Adverse events were monitored throughout the
study. Blood pressure and heart rate were moni-
tored, and clinical laboratory tests (including chem-
ical and hematologic studies) were conducted at
each visit. Physical examination and electrocardi-
ography 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 lab-
oratory night shifts. Melatonin concentrations were
measured from saliva samples.

STATISTICAL ANALYSIS
A total of 204 patients were selected for enrollment
in the study (see the Supplementary Appendix for
calculations regarding the sample size). Random-
ization was performed with the use of a central ran-
domization 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 (assum-
ing an alpha level of 0.05).

Comparisons of continuous demographic vari-
bles between groups were conducted with the
use of analysis of variance, with treatment as a fac-
tor. 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 be-
fore the third month were used.

Comparisons between the groups were con-
ducted on the change between the baseline visit
and the final visit with regard to variables on the
Multiple Sleep Latency Test, scores on the Karo-
limska Sleepiness Scale, polysomnographic mea-
sures, and data from patients’ diaries related to
sleepiness ratings, unintentional and intentional
sleep episodes during the night shift, the consump-
tion of caffeinated drinks, and sleep efficiencies.

All of these variables were analyzed with the use of
analysis of variance, with treatment and site as fac-
tors. Data from the Clinical Global Impression of
Change test were evaluated with the use of a Coch-
ran–Mantel–Haenszel chi-square test, with adjust-
ment 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 dia-
aries 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 multi-
ple testing.

Six academic investigators and four represen-
tatives of the sponsor designed the study and anal-
yzed the data. Drs. Czeisler, Walsh, Roth, and
Dinges conceived of and designed the study in col-
laboration with representatives of the corporate
sponsors, Drs. Hughes, Niebler, Arora, and Kings-
bury. Data were fully accessible to all group mem-
bers, 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 prepa-
rating 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 (±SD) sleep latencies of 2.0±1.8 minutes and 2.1±1.5 minutes for the baseline, with overall mean (±SD) sleep latencies of 2.0±1.8 minutes and 2.1±1.5 minutes for the placebo group (P<0.001) (Fig. 2A, and Table 2 in the Supplementary Appendix). Overall mean (±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.

Specific 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).

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 (±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.

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
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).

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

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

* 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.
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; 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, physiologic outcomes, or body weight were observed between the groups. The incidence of adverse events was not different between the groups in the analysis of variance (P=0.95).

The mean (±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 (P=0.005). Panel E, 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=0.008). 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=0.002). 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 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).
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).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=108)</th>
<th>Modafinil (N=96)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After</td>
<td>Change</td>
</tr>
<tr>
<td><strong>During night shift</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum level of sleepiness — score†</td>
<td>7.4±1.0</td>
<td>6.6±1.3</td>
<td>–0.9±1.0</td>
</tr>
<tr>
<td>No. of unintentional sleep episodes‡</td>
<td>1.2±1.3</td>
<td>0.6±0.7</td>
<td>–0.6±1.0</td>
</tr>
<tr>
<td>No. of intentional sleep episodes†</td>
<td>0.5±0.8</td>
<td>0.4±0.5</td>
<td>–0.1±0.5</td>
</tr>
<tr>
<td>No. of caffeinated drinks consumed‡</td>
<td>1.3±1.1</td>
<td>1.1±0.9</td>
<td>0.2±0.9</td>
</tr>
<tr>
<td>Patients reporting mistakes, accidents, or near accidents — no. (%)§</td>
<td>59 (55)</td>
<td>46 (48)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>During the commute home</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of sleepiness — score†</td>
<td>5.9±1.8</td>
<td>5.4±1.7</td>
<td>–0.6±1.2</td>
</tr>
<tr>
<td>Patients reporting unintentional sleep episodes — no. (%)§</td>
<td>47 (44)</td>
<td>34 (35)</td>
<td>0.24</td>
</tr>
<tr>
<td>Patients reporting accidents or near accidents — no. (%)§</td>
<td>58 (54)</td>
<td>28 (29)</td>
<td>&lt;0.001¶</td>
</tr>
<tr>
<td><strong>During days after night shift</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of caffeinated drinks consumed††</td>
<td>1.0±1.3</td>
<td>0.6±0.7</td>
<td>–0.4±1.0</td>
</tr>
<tr>
<td>Sleep efficiency — %**†††</td>
<td>78.0±20.7</td>
<td>87.5±14.1</td>
<td>9.5±18.3</td>
</tr>
</tbody>
</table>

* 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.
† P value is for the change from baseline for modafinil versus placebo.
‡ Data were available for 84 patients receiving placebo and for 79 patients receiving modafinil.
§ 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.

### 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...
disorder range from 5 to 10 percent.\textsuperscript{4-6,24} The burden of illness in persons with shift-work sleep disorder is substantial, as compared with shift workers without the disorder.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{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\textsuperscript{32,33} and is recommended for assessing sleepiness at night in this population,\textsuperscript{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,\textsuperscript{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-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
\textbf{Adverse Event} & \textbf{Placebo (N=108)} & \textbf{Modafinil (N=96)} \\
\hline
Headache & 21 (19) & 25 (26) \\
\hline
Infection & 11 (10) & 6 (6) \\
\hline
Nausea & 3 (3) & 9 (9) \\
\hline
Rhinitis & 7 (6) & 9 (9) \\
\hline
Accidental injury & 9 (8) & 6 (6) \\
\hline
Abdominal pain & 2 (2) & 6 (6) \\
\hline
Nervousness & 1 (<1) & 6 (6) \\
\hline
Insomnia & 0 (0) & 6 (6)† \\
\hline
Dry mouth & 4 (4) & 5 (5) \\
\hline
Tooth disorder & 1 (<1) & 5 (5) \\
\hline
\end{tabular}
\caption{Adverse Events in Patients Diagnosed with Shift-Work Sleep Disorder Treated with Modafinil or Placebo.\textsuperscript{*}}
\end{table}

\textsuperscript{*} 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.
order are only a subgroup of shift workers,\textsuperscript{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 clinical 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.

APPENDIX


Supported by Cephalon, Frazer, Pa.

Drs. Czeisler and Dinges report having received consulting fees and speaker’s fees from Cephalon and having received clinical trial research contracts, investigator-initiated research grants, and unrestricted research and education funds from Cephalon. Dr. Czeisler serves as the incumbent of an endowed professorship provided to Harvard University by Cephalon. Drs. Walsh, Roth, and Wright report having received consulting fees and speaker’s fees from Cephalon and having received clinical trial research contracts and investigator-initiated research grants from Cephalon. Drs. Hughes, Kingsbury, Arora, and Niebler are employees of and report having an equity interest in Cephalon. Dr. Schwartz reports having received consulting fees and clinical trial research contracts from Cephalon and serving on the speakers bureau for Cephalon.

We are indebted to Mark Riiotto, Angela Kaya, and Richard Malone for assistance in the preparation of the manuscript.

\begin{table}
<table>
<thead>
<tr>
<th>Polysomnographic Variable</th>
<th>Placebo (N=78)</th>
<th>Modafinil (N=72)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed (min)</td>
<td>479.7±23.3</td>
<td>478.0±9.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Time awake (min)</td>
<td>118.9±59.9</td>
<td>110.1±75.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Time asleep (min)</td>
<td>355.4±60.4</td>
<td>360.0±79.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>8.0±10.9</td>
<td>9.3±10.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>476.2±2.8</td>
<td>12.8±10.6</td>
<td>0.16</td>
</tr>
<tr>
<td>No. of patients who required &gt;30 sec to awaken</td>
<td>19.1±10.4</td>
<td>16.9±10.9</td>
<td>0.85</td>
</tr>
<tr>
<td>No. of patients who required &gt;2 attempts to awaken</td>
<td>7.2±4.1</td>
<td>6.1±3.8</td>
<td>0.70</td>
</tr>
</tbody>
</table>

a) 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.

In the table, the values are expressed as means ± standard deviation (SD), and the significance of the differences between the groups is determined using a two-sample t-test. The table includes measures such as time in bed, time awake, time asleep, sleep latency, sleep efficiency, and the number of patients who required more than 30 seconds to awaken or more than two attempts to awaken. The significance levels are indicated by the P values, with values less than 0.05 considered statistically significant.
REFERENCES


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