Modafinil Improves Alertness, Vigilance, and Executive Function During Simulated Night Shifts

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Study Objectives: To assess the effect of 200 mg of modafinil compared to placebo on alertness, neurobehavioral performance, and executive function during 4 consecutive simulated night shifts.

Design: Double-blind, randomized, parallel groups.

Setting: Sleep research facility.

Participants: 32 male and female volunteers between the ages of 18 and 55 years.

Interventions: 200 mg of modafinil or placebo given nightly on the 4 consecutive simulated night shifts.

Measurements and Results: Subjects were randomly assigned to 1 of the 2 treatment conditions, following medical, psychiatric, and polysomnographic screening. On 4 consecutive nights, subjects took study drug at 2200, and then from about 2300 to 0730 participated in a simulated night shift that included the Maintenance of Wakefulness Test, Psychomotor Vigilance Test, Digit Symbol Substitution Test, measures of subjective alertness, and multiple executive-function measures. At 0800, daytime sleep periods were recorded polysomnographically for 6 to 8 hours. Alertness—as measured by the MWT, vigilance and reaction time as indexed by Psychomotor Vigilance Test lapses, and slowest 10% of reaction times—and 3 executive-function tasks showed significant enhancement with modafinil versus placebo. Subjective sleepiness at night and some performance measures did not show consistent treatment differences. Daytime sleep showed minimal differences between conditions.

Conclusions: The physiologic sleepiness and neurobehavioral deficits that occurred during the hours of a typical night shift were clearly attenuated by modafinil. Modafinil also had beneficial effects on some measures of executive function.

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INTRODUCTION

MILLIONS OF AMERICANS MUST WORK AT NIGHT AND SLEEP DURING THE DAY. Estimates for 1997 by the Bureau of the Census indicate that 16.8% of full-time workers are shift workers, including 3.5% working a steady night shift and 2.9% working rotating shifts.1 Night work is associated with impaired alertness, decreased performance, disturbed sleep, and an increased rate of accidents.2-4 Among rotating-shift workers, 53% report falling asleep during the night shift at least once each week, in contrast to 23% of rotating workers on the day shift, and 8% of permanent day workers.5 A study using ambulatory electroencephalogram (EEG) recordings indicated that 20% of shift workers fell asleep during a single night shift, whereas none slept during the afternoon/evening shift.6 Human performance also declines to its lowest in the early morning for most skills.6-8 Impaired alertness and performance associated with night-shift work have contributed to an increased risk of accidents in the transportation industry,9-13 as well as to industrial disasters such as the Exxon-Valdez oil spill14 and the Chernobyl nuclear power-plant meltdown.15,16

Sleepiness on the night shift is caused by (1) the desynchronization between circadian sleep tendency and the schedule of sleep and wakefulness required by night work and (2) cumulative sleep deprivation. Extension of daytime sleep via napping17,18 or use of hypnotic medication19,20 may mildly reduce the severity of sleepiness and performance on the night shift, but significant impairments remain. The use of caffeine20,21 and methamphetamine22 have also been shown to reduce sleepiness, performance impairment, and negative mood associated with simulated night shifts.

Modafinil is a unique wake-promoting agent with an unknown specific mechanism of action. Studies of mice with deletion of the dopamine transporter gene indicate that the dopamine transporter is necessary for the wake-promoting action of modafinil and amphetamines.24 Moreover, the degree of wake promotion with amphetamines correlates with the increase in extracellular dopamine, but not extracellular norepinephrine,23 and wake time is increased in mice exposed to a specific dopamine-transporter inhibitor.26 Thus, increased dopaminergic transmission appears to mediate the wake-promoting effects of modafinil, which has been demonstrated in patients with narcolepsy,27,28 treated sleep apnea,29 and following sleep deprivation.30

The purpose of this study was to assess the effect of 200 mg of modafinil compared to placebo on physiologic and self-reported alertness, sustained attention and psychomotor performance, and executive function during 4 consecutive simulated night shifts. By executive function, we mean neuropsychological functions typically attributed to frontal-lobe activity, such as decision making, planning, assigning priority, sequencing, inhibition, problem solving, impulse control, and self-correction.

METHODS

SUBJECT SELECTION, TRAINING, AND INSTRUCTION

Healthy men and women between the ages of 18 and 65 years were recruited primarily through the media. All subjects signed a consent form, which had been approved by the institutional review board along...
Thirty-nine subjects were screened for the study. Seventeen failed screening (3 failed the drug screen; 4 failed the MSLT; 5 were disqualified because of abnormal laboratory results, medical history, physical examination, or use of concomitant medication; and 5 withdrew for personal reasons). A total of 22 individuals was randomly assigned to receive modafinil or placebo, including 3 replacements for individuals who did not complete study participation. Inability to fulfill obligations of the study (because of job interview, ill family member, meeting attendance) was the reason 2 subjects in the modafinil group and 1 in the placebo group did not complete the study. No subject discontinued because of an event related to study drug. The present report includes the 19 subjects who completed the protocol (16 assigned to modafinil, 3 to placebo) and identical entry criteria. Neither the 19 subjects enrolled in a simultaneous study with an identical design (examining caffeine versus placebo) nor sex (modafinil versus placebo) and identical entry criteria. Neither the 19 subjects enrolled in this protocol nor study staff involved in the scoring of data knew the proportion of subjects to be assigned to modafinil or placebo. The final sample for this study included 32 subjects (16 in each group). There were no group differences in age (modafinil mean age = 29.7 ± 13.2 years; placebo mean age = 33.2 ± 11.4 years; \( t = -0.790, P = 0.436 \)) or sex (modafinil = 7 men, 9 women; placebo = 10 men, 6 women; \( \chi^2 = 1.129, P = 0.288 \)).

Training for all tests and questionnaires to be used in the study occurred during an initial office visit and during the day of the MSLT. Individuals who met all screening criteria were instructed to sleep 8 hours or more per night, with bedtime at their habitual bedtime ± 1 hour, for a minimum of 1 week prior to randomization. Subjects kept daily sleep logs and were monitored via actigraphy (Actiwatch, Mimi-Mitter, Bend, OR) to encourage compliance but were not excluded if they did not follow instructions.

### Experimental Design, Methods, and Measures

Each subject participated in a 4-night, 4-day simulated night-shift schedule (see Figure 1). Subjects were randomly assigned to receive either placebo or 200 mg of modafinil in double-blind fashion, administered at 2200 nightly. From 2300 until approximately 0700, subjects participated in a variety of tasks, including the Maintenance of Wakefulness Test (MWT), the Psychomotor Vigilance Task (PVT), the Digit Symbol Substitution Test (DSST), and subjective measures including the Stanford Sleepiness Scale (SSS) and the Karolinska Sleepiness Scale. Each task was administered 4 times nightly at approximately 2-hour intervals. In addition, tests of executive function (which varied nightly) were conducted at 0215 and either 0415 or 0500 (counterbalanced between conditions). Following breakfast, a 30-minute period of sunlight exposure ensued (near a large window) to partially simulate the light exposure during a morning commute. Actual intensity of light exposure was not controlled or measured on each morning, but illumination measures in the location the subjects occupied, taken on multiple days, showed a range of approximately 500 to 1500 lux. Sleep was monitored polsomnographically each day, beginning between 0815 and 0830. Subjects slept in noise-attenuated, darkened, single rooms. Subjects slept ad libitum with the restriction that time in bed was a minimum of 6 hours and maximum of 8 hours. The minimum time in bed guarded against subjects prematurely terminating the study for personal reasons and imposing significant sleep restriction upon themselves. Since night-shift workers rarely sleep more than 8 hours during the day, the maximum time in bed was set at 8 hours.

Following each polysomnogram, subjects were free to leave the laboratory to carry out their usual activities. Typically subjects left the laboratory between 1500 and 1715 and returned at 2130 each night. They were instructed to avoid naps, not to use medications unless approved by the investigator, and to limit caffeine consumption to 1 cup or can of a caffeinated beverage per day. Compliance was monitored via actigraphy and daily diary. Food consumption, light exposure, and exercise were not controlled during the time away from the laboratory.

To promote a constant level of subject motivation over repeated nights of MWT testing, the criterion for termination (but not scoring) of each subtest was modified. Each 30-minute subtest of the MWT was conducted using standard procedures until the sleep-latency criterion was met. Terminating the test at that time (in accord with standard research MWT guidelines) could serve as a “reward” because it would end the aversive experience of fighting sleep during a time of intense sleep pressure. Instead, the test was extended by instructing subjects to “keep their
eyes open” 2 to 5 times at the appearance of drowsiness or sleep. In this way, subjects were not “rewarded” for low motivation levels by terminating the test as soon as they fell asleep. This procedure continued to minimize the amount of sleep obtained during each subtest and avoided providing subjects with a cue that the test would be terminated if they fell asleep, which also could reduce motivation to stay awake. Mean latency to the first epoch of any sleep stage was the dependent measure. A latency of 30 minutes was recorded if a subject remained awake during the entire 30-minute subtest.

The PVT is a computer-based reaction-time test requiring sustained attention that has been demonstrated to be sensitive to fluctuations in alertness in a variety of situations and conditions. Each of the 4 nightly PVT presentations lasted 15 minutes. PVT-dependent measures were the frequency of lapses (the number of reaction times ≥ 500 milliseconds) and mean duration of the 10% slowest reaction times, a measure reflecting vigilance response slowing.

The Optimal Telegram, a test of verbal reasoning, was administered each night at 0215. During a second test period each night, which was either from 0415 to 0445 or 0500 to 0530, (time varied for logistical reasons), the following tests were given:

- Night 1. Torrance Test of Creative Thinking-Verbal (TTCT-V), which measures verbal fluency, originality, and flexibility.
- Night 2. Wisconsin Card Sorting Test (WCST), Thurstone’s Word Fluency Test (WFT), and Anagram Task. The WCST assesses concept formation and abstraction ability. The WFT has 2 versions that both evaluate verbal fluency. The Anagram Task is a short verbal test of convergent thinking.
- Night 3. Torrance Test of Creative Thinking-Figural (TTCT-F), which involves communicating unusual and unique ideas through drawing.
- Night 4. Category Test, Letter-Number Sequencing (LNS), and Haylings Sentence Completion Test (SCT). The Category Test measures the ability to identify connecting ideas or principles. LNS is a subtest of the Wechsler Memory Scale-III and is a test of working memory. SCT evaluates an individual’s ability to resist closure and avoid perseveration.

Baseline data were obtained for the Optimal Telegram, TTCT-V, and TTCT-F on the day of the screening MSLT, typically between the third and fourth MSLT subtests, approximately 6.5 to 7.5 hours after awakening (about 1330 to 1530).

### Statistical Analysis

All data were scored without knowledge of treatment condition. Data analyses consisted of mixed-model analyses of variance (2 groups by 4 nights by 4 time points) for MWT, PVT, and most subjective measures; 2 groups by 4 days/night for daytime sleep data and Optimal Telegram (change from baseline). The Huynh-Feldt adjustment was used to control for sphericity for within-subject factors. Follow-up analyses varied depending on the question of interest, the model, and the results of the omnibus ANOVA but typically involved examination of group differences on a nightly basis. Prior to undergoing ANOVA procedures, PVT lapses underwent square-root transformation to normalize distributions, compress large counts, and prevent scores of 0. Slowest 10% of responses on the PVT underwent reciprocal transformation to compress the range of scores. Multivariate ANOVAs were conducted on the difference scores (change from baseline) for the TTCT-V (2 groups, 3 variables) and the TTCT-F (2 groups, 5 variables), with follow-up t tests for between-group comparisons of each variable. T tests were conducted on the remaining executive-function tests.

### RESULTS

#### Polysomnographic Data

Daytime polysomnography data are presented in Table 1. ANOVA revealed no group difference or group by day interaction for total recording time; however, there was a decrease in total recording time across days (F₁,3₀=16.4, P<.001). There were no differences in total sleep time between groups (F₁,3₀=0.26, P=.614) or across days (F₃,₉₀=1.67, P=.18). Mean total sleep times for the 4 daytime sleep periods were 333.9 ± 54.7 minutes and 344.7 ± 65.1 minutes for the modafinil and placebo groups, respectively. Mean latency to persistent sleep (the first of 20 consecutive epochs of sleep) showed a trend (F₁,₃₀=2.9, P=.097) for the placebo group to fall asleep slightly faster (mean for 4 days = 6.0 ± 4.8 minutes) than the modafinil group (8.9 ± 4.8 minutes). Sleep latency increased slightly, but significantly, across days (F₁,₃₀=5.5, P=.002) for both groups. There was no interaction. Notably, despite the fact that mean total recording time never exceeded 434.8 minutes, mean sleep efficiencies ranged from 77.0% to 84.2%, consistent with the frequently demonstrated reduction of sleep time when sleep is attempted during the day.

Except for a slight decrease in minutes of stage 1 sleep across the 4 days for both groups (F₁,₃₀=3.7, P=.015), there were no significant group effects, day effects, or group by day interactions for any other absolute polysomnography variable. When sleep stages were evaluated as percentage of total sleep time, there was a group by day interaction (F₁,₃₀=3.4, P=.03) for stage 3-4 sleep, with a greater percentage of stage 3-4 sleep on day 3 for the modafinil group compared to placebo (26.4% vs 15.3%, respectively, t=2.8, P=.01). The main effect for group showed a trend (F₁,₃₀=3.5, P=.072) for the modafinil group to have a higher percentage of stage 3-4 sleep.

#### MWT Data

Mean latencies to sleep onset for the MWT on each of the 4 nights are shown in Figure 2. Table 2 shows the statistical results for the overall ANOVA. There was a significant main effect for group. Mean MWT latencies on the 4 nights were 23.8 ± 6.5, 21.9 ± 4.7, 24.1 ± 6.3, and 25.1 ± 5.4 minutes for the modafinil group, as compared to 15.0 ± 7.4, 19.5 ± 9.8, 19.2 ± 9.9, and 19.9 ± 10.7 minutes for the placebo group. Significant main effects were also found for night, and time of night, as well as significant interactions for time of night by group and night by time of night by group, with a trend for a night by group interaction. Polynomial contrasts indicated a strong linear decrease in MWT sleep latencies during the night, every night (F₁,₃₀=89.7, P<.001).

![Figure 2](image)
Because of the night by time of night by group interaction, follow-up group comparisons were done at each time point for each night. On night 1, the modafinil group was significantly more alert than the placebo group at 0145, 0345 and 0630 ($F_{1,30}=12.775, 9.792, \text{ and } 14.123$, respectively, $P<.01$ for all). On night 2, there was a trend for modafinil subjects to be more alert at 0345 ($F_{1,30}=3.372, P=.076$). On night 3, the modafinil group was more alert at 0345 ($F_{1,30}=7.804, P<.01$), while on night 4, the modafinil group was more alert at 2345 ($F_{1,30}=4.92, P=.034$) with a trend at 0145 ($F_{1,30}=3.219, P=.083$).

The placebo group displayed an increase in alertness across nights ($F_{1,15}=8.09, P=.012$) whereas the modafinil group maintained approximately the same level of alertness each night ($F_{3,45}=1.315, P>.2$).

In addition to analyzing group mean MWT data, the percentage of subjects with a mean MWT latency > 15 minutes was examined for each group. Averaging across nights 1 to 4, significantly more modafinil subjects (93.7%) met this criterion as compared to placebo subjects (62.5%; $\chi^2=4.6, P=.033$). For nights 1 to 4 individually, the percentages of subjects in the modafinil group with a mean MWT latency > 15 minutes were 87.5%, 87.5%, 87.5%, and 93.7%, respectively, whereas for the placebo group, the comparable percentages were 43.8%, 68.8%, 75.0%, and 62.5%, respectively.

### Performance Data

#### PVT Lapses

Mean PVT lapses by time of night are shown for each night in Figure 3, and ANOVA results are shown in Table 2. On each night, the mean number of lapses per night in the placebo group was between 40% and 200% higher than in the modafinil group. There were significant main effects for group, night, and time of night and significant interactions for time of night by group and night by time of night, plus a trend for a night by group interaction.

Polynomial contrasts indicated a significant increase in the frequency of lapses as the night progressed ($F_{1,30}=42.634, P<.001$). The placebo group made significantly more lapses than the modafinil group at 0315 and 0600 on night 1 ($F_{1,30}=12.119, 4.655, 7.528$, respectively, $P<.01$). Follow-up analyses showed a trend for the placebo group to be sleepier than the modafinil group at the first time point on the third night ($F_{1,30}=3.4, P=.058\text{ and }.103$, respectively.) The Karolinska Sleepiness Scale showed significant increase in sleepiness across time of night ($F_{3,90}=88.7$ and 111.0, $P<.001$, respectively), and a night by group interaction ($F_{3,90}=3.6$ and 3.2, $P<.03$). Follow-up analyses showed a trend for the placebo group to be sleepier than than the modafinil group on night 1 ($F_{1,30}=3.9$ and 2.8, $P=.058\text{ and }.103$, respectively.)

The placebos group displayed an increase in the number of lapses across the 4 nights ($F_{3,45}=6.149, P=.003$), whereas the modafinil group maintained approximately the same level of lapses nightly ($F_{1,34}<1, P>.5$).

### Slowest 10% Reaction Times on PVT

This variable showed results compatible with data on PVT lapses. There were main effects for group ($F_{1,30}=6.118, P=.019$), night ($F_{3,90}=3.832, P=.018$), and time ($F_{3,90}=36.909, P<.001$), as well as interactions of time of night by group ($F_{3,90}=5.232, P=.002$) and night by time of night ($F=2.613, P=.016$). The night by group interaction was not significant ($F_{1,90}=2.070, P=.122$). The placebo group had slower reaction times in this response domain than did the modafinil group at 0115, 0315, and 0600 on night 1 ($F_{1,30}=12.119, 4.655, 7.528$, respectively, $P<.04$), at 0115, 0315, and 0600 on night 2 ($F=4.337, 7.178, 8.451$, respectively, $P<.05$), and during all subtests on night 4 ($F=7.048, 8.517, 6.002, 8.809$, respectively, $P<.02$).

#### Digit Symbol Substitution Test

There was a significant main effect of night for the DSST, indicating improvement in performance from night 1 to night 4 ($F_{3,87}=19.365, P<.001$), likely a practice effect. Performance decreased significantly across time of night ($F_{5,87}=5.67, P=.002$) for both groups. There was no main effect for group. The modafinil group completed a mean of 51.4, 55.5, 57.1, and 58.4 items on nights 1 through 4, respectively, as compared to 52.0, 54.6, 56.3, and 56.6 by the placebo group.

#### Subjective Sleepiness-Alertness

The SSS was completed prior to (SSS-a) and following (SSS-b) each of the 4 PVT sessions. SSS-a and SSS-b were analyzed separately. Both showed main effects for night ($F_{3,90}=11.0$ and 5.428, $P<.001$, respectively), a trend for a night by group interaction ($F_{3,90}=2.1, P=.044$), night (F3,90 = 90.1, $P<.001$), and time (F3,90 = 36.909, $P<.001$). The placebo group was sleepy than the modafinil group on night 1 ($F_{1,30}=3.9$ and 2.8, $P=.058\text{ and }.103$, respectively.) The Karolinska Sleepiness Scale showed main effects for night ($F_{3,90}=3.5, P=.018$) and time of night ($F_{3,90}=90.1, P<.001$), a trend for a night by group interaction ($F_{3,90}=2.1, P=.10$), and a night by time of night by group interaction ($F_{9,270}=2.6, P=.01$). The placebo group was sleepier than the modafinil group at the first time point on the first night ($F_{1,30}=7.5, P=.01$). However, the modafinil group was sleepier at the placebo group at the first time point on the third night ($F_{1,30}=3.4, P=.044$).

![Figure 3](https://example.com)  
Figure 3—Mean number of lapses (and SEM bars) on the Psychomotor Vigilance Test (PVT) for modafinil (solid line) and placebo (dashed line) groups at each time point during all 4 simulated night shifts. Statistical results are presented in text.

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Table 2—ANOVA Summary Table for the MWT and PVT

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ANOVA refers to analysis of variance; MWT, Maintenance of Wakefulness Test; PVT, Psychomotor Vigilance Test
Executive Function

Figure 4 displays mean difference from baseline, expressed as standard scores, for the TTCT-V, which was conducted on night 1. Test performance was worse during the night shift compared to baseline ($F_{1.30} = 19.2$, $P < .001$). Multivariate ANOVA on the change from baseline revealed an overall group difference ($F_{3.28} = 4.17$, $P = .015$). Follow-up t tests showed that the placebo group performed more poorly than the modafinil group in the areas of verbal flexibility ($t = -3.131$, $P = .004$) and verbal originality ($t = -2.492$, $P = .019$). A trend in the same direction was seen for verbal fluency ($t = -1.736$, $P = .093$).

The mean numbers of total errors and of perseverative errors on the WCST from night 2, expressed as standard scores, are shown for each group in Figure 5. Both counts of errors were significantly more frequent for the placebo group than for the modafinil group ($t = 3.003$, $P = .006$ and $2.097$, $P = .007$, respectively). Errors on the SCT conducted on night 4 were also significantly different between groups ($t = -2.083$, $P = .049$). The mean number of errors was approximately 66% higher for the placebo group (mean = 7.47), as compared to the modafinil group (mean = 4.50).

The other executive-function assessments showed no significant main effects for group; in addition to the lack of a group effect, the Optimal Telegram did not show a main effect for night or an interaction.

DISCUSSION

Consistent attenuation of the physiologic and neurobehavioral deficits that occur during the hours of a typical night shift was demonstrated to occur with 200 mg of modafinil. Alertness, as measured by the MWT, and vigilance and reaction time, as indexed by the PVT, showed significant differences between groups, all in favor of modafinil. Additionally, 3 executive-function tasks demonstrated better performance with modafinil than with placebo. These findings are theoretically consistent with the premise that night shift-related errors and accidents would be expected to occur with circadian and/or homeostatic factors in normal individuals. For example, Caldwell et al documented improved flight-simulator performance and enhanced alertness with modafinil in sleep-deprived helicopter pilots. During periods of sleep deprivation, modafinil has also been shown to improve performance on perceptual judgment, complex addition, and 4-choice reaction-time tasks.

The significantly better performance with modafinil on the PVT, but not on the DSST, may in part be related to task duration. The PVT was 15 minutes in duration, whereas the DSST lasted 90 seconds. Task duration has long been known to be an important determinant of sleepiness-related performance deficits.

The executive-function benefits of modafinil have recently been reported to be selective, rather than global, in terms of the specific domain of ability tested. Whether those observations are related to the doses tested, or to the use of nonsleepy subjects, as opposed to true differential effects of the drug, cannot be determined with certainty. However, enhancement of adaptive response inhibition was one of the executive-function domains found to consistently improve with modafinil by Turner et al, and in the present study, two of three tasks measuring response inhibition (WCST and SCT but not Category Test) were improved with modafinil. Reduction of impulsive and/or perseverative responding suggests potential benefit of modafinil for attention-deficit/hyperactivity disorder.

More generally, what should be the role of wake-promoting agents in attempts to reduce the risks associated with work schedule-related sleepiness? Certainly this is a complex and challenging question requiring consideration from multiple viewpoints by many segments of society. Whenever possible, reduction or elimination of sleep deprivation through lifestyle management would be preferred; however, there are instances in which sleepiness cannot be adequately managed in this way,
and employment and other obligations continue. For some of these situations, adding wake-promoting drugs to behavioral strategies would appear to be appropriate. Research and clinical experience have proven modafinil to be well tolerated, with extremely rare serious adverse events. Nevertheless, given the systematic study of modafinil in patients with hypertension, recent myocardial infarction, unstable angina, and other cardiovascular signs or abnormalities, the drug is not recommended for such individuals. Also, with the increased dopaminergic activity in common with amphetamines, prudence in assessment of risk/benefit ratio for each individual patient is suggested, even though abuse or dependence liability appears to be quite low. A number of studies demonstrate that modafinil is reliably discriminated from, and has much lower abuse potential than, other stimulants such as cocaine, amphetamine, and methylphenidate. 49-52 We conclude that the potential for reducing the risk of sleepiness-related accidents and injuries in shift workers with modafinil would appear to represent a favorable risk/benefit ratio in carefully selected and monitored individuals.

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