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ORIGINAL INVESTIGATION

**Nancy Jo Wesensten · Gregory Belenky**
**Mary A. Kautz · David R. Thorne**
**Rebecca M. Reichardt · Thomas J. Balkin**

# Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine

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**Abstract** *Rationale:* The performance and alertness effects of modafinil were evaluated to determine whether modafinil should replace caffeine for restoring performance and alertness during total sleep deprivation in otherwise healthy adults. *Objectives:* Study objectives were to determine (a) the relative efficacy of three doses of modafinil versus an active control dose of caffeine 600 mg; (b) whether modafinil effects are dose-dependent; and (c) the extent to which both agents maintain performance and alertness during the circadian trough. *Methods:* Fifty healthy young adults remained awake for 54.5 h (from 6:30 a.m. day 1 to 1:00 p.m. on day 3) and performance and alertness tests were administered bihourly from 8:00 a.m. day 1 until 10:00 p.m. day 2. At 11:55 p.m. on day 2 (after 41.5 h awake), subjects received double blind administration of one of five drug doses: placebo; modafinil 100, 200, or 400 mg; or caffeine 600 mg ($n$=10 per group), followed by hourly testing from midnight through 12:00 p.m. on day 3. *Results:* Performance and alertness were significantly improved by modafinil 200 and 400 mg relative to placebo, and effects were comparable to those obtained with caffeine 600 mg. Although a trend toward better performance at higher modafinil doses suggested a dose-dependent effect, differences between modafinil doses were not significant. Performance enhancing effects were especially salient during the circadian nadir (6:00 a.m. through 10:00 a.m.). Few instances of adverse subjective side effects (nausea, heart pounding) were reported. *Conclusions:* Like caffeine, modafinil maintained performance and alertness during the early morning hours, when the combined effects of sleep loss and the circadian trough of performance and alertness trough were manifest. Thus, equivalent performance- and alertness-enhancing effects were obtained with drugs possessing different mechanisms of action. However, modafinil does not appear to offer advantages over caffeine (which is more readily available and less expensive) for improving performance and alertness during sleep loss in otherwise normal, healthy adults.

**Keywords** Cognitive performance · Sleep deprivation · Modafinil · Caffeine · Reaction time

N.J. Wesensten (✉) · G. Belenky · M.A. Kautz · D.R. Thorne
R.M. Reichardt · T.J. Balkin
Department of Neurobiology and Behavior,
Division of Neuropsychiatry,
Walter Reed Army Institute of Research, Silver Spring,
MD 20910-7500, USA
e-mail: nancy.wesensten@na.amedd.army.mil
Tel.: +1-301-3199248, Fax: +1-301-3199979

N.J. Wesensten
MRMC-UWI-C, Walter Reed Army Institute of Research,
503 Robert Grant Avenue, Silver Spring, MD 20910-7500, USA

## Introduction

The cognitive performance and alertness deficits that result from sleep loss are a threat to productivity and safety in both industrial and military operational settings. Both total and partial sleep deprivation impair ability to maintain wakefulness, increase subjective sleepiness, reduce motivation, and, perhaps most critically, degrade cognitive performance (for reviews see Horne 1988; Dinges and Kribbs 1991). Sleep deprivation-induced deficits are primarily characterized by reduced speed, although accuracy also is affected (Dinges and Kribbs 1991). The magnitude of sleep deprivation-induced performance deficits is a function of both (a) the extent of prior sleep loss, and (b) phase of the circadian rhythm of cognitive performance. Sleep deprivation-induced cognitive performance deficits are typically most severe in the early morning (approximately 6:00 a.m. to 8:00 a.m.) near the nadir of the circadian rhythm of performance. Performance tends to recover later in the day (approximately 4:00 p.m. to 8:00 p.m.), when the effects of sleep deprivation are offset by the ascending phase of the circadian rhythm (Naitoh 1981; Angus and Heslegrave 1985).

Over-the-counter formulations of caffeine are routinely used to minimize/reverse performance and alertness-

impairing effects of both total and partial sleep deprivation, and caffeine's effectiveness is well established (e.g. Bonnet and Arand 1994; Muehlbach and Walsh 1995; Wright et al. 1997; Reyner and Horne 2000). Modafinil (2-[(diphenyl-methyl)-sulfinyl]acetamide) is a newer medication approved in both North America and Europe for treatment of the daytime sleepiness associated with narcolepsy. The mechanism by which modafinil promotes alertness is thought to be inhibition of the dopamine reuptake transporter (Wisor et al. 2001). In contrast, caffeine acts as an antagonist at the central adenosine (AD) receptor (Nehlig et al. 1992), and its alertness-enhancing effects do not appear to involve the dopaminergic system (Wisor et al. 2001).

Cognitive performance-enhancing effects of modafinil during sleep deprivation in normal, healthy adults have been studied previously. For example, Pigeau et al. (1995) reported that modafinil improved performance on a four-choice serial reaction time task for up to 6 h when administered after 47 h of sleep deprivation, an effect that was most notable in the early morning hours of testing. They also reported that logical reasoning and digit-span performance were improved with modafinil, and concluded that modafinil was a good alternative to amphetamine for maintaining mood and performance during sleep deprivation. More recently, Brun et al. (1998) reported that modafinil (300 mg dose repeated two times across 36 h of sleep deprivation) improved response time and prevented an early morning performance decrement during 1 night of sleep deprivation. Similarly, Lagarde and Batejat (1995) reported that modafinil (200 mg repeated every 8 h across 60 h of sleep deprivation) improved average performance across the sleep deprivation period, although few statistically significant effects were found. Caldwell et al. (2000) reported that modafinil (200 mg repeated three times across 40 h of sleep deprivation) improved pilot performance in a helicopter simulator, again with the most pronounced effects evident during the early morning hours.

In summary, evidence suggests that modafinil improves cognitive performance during sleep deprivation in normals, and that these effects are most noticeable during the circadian trough of alertness and performance. However, it has yet to be determined whether modafinil provides any advantages over caffeine, a widely available, safe and effective stimulant (Penetar et al. 1994) that is commonly used for this purpose. For modafinil to replace caffeine as the drug of choice for restoration and maintenance of performance and alertness during sleep deprivation in normal, healthy adults, it would be necessary to show that modafinil is at least as efficacious as caffeine and that it displays a comparable, or more favorable, side effect profile. From the literature reviewed above, it is not known whether modafinil meets these criteria.

Despite the fact that current labeling and prescribing practices allow for a maximum single dose of 400 mg, the cognitive performance effects of modafinil at a single dose higher than 300 mg are unknown. Further, since no study to date has included more than two different doses of modafinil, the extent to which modafinil dose-dependently enhances cognitive performance and alertness is unknown. These issues (modafinil efficacy versus caffeine; modafinil dose-dependency; efficacy during the circadian trough) are addressed in the present study by evaluating the effects of a single administration of modafinil 100, 200, or 400 mg, caffeine 600 mg or placebo on cognitive performance during the early morning hours of a second night of total sleep deprivation. Caffeine 600 mg was chosen as the comparison dose because results from a previous study (Penetar et al. 1993, 1994) indicate that this dose is safe and effective for improving performance and alertness after 48 h of sleep deprivation.

## Materials and methods

### Subjects

Subjects were 50 (age range 18–30 years, mean=22.4) healthy, non-smoking men ($n$=37) and women ($n$=13) who responded to advertisements posted at local universities. Informed consent was obtained prior to inclusion in the study, and included an explanation of all procedures as well as possible drug side effects. Subjects were screened for past and current physical/mental health problems, sleep problems, and drug use. To minimize withdrawal effects from caffeine, subjects were excluded if they reported a daily caffeine consumption exceeding 400 mg, and they were required to abstain from caffeine starting 48 h prior to the study. Eight subjects reported that they did not use caffeine on a daily basis. Subjects also were instructed to abstain from alcohol and all other drugs starting 48 h prior to the study. Compliance with abstinence from commonly abused psychoactive substances (e.g. marijuana, cocaine, nicotine) was determined via immunoassay conducted on urine samples collected on the morning of the study. Compliance with caffeine abstinence was verified through self-report. Otherwise, no attempt was made to control for caffeine use or caffeine withdrawal. Payment was $600 for completion of the study, plus a possible $400 performance bonus (described below). This study was reviewed and approved by the United States Army Surgeon General Human Subjects Review Board.

### Computerized performance assessment battery (PAB)

Cognitive performance, mood, and subjective alertness tests were administered by personal computer as per the schedule outlined below (see Procedures). Tests were part of the Walter Reed Performance Assessment Battery (Thorne et al. 1985). Tests were selected based on their demonstrated sensitivity to sleep deprivation (Thorne et al. 1983) and caffeine (Penetar et al. 1994), and were administered in the following order.

#### *Profile of Mood States (POMS)*

The Profile of Mood States (McNair et al. 1971) is a 65-item adjective checklist that measures current mood states along six subscales: tension-anxiety, anger-hostility, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment. In this test, an adjective (e.g. "upset") appeared on the computer screen. Subjects rated themselves on the adjective from 0 (meaning not at all) to 4 (meaning extremely so). A response initiated the next trial. Sixty-five separate adjectives were presented. Task duration was approximately 2 min. Dependent measures were the composite ratings along each of the six subscales.

*Cognitive performance*

Three tasks of cognitive function were administered. In the first (designed to measure working memory and mathematical ability), two randomly selected single digits were presented sequentially, followed by either an addition (+) or subtraction (–) operator, then a prompt signal. Subjects mentally performed the indicated operation, and then entered the least significant digit of the result (e.g. ‘‘8,’’ ‘‘6,’’ ‘‘+’’ results 14; subject enters ‘‘4’’) on the keyboard’s numeric keypad. However, if the operation resulted in a negative value, then the subject was required to add 10 and then enter the positive single digit remainder (e.g. ‘‘3,’’ ‘‘9,’’ ‘‘–’’ results in –6; subject adds 10 to this value to obtain 4, and therefore enters ‘‘4’’). A response initiated the next trial. Fifty trials were administered. Task duration was approximately 3 min. The second task (choice reaction time or RT) was designed to measure short-term vigilance and attention. In that task, a single digit (0 through 9) appeared, and subjects pressed the corresponding number on the keypad. A response initiated the next trial. Fifty trials were administered. Task duration was approximately 1 min. The third task (four-choice serial RT) also was designed to measure vigilance and attention and was an adaptation of the original Wilkinson and Houghton (1975) task. In that task, an array of four half-inch squares was displayed, and corresponded to four keys (1, 4, 5, and 2) on the keypad. When a red dot randomly appeared in one of the four squares, the subject pressed the corresponding keypad key. This response initiated the next trial. One hundred trials were administered. Task duration was approximately 2 min.

For serial addition/subtraction, ten-choice RT, four-choice RT, dependent measures included speed to correct responses (reciprocal of response time in ms to correct responses) and accuracy (percent correct).

*Psychomotor vigilance task (PVT)*

Ability to maintain vigilance was measured using a computerized version of the task developed by Dinges and Powell (1985; see also Dinges et al. 1997). In this task, a time display appeared (initially set to "000”), and subjects pressed a response key as soon as the time display began to increment. A response stopped the time display, and initiated the next trial. The delay between the subject’s response and the next time display increment was 2, 4, 6, 8, or 10 s, and was randomly selected across trials. Task duration was 10 min. The dependent measure was response speed (reciprocal of response time as measured in ms). Accuracy was not a relevant dependent measure.

*Stanford sleepiness scale (SSS)*

This measure of self-evaluated subjective sleepiness was a computerized version of the scale developed by Hoddes et al. (1973). In this test, seven statements pertaining to current state of alertness appeared on the computer screen simultaneously, and ranged from ‘‘1 – feeling active and vital; alert; wide awake” to ‘‘7 – almost in reverie; sleep onset soon; losing struggle to remain awake.” The subject’s self-rating (1–7) served as the dependent measure.

Symptom checklist

Subjects were asked to indicate whether they were currently experiencing certain symptoms by responding “yes” or “no” to the experimenter’s verbal query regarding the following: nervousness, excitation, feelings of aggression, headache, feelings of happiness or elation, pain in abdomen or stomach area, dry mouth, disorientation, pounding heart, racing heart beat, tremor, nausea, gastric or stomach discomfort, feeling as though the room is spinning. If subjects responded “Yes” to an item, they were then asked whether the symptom was mild, moderate or severe. The list of symptoms included those most commonly reported with modafinil use during clinical trials (data on file, Cephalon Inc.). Subjects also were given the opportunity to indicate any symptoms not queried by the experimenter.

Polysomnography

Oxford Medilog 9000-II recording units (Oxford Medical Systems, Oxon, UK) were used to record polysomnographic signals. Polysomnographic (PSG) data were used (1) for a modified maintenance of wakefulness test; (2) for a modified alpha attenuation test (Caldwell et al. 2000); and (3) to verify that subjects were awake or asleep at appropriate times throughout the study. Due to technical difficulties, portions of the PSG corresponding to the modified alpha attenuation test could not be identified.

*Modified maintenance of wakefulness*

For the modified maintenance of wakefulness test, subjects were allowed to lie down in bed, and were instructed to close their eyes but try to stay awake. Lights were then turned off, and subjects were allowed to lie undisturbed for 15 min after which lights were turned on and subjects awakened if asleep. A technician who remained blind to drug condition scored latency to the first 30 s of stage 2 sleep off-line. The technician’s sleep scoring reliability was within 90% of scoring conducted by a sleep medicine specialist certified by the Association of Sleep Disorders Medicine (ASDA).

Tympanic temperature

Tympanic temperature (°C) was recorded using Thermoscan tympanic temperature probes. Temperature was included for comparison with previous results indicating that modafinil increases body temperature (Bourdon et al. 1994; Pigeau et al. 1995; Brun et al. 1998).

Testing facilities

During computerized testing, objective alertness testing and sleep periods, each subject was housed individually in a sound attenuated 10’×10’ room which included a bed and computer test station. Ambient temperature was approximately 74°C and lighting during computerized testing was approximately 200 lux.

Procedure

Subjects participated in groups of two to four, and underwent 54.5 consecutive hours of total sleep deprivation. They reported to the laboratory at 7:00 p.m. (day 1). Vital signs (sitting blood pressure and pulse, and tympanic temperature) were measured. Next, Oxford tin-cup electrodes used for recording polysomnograms (electroencephalography, electromyography, electrooculography) were attached, and continuous polysomnographic recordings began at 8:00 p.m. day 1. Subjects also wore an activity monitor on their nondominant wrist throughout the study. They then received three practice sessions of the computerized PAB. Decaffeinated food and beverages were allowed ad libitum throughout the study except from 7:30 p.m. day 3 (approximately 4.5 h prior to drug administration) through 1:45 a.m. day 4 (approximately 2 h post-drug administration). Water was allowed ad libitum at all times, including during food abstinence.

Lights out on day 1 was 11:30 p.m. Subjects were awakened at 6:30 a.m. on day 2. Blood samples for serum pregnancy testing (women only) and urine samples for drug screening (all subjects) were collected, then electrodes were checked and repaired and vital signs (pulse, blood pressure, tympanic temperature) taken.

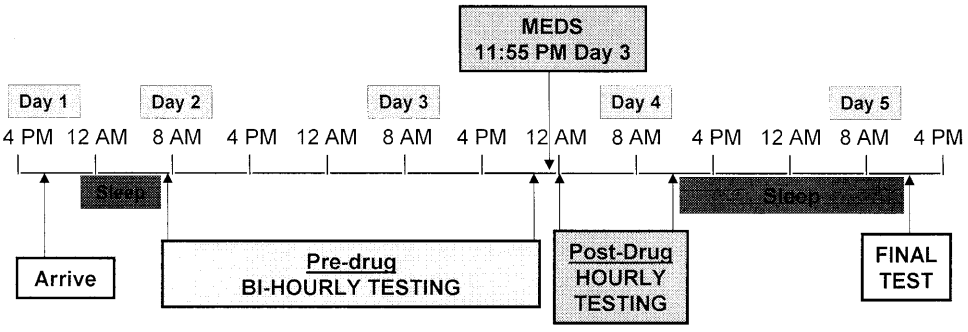


**Fig. 1** Time line for study procedures, testing, and drug administration

Starting at 8:00 a.m. day 2, and continuing through 10:00 p.m. day 3, subjects performed the test battery described above at bi-hourly intervals. Vital signs also were taken bi-hourly, and meals served approximately every 5 h. During any time not occupied with testing, subjects were free to engage in reading, watching movies, etc., within a common living area and under constant staff supervision. Wakefulness during the entire sleep deprivation period (except during the modified MWT) was verified by observation and by continuous PSG recordings. The purpose of pre-drug testing sessions was to verify that tasks were sensitive to sleep deprivation and circadian rhythmicity.

At 11:50 p.m. day 3 (just under 41.5 h of sleep deprivation), subjects ingested an oral dose of modafinil 100 mg (four women, six men), 200 mg (one woman, nine men), 400 mg (two women, eight men), caffeine 600 mg (three women, seven men), or placebo (four women, six men) in a double-blind fashion via pseudo-random assignment in blocks of five (corresponding to the five drug groups). Because there is no evidence that gender interacts with cognitive test performance, no attempt was made to assign equal numbers of men and women to each drug group. The purpose of administering drug just prior to midnight was to test drug efficacy at a time when individuals are most likely to incur performance deficits due to combined effects of sleep deprivation and circadian rhythmicity. In practical use, an alertness-enhancing substance would most likely be required during these hours. Starting at midnight on day 4, subjects performed the computerized PAB every hour until noon on day 4. The symptom checklist was administered immediately following the 2:00 a.m., day 4, test session (i.e. approximately 2.5 h post-drug), then bi-hourly thereafter through noon on day 4. Subjects began a 24-h recovery sleep period at 1:00 p.m. on day 4 followed by a final post-recovery sleep test session at 1:15 p.m. on day 5. Electrodes were then removed. Subjects underwent a brief physical examination, were given a meal, then were administered the symptom checklist. They were debriefed and released at 2:30 p.m. on day 5.

To help maintain motivation and thereby maximize performance throughout the study, subjects were informed in writing (informed consent form) during the screening visit that they could earn a $400.00 bonus if their performance on the computerized test exceeded a criterion. They were not told the criterion (60% accuracy on serial addition-subtraction during the pre-drug test sessions) but were informed that the criterion was easy to obtain and that all subjects in previous studies had earned the bonus. They were not reminded of the bonus during the study. As anticipated, all subjects earned the bonus.

A general timeline of study procedures and testing is illustrated in Fig. 1.

### Statistical analyses

Data were analyzed using a two-way mixed analysis of variance (ANOVA) with group as the between-subjects factor (five groups: modafinil 0, 100, 200, or 400 mg, or caffeine 600 mg) and session as the within-subjects factor (Kirk 1982).

Because the interval between sessions was 2 h pre-drug and 1 h post-drug, separate ANOVAs were conducted on the 20 pre-drug sessions (8:00 a.m. day 2 through 10:00 p.m. day 3), and the 13 post-drug sessions (midnight day 4 through noon day 4) for all tasks and dependent measures. Greenhouse-Geisser corrections were applied to repeated measures effects; reported *P* values reflect this correction. Significant interactions were followed by simple effects analyses (Kirk 1982) separately for either drug group or session, as deemed appropriate. For significant main effects (e.g. drug group or session), post-hoc comparisons among every possible pair of groups (e.g. M100 versus M400; M200 versus C600) were then conducted using Tukey Honestly Significant difference (HSD) tests (Kirk 1982); i.e. comparisons were not restricted to comparing drug groups with placebo only. Symptom checklist data were analyzed using Chi-square tests. Unless otherwise noted, statistical significance was $P<0.05$.

## Results

In text, table and figures, drug groups are abbreviated as follows: placebo=PLA; modafinil 100 mg=M100; modafinil 200 mg=M200; modafinil 400 mg=M400; caffeine 600 mg=C600. The first post-drug session was at midnight day 4 (0 h post-drug). Neither mean age ($P>0.05$, one-way ANOVA), nor the distribution of men and women ($P>0.05$, Chi-squares analyses) differed among drug groups.

Prior to drug administration (sessions from day 2 at 8:00 a.m. through day 3 at 10:00 p.m.), no drug group differences were found for response speed or accuracy for any of the cognitive performance tests (all pre-drug group main effects and Group×Session interactions, $P>0.05$). Analyses for session main effects (pre-drug) for response speed and accuracy (reported below) were conducted to determine whether tasks were sensitive to sleep deprivation and circadian rhythmicity.

### Performance

#### *Psychomotor vigilance (PVT)*

PVT data for one subject (PLA group) were excluded from analyses because it appeared that the subject did not follow task instructions (prior to drug administration). Analyses reported below are for 49 subjects.

*Pre-drug*. Response speed declined as a function of both time of day (trough at 10:00 a.m. day 3) and sleep deprivation [day 3 less than day 2), session $F(19,836)=37.93$, $P<0.001$].

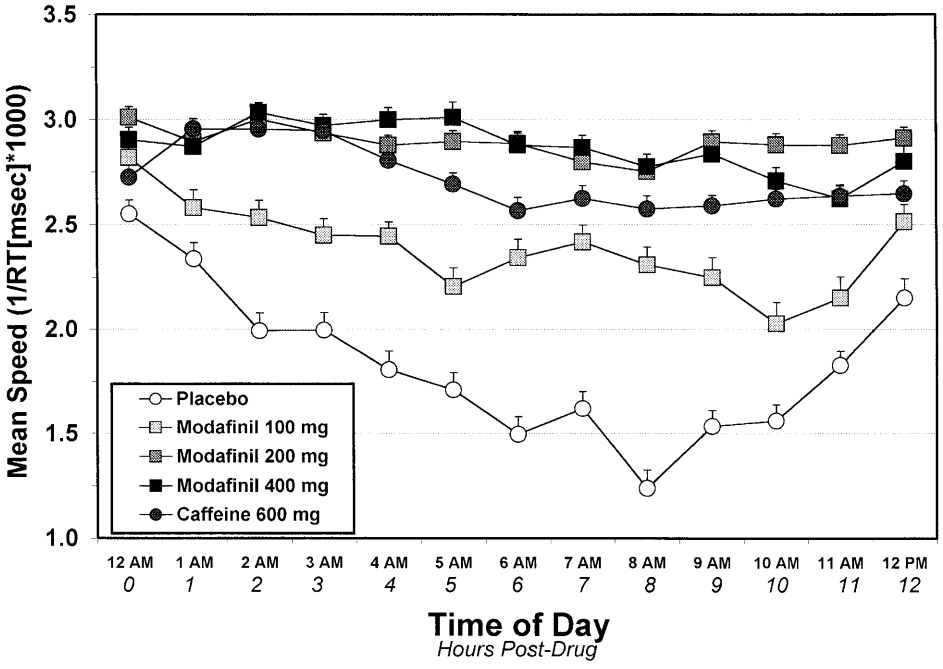


**Fig. 2** Psychomotor vigilance task (*PVT*) mean speed (1/reaction time×1000) across post-drug sessions as a function of drug group. The first session (at midnight) corresponds to 0 min post-drug. Error bars represent SEM

*Post-drug*. Response speed across post-drug sessions as a function of group is shown in Fig. 2. Following drug administration, speed for M200, M400, and C600 was maintained at or near pre-drug, pre-sleep deprivation levels while speed for PLA declined until 8:00 a.m. [group $F(4,44)=7.66$, $P<0.001$; Group×Session $F(48,528)=2.19$, $P<0.01$]. Speed for M200, M400 and C600 was significantly better than PLA from 0200 through 11:00 a.m. (HSD $P<0.05$). Although it appeared that M100 also maintained performance across post-drug sessions, this difference was significant (versus PLA) only at 6:00 a.m. and 8:00 a.m. (HSD $P<0.05$). M100, M200, M400, and C600 did not differ among each other at any post-drug session (HSD $P>0.05$). Accuracy was not a relevant dependent variable for PVT.

*Ten-choice reaction time*

*Pre-drug*. Response speed was affected by circadian rhythmicity (trough at 8:00 a.m. day 3) but was relatively stable from day 2 to day 3 [session $F(19,855)=9.06$, $P<0.001$]. Response accuracy remained relatively stable, showing a decrement only at 8:00 a.m. (mean=95.8, SEM=0.70) and 10:00 a.m. (mean=96.4, SEM=0.56) day 3 [session $F(19,855)=2.71$, $P<0.01$].

*Post-drug*. Following drug administration, response speed was maintained by all groups except for PLA, which continued to decline until 7:00 a.m. [mean=1.36, SEM=0.10; Group×Session $F(48,540)=1.93$, $P<0.01$; session $F(12,540)=2.31$, $P<0.05$; group effect $P>0.05$]. M100, M200, M400, and C600 did not differ among each other at any post-drug session (HSD $P>0.05$). Response accuracy was not improved by modafinil or caffeine (Group and Group×Session effects, $P>0.05$), but rather continued to decline until 10:00 a.m. [mean=95.4, SEM=0.66 averaged across drug groups; session $F(12,540)=3.59$, $P<0.001$].

*Four-choice reaction time*

*Pre-drug*. Both response speed and accuracy were affected by circadian rhythmicity [trough during the morning hours of day 3, speed session $F(19,855)=10.6$, $P<0.001$; accuracy session $F(19,855)=2.46$, $P<0.01$].

*Post-drug*. Response speed was unaffected by drug group, nor did it change across sessions (Group, Session, and Group×Session effects, $P>0.05$). Response accuracy showed a pattern similar to that seen for PVT speed in Fig. 2. Accuracy for M200, M400, and C600 was maintained near pre-drug levels while accuracy for PLA declined until 8:00 a.m. [mean=92.8, SEM=2.00; group $F(4,45)=3.69$, $P<0.05$; Group×Session $F(48,540)=1.62$, $P<0.05$; HSD $P<0.05$]. Although it appeared that M100 also maintained accuracy across post-drug sessions, this difference was not significant at any session (HSD $P>0.05$). M100, M200, M400, and C600 did not differ from each other at any post-drug session (HSD $P>0.05$).

*Serial addition/subtraction*

*Pre-drug*. Response speed was affected by circadian rhythmicity (trough at 6:00 a.m. day 3) but not sleep deprivation (day 3>day 2) [Session effect $F(19,855)=9.06$, $P<0.001$]. Accuracy was not affected by circadian rhythmicity or sleep deprivation (Session effect $P>0.05$).

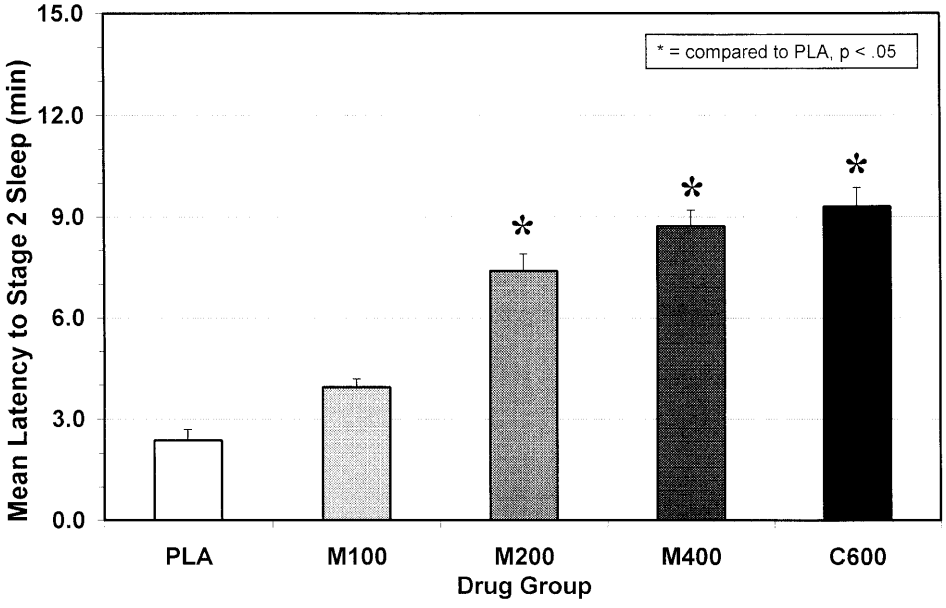


**Fig. 3** Modified Maintenance of Wakefulness latency to stage 2 sleep (in minutes) as a function of drug group. Means are averaged across post-drug sessions. Error bars represent SEM

*Post-drug*. Drug marginally affected response speed [group $F(4,45)=2.09$, $P<0.10$] with speed improved by M100 (mean averaged across post-drug sessions=1.37, SEM=0.05) and C600 (mean=1.31, SEM=0.05) compared to PLA (mean=0.10, SEM=0.03; HSD $P>0.05$). M100, M200, M400, and C600 did not differ among each other (HSD $P>0.05$). Overall, response speed declined until 7:00 a.m. [mean=1.02, SEM=0.05 averaged across drug groups; session $F(12,540)=6.45$, $P<0.001$]. The Group×Session interaction was not significant ($P>0.05$). Response accuracy declined across post-drug sessions [$F(12,540)=2.84$, $P<0.05$], but was not improved by drug (Group and Group×Session effects, $P>0.05$).

## Alertness

### *Modified maintenance of wakefulness – latency to stage 2 sleep*

Due to equipment failure, polysomnographic data were missing for 22 subjects. Sleep latency analyses therefore reflect data from 28 subjects (PLA=3; M100=6; M200=6; M400=7; C600=6).

*Pre-drug*. Overall, sleep latency decreased from day 2 to day 3 (sleep deprivation effect), and was minimal in the morning hours (circadian effect); session $F(19,836)=37.93$, $P<0.001$.

*Post-drug*. Sleep latency as a function of group is shown in Fig. 3 (collapsed across post-drug sessions). Following drug administration, sleep latency increased for M200, M400, and C600 compared to PLA [group $F(4,23)=12.65$, $P<0.001$; HSD $P<0.05$]; latencies for M400 and C600 also were higher than latency for M100 (HSD $P<0.05$). M200, M400 and C600 did not differ from one another (HSD $P>0.05$). Despite significant drug effects, sleep latencies for all groups declined through the morning hours [session $F(12,276)=3.91$, $P<0.001$]. The Group×Session interaction was not significant ($P>0.05$).

### *Stanford sleepiness scale*

*Pre-drug*. Subjective sleepiness ratings were affected by circadian rhythmicity (greatest subjective sleepiness at 8:00 a.m. day 3) and sleep deprivation [sleepiness day 3>day 2, session $F(19,855)=29.8$, $P<0.001$].

*Post-drug*. Sleepiness ratings were lowered (improved) by C600 (mean=2.86, SEM=0.1332 averaged across sessions), M400 (mean=3.12, SEM=0.1371), and M200 (mean=3.31, SEM=0.1080) but increased by M100 (mean=4.56, SEM=0.1315) relative to PLA [mean=4.0923, SEM=0.1577; group, $F(4,45)=3.49$, $P<0.05$]; however, only the difference between C600 and M100 was significant (HSD $P<0.05$).

## Mood, symptoms, and tympanic temperature

### *Profile of Mood States*

*Pre-drug*. Scores on the tension-anxiety, fatigue-inertia, and confusion-bewilderment, and vigor-activity subscales were affected by circadian rhythmicity (worst mood at 8:00 a.m. day 3) session, $P<0.05$ for all four subscales. Although depression-dejection peaked at 6:00 a.m. on day 3 ($P=0.08$), pre-drug group differences (group, $P<0.05$) indicated higher reported depression-dejection for M100 (mean=6.14, SEM=0.65) versus

**Table 1** Summary of drug group differences for cognitive performance, objective and subjective alertness, and mood measures

| Task | Variable | Drug group comparisons, Tukey HSD, $P<0.05$ |
|---|---|---|
| Psychomotor vigilance | Speed | M200, M400, C600>PLA (2:00–11:00 a.m.); M100>PLA (6:00 and 8:00 a.m.) |
| Ten-choice RT | Speed | C600>PLA (7:00 a.m.) |
| | Accuracy | NS |
| Four-choice RT | Speed | NS |
| | Accuracy | Despite significant Group×Session interaction, Tukey HSD failed to reveal differences |
| Serial add-subtract | Speed | M100, C600>PLA |
| | Accuracy | NS |
| Modified MWT | Latency to stage 2 | M200, M400, C600>PLA; M400, M600>M100 |
| Stanford sleepiness scale | Self-rating | M100 (greater sleepiness)>C600 |
| POMS self-ratings | Tension-anxiety | Despite marginal group main effect, Tukey HSD failed to reveal differences |
| | Fatigue-inertia | M100 (more fatigue)>C600 |
| | Confusion-bewilderment | M100 (more confusion)>C600 |
| | Vigor-activity | NS |
| | Depression-dejection | M100 (more depression)>M400 |
| | Anger-hostility | NS |

M400 (mean=0.25, SEM=0.08). Anger-hostility was unchanged across pre-drug sessions ($P>0.05$).

*Post-drug*. A marginal Group × Session interaction [$F(48,540)=1.44$, $P<0.10$] for tension-anxiety was due to increases for M400 at 3:00 a.m. and 4:00 a.m. (mean for both sessions=19.44). Fatigue-inertia (mean=18.82, SEM=1.61) and confusion-bewilderment (mean=10.91, SEM=0.75) were lower for C600 than for M100 (fatigue, mean=44.15, SEM=2.03; confusion, mean=24.12, SEM=1.38) [fatigue group $F(4,45)=2.45$, $P<0.10$; confusion group $F(4,45)=3.27$, $P<0.05$]. Because post-drug group differences for depression-dejection [group $F(4,45)=2.86$, $P<0.05$] were similar to those seen pre-drug (higher scores for M100 versus M400), it is unlikely that this reflected an effect of drug. Drug Group effects were not significant for vigor-activity or anger-hostility ($P>0.05$). Mood worsened across post-drug sessions for tension-anxiety [$F(12,540)=2.79$, $P<0.01$]; fatigue-inertia [$F(12,540)=16.75$, $P<0.001$]; confusion-bewilderment [$F(12,540)=4.38$, $P<0.001$]; vigor-activity [$F(12,540)=12.41$, $P<0.001$]; and anger-hostility [$F(12,540)=2.26$, $P<0.05$] but not for depression-dejection ($P>0.05$).

*Tympanic temperature*

*Pre-drug*. Tympanic temperature displayed circadian rhythmicity, showing a peak at 9:00 p.m. on both day 2 (mean=35.8°C, SEM=0.09 averaged across drug groups) and day 3 (mean=35.9, SEM=0.09) and a trough at 7:00 a.m. [day 2 mean=35.3, SEM=0.09; day 3 mean=35.4, SEM=0.08; session $F(20,900)=6.21$, $P<0.001$].

*Post-drug*. Although it appeared that M400 and C600 increased body temperature at some post-drug sessions, ANOVA did not reveal a significant effect for drug group or a significant Group×Session interaction ($P>0.05$). Circadian rhythmicity was maintained across post-drug sessions – tympanic temperature declined to a minimum at 5:00 a.m. (mean=35.4, SEM=0.09, averaged across drug groups), then increased across the remaining sessions [session, $F(5,225)=3.47$, $P<0.01$].

A summary of group comparisons (Tukey HSD results) for post-drug analyses of variance (performance, alertness, and mood) is found in Table 1.

*Symptom checklist*

The symptom checklist was administered post-drug only. Chi-square analyses of symptom ratings among drug groups were conducted separately for each post-drug session. At the first post-drug session (0240), subjects in the C600 and M400 groups reported heart pounding ($n=4$ for C600; $n=3$ for M400; Chi-square=21.07, $P<0.05$) and nausea ($n=3$ for both C600 and M400; Chi-square=10.23, $P<0.05$) more frequently than those in the other drug groups. No drug group differences were found for other symptoms or sessions ($P>0.05$). Symptoms observed by the investigator included two instances of vomiting in the C600 group and one instance of extreme jitteriness and shaking in the M400 group, all occurring approximately 3 h after drug administration.

## Discussion

In the present study the objective, cognitive performance- and alertness-enhancing effects of modafinil were compared to a dose of caffeine shown previously to improve these measures during prolonged (greater than one night) total sleep deprivation (Penetar et al. 1993, 1994). The results indicate that the objective cognitive performance improvements that result from administration of modafinil 200 and 400 mg are comparable to those obtained with caffeine 600 mg. Although there was a trend suggesting that modafinil 400 mg may be more

efficacious than caffeine 600 mg for improving PVT speed and ten-choice RT throughput, there were no statistically significant differences between these groups. The ability to maintain wakefulness in a sleep-conducive environment also was improved significantly by modafinil 400 mg, but again, a comparable improvement was evident in those subjects administered caffeine 600 mg.

## Methodological considerations

A single administration of caffeine 600 mg is three times higher than the recommended over-the-counter dosage of 200 mg. This dosage may appear to be unnecessarily high since under most circumstances, individuals would likely use over-the-counter caffeine to sustain alertness and performance during shorter-term (e.g. 1 night) sleep loss. In the present study, 600 mg was chosen as the comparison dose because it is the only dose that is effective for both improving and maintaining performance and alertness after 48 h of sleep deprivation compared to dosages of 150 and 300 mg, whose efficacy is not maintained beyond several hours post-administration (Penetar et al. 1993, 1994). Modafinil 400 mg also is a relatively high dosage, albeit within the recommended prescribing range. Again, however, results from the present study indicate that these dosages may be necessary to improve and sustain cognitive performance during prolonged (more than 1 night) sleep loss.

It is possible that the monetary performance bonus used in the present study attenuated drug effects by increasing performance in all groups, particularly the placebo group. Horne and Pettit (1985) failed to improve performance following a second night of sleep deprivation (corresponding to the time that drug was administered in the present study) using monetary incentives higher than those used in the present study. Even if the performance bonus did attenuate group differences, significant drug effects were still evident (versus placebo), particularly during the circadian trough of performance and alertness, corresponding to the time of day when Horne and Pettit noted that performance incentives during the first 24 h of sleep deprivation were only minimally effective.

It is also possible that the minimal controls exerted over subjects' prior caffeine exposure in the present study attenuated the effects of caffeine (subjects were excluded only if their reported daily caffeine intake exceeded 400 mg). Subjects may have entered the study tolerant to caffeine's performance- and alertness-enhancing effects and therefore also undergoing caffeine withdrawal. Symptom data from the placebo group, however, suggest that this is unlikely; subjects in the placebo group would have reported a higher incidence of withdrawal-related symptoms (such as headache) than the other groups. Overall, however, symptom reports in the placebo group were lower than those in the other drug groups.

## Dose dependency

The extent to which modafinil's effects on performance and alertness during sleep deprivation are dose-dependent has received scant attention. Previous studies used either single doses of modafinil repeated over time (e.g. Lagarde et al. 1995; Pigeau et al. 1995) or no more than two dose levels of modafinil (e.g. Saletu et al. 1989). In the present study, dose-response effects among three different dosages of modafinil were suggested for some measures such as PVT and ten-choice RT speed. However, these dose effects were not statistically significant, and were not consistent across tasks. For example, serial addition-subtraction performance was better for the group receiving modafinil 100 mg. Also, there generally appeared to be little difference between the modafinil 200 and 400 mg doses. Thus, results of the present study do not convincingly establish dose-dependent effects of modafinil.

## Efficacy during the circadian trough

Consistent with previous studies (e.g. Pigeau et al. 1995; Brun et al. 1998; Caldwell et al. 2000), modafinil (200 and 400 mg) sustained performance across the circadian trough (2:00–10:00 a.m.). Similar effects were seen with caffeine 600 mg. The early morning hours were selected for comparison of drug/dose effects because under real-world conditions, individuals are likely to experience subjective sleepiness and initiate interventions at this time. Despite its elimination half-life of 10–15 h, modafinil maintained efficacy (compared to placebo) for approximately 10 h (compared to placebo). Convergence after this point may have been due to circadian rhythm-mediated late morning performance improvements in all groups, including placebo. In a prior study evaluating caffeine, performance and objective alertness improved similarly across daytime hours after 48 h of sleep deprivation (Penetar et al. 1993, 1994), even in the placebo group. In short, circadian rhythm-mediated performance improvements may serve to mask modafinil's effects at certain times of the day. In other words, had modafinil been administered earlier (for example at 8:00 p.m. versus 11:55 p.m.), the circadian trough in performance would have been reached at 14 h post-drug rather than 8 h post-drug, and significant performance enhancement versus placebo during the circadian trough would have suggested a longer duration of action, a duration that is more consistent with its pharmacokinetic profile.

Pigeau et al. (1995) and Brun et al. (1998) reported that modafinil blocks the nighttime drop in core body temperature. Similarly, in the present study the overall trend post-drug was for higher tympanic temperature with modafinil 200 and 400 mg (as well as caffeine 600 mg) versus placebo. However, these trends were not significant, perhaps because tympanic temperature is not an adequately sensitive index of core temperature.

Side-effects

Consistent with the findings from previous studies (Lagarde et al. 1995; Lagarde and Batejat 1995; Pigeau et al. 1995; Caldwell et al. 2000), side-effects of modafinil were minimal. Headache (the most frequently cited side-effect of modafinil according to the package insert) was infrequently reported. The present results confirm that modafinil has a relatively favorable side-effect profile compared to other CNS stimulants such as *d*-amphetamine (Pigeau et al. 1995). One exception may be the negative effects of modafinil on subjective performance appraisal accuracy (Baranski and Pigeau 1997), which was not measured in the present study.

Of particular interest were the relative side effects profiles of the various doses of modafinil versus caffeine 600 mg. In the present study, subjects receiving caffeine 600 mg reported the greatest number of symptoms. However, because none of the reported symptoms were serious or debilitating, it can be argued that these differences provide little rationale for choosing to use one drug over the other in the operational environment.

Likewise, at appropriate doses, the performance-enhancing effects of modafinil and caffeine were found to be comparable. Thus, based on the facts that (a) caffeine is more widely available (as an over-the-counter drug and as a component of various foods), and (b) caffeine is less expensive, it will probably remain the "drug of choice" for restoring and maintaining cognitive performance and alertness during sleep loss in otherwise normal (non-narcoleptic) adults.

Recent evidence indicates that modafinil and caffeine have different mechanisms of action (Wisor et al. 2001). The findings of comparable effects on performance in sleep deprivation speak to the neurobiological mechanisms underlying the generation and amelioration of these performance deficits and suggest further possible value in combined treatment with both drugs.

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