USAARL Report No. 99-17


# The Effects of Modafinil on Aviator Performance During 40 Hours of Continuous Wakefulness: A UH-60 Helicopter Simulator Study

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June 1999

19990712 019

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U.S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama 36362-0577

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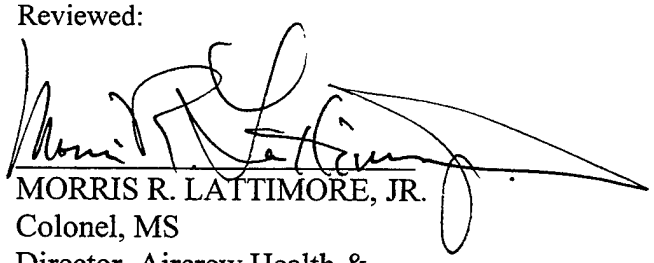

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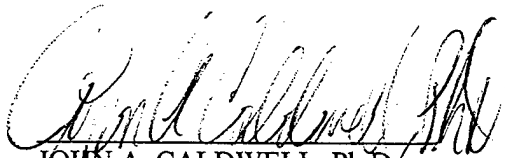

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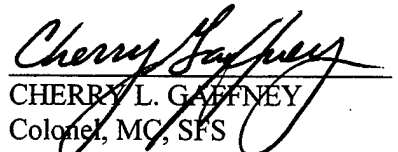

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Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

# REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION
Unclassified

1b. RESTRICTIVE MARKINGS

2a. SECURITY CLASSIFICATION AUTHORITY

3. DISTRIBUTION / AVAILABILITY OF REPORT
Approved for public release, distribution unlimited

2b. DECLASSIFICATION / DOWNGRADING SCHEDULE

4. PERFORMING ORGANIZATION REPORT NUMBER(S)
USAARL Report No. 99-17

5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION
U.S. Army Aeromedical Research Laboratory

6b. OFFICE SYMBOL (If applicable)
MCMR-UAD

7a. NAME OF MONITORING ORGANIZATION
U.S. Army Medical Research and Materiel Command

6c. ADDRESS (City, State, and ZIP Code)
P.O. Box 620577
Fort Rucker, AL 36362-0577

7b. ADDRESS (City, State, and ZIP Code)
Fort Detrick
Frederick, MD 21702-5012

8a. NAME OF FUNDING / SPONSORING ORGANIZATION

8b. OFFICE SYMBOL (If applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER

8c. ADDRESS (City, State, and ZIP Code)

10. SOURCE OF FUNDING NUMBERS

| PROGRAM ELEMENT NO. | PROJECT NO. | TASK NO. | WORK UNIT ACCESSION NO. |
|---|---|---|---|
| 0602787A | 3M162787A879 | OC | DA336185 |

11. TITLE (Include Security Classification)
The effects of modafinil on aviator performance during 40 hours of continuous wakefulness: A simulator study (u)

12. PERSONAL AUTHOR(S) JA Caldwell, NK Smythe, JL Caldwell, KK Hall, DN Norman, BF Prazinko, A Estrada, PA Johnson, JS Crowley, and ME Brock

| 13a. TYPE OF REPORT | 13b. TIME COVERED FROM | TO | 14. DATE OF REPORT (Year, Month, Day) | 15. PAGE COUNT |
|---|---|---|---|---|
| Final | | | 1999 June | 55 |

16. SUPPLEMENTAL NOTATION

| 17. COSATI CODES | | |
|---|---|---|
| FIELD | GROUP | SUB-GROUP |
| | | |
| | | |

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
modafinil; sleep deprivation; stimulants; aviators; performance; EEG; sleep; mood

19. ABSTRACT (Continue on reverse if necessary and identify by block number)
This research evaluated the efficacy of the stimulant modafinil for sustaining simulator flight performance, cognitive skill, psychological mood, and central nervous system (CNS) activation in helicopter pilots who had been deprived of sleep. Six Army helicopter pilots were each exposed to two 40-hour periods of continuous wakefulness separated by one night of recovery sleep. In one of the periods, three 200-mg doses of modafinil were given (at 2300, 0300, and 0700) and in the other period, matching placebo tablets were administered. Testing sessions, which included UH-60 simulator flights, EEG evaluations, Profile of Mood States (POMS) and Visual Analog Scale (VAS) questionnaires, a desktop flight simulator task, and the Multi-Attribute Task Battery (MATB), were conducted at 0900, 1300, and 1700 on baseline days, and at 0100, 0500, 0900, 1300, and 1700 during sleep deprivation periods.

Modafinil significantly attenuated the effects of sleep deprivation on four of the six flight maneuvers. Performance on the straight-and-levels, straight descents, left standard-rate turns, and left descending turn was maintained at or near baseline levels by

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS

21. ABSTRACT SECURITY CLASSIFICATION
Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL
Chief, Science Support Center

22b. TELEPHONE (Include Area Code)
(334) 255-6907

22c. OFFICE SYMBOL
MCMR-UAX-SS

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

19. (continued)
modafinil, whereas performance suffered under placebo. In addition, modafinil reduced the amount of slow-wave EEG activity (indicative of reduced CNS activation), lessened self-reported problems with mood and alertness (diminished vigor, energy, confidence, etc.), and curtailed the performance decrements (slower response times, increased response lapses, and elevated tracking errors) that were found under placebo. The most noticeable benefits from the drug were seen between approximately 0330 and 1130 when the combined impact of sleep loss and the circadian trough was most severe. The positive effects of this compound were not offset by disruptions in recovery-sleep architecture.

The most frequently associated side effects with modafinil administration were vertigo, nausea, and dizziness. These were especially problematic during the simulator flights. It may be that some of these difficulties would subside under actual flight conditions since simulators have been found to increase the incidence of motion sickness in susceptible individuals (and modafinil may have lowered the threshold for this "simulator sickness"). In addition, it is possible that some of the side effects could be eliminated or reduced by lowering the drug dosage from 600 to 400 mg (if the difficulties are dose related).

Although direct statistical comparisons between modafinil and dextroamphetamine have yet to be conducted, there are indications that modafinil is the less efficacious of the two stimulants. Also, it appears that modafinil (at 600 mg) is more likely to produce side effects which could be problematic in aviation operations. Both of these issues will be further addressed in a follow-on, quasi-experimental comparison between the two compounds (i.e., data from this investigation will be contrasted with data from our earlier dextroamphetamine studies). In addition, a future double-blind, within-subjects experimental comparison between modafinil and dextroamphetamine is being planned.

## Acknowledgments

The authors are sincerely grateful to Cephalon, Inc. for granting permission to conduct an investigational new drug (IND) study with modafinil and for supplying (free-of-charge) the modafinil and matching placebos used in this investigation. Mr. Michael Nelson of Cephalon was especially helpful in facilitating the approval of this protocol and providing helpful consultations throughout the study. We also deeply appreciate three of USAARL's aviators, CPT Ian Ashcroft, CPT Victor Estes, and MAJ Bruce Bates for their assistance with this study. In addition, we would like to thank SPC Ronnie Williamson and SGT Dean Riley who helped with the testing schedule, Dr. Patricia LeDuc for assisting with various aspects of the study, the personnel at Raytheon Systems Company who expertly maintained the simulator, Dr. Heber Jones and Mr. Andy Higdon who ensured proper functioning of the flight data collection systems, Mr. Dan Ranchino and Mr. Robert Haygens for superb computer support, and all of our coworkers at USAARL who made this project a success. Lastly, we deeply appreciate the professionalism of each of the aviators who selflessly volunteered to serve as research subjects.

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## General objective

The purpose of this research was to determine the efficacy of the stimulant modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) for sustaining simulator flight performance, cognitive skill, psychological mood, and central nervous system (CNS) activation in helicopter pilots who have been deprived of sleep. This investigation was a systematic replication of earlier studies of the efficacy of dextroamphetamine designed to facilitate direct comparisons between the two compounds (modafinil versus dextroamphetamine).

## Military relevance

This research is important to the Department of Defense because pharmacological methods may be the only viable alternative for maintaining pilot alertness and ensuring the safety of aircraft and crews during sustained or continuous combat operations. Because it is impossible to ensure that aviators and crew members will receive adequate sleep and rest in the operational environment, a variety of countermeasures must be explored to prevent the attentional lapses, slower reaction times, and increased errors associated with fatigue (Krueger, 1989). Although dextroamphetamine is one effective alternative for maintaining the performance of sleep-deprived personnel, a study of the newer compound modafinil was required because modafinil appeared to be efficacious while at the same time manifesting a more favorable side-effect profile (than dextroamphetamine). In addition, modafinil appears to have a lower abuse potential than dextroamphetamine.

## Introduction

Current military doctrine indicates the requirement for Army aviation units to operate around the clock during times of conflict. The success of battlefield operations depends on maintaining the speed and momentum of continuous day-night operations (Department of the Army, 1989). Night helicopter operations which were not feasible 20 years ago, now constitute a significant component of the modern aviation mission. The advent of night vision technology (and the subsequent improvement in night fighting capability) has created a tactical advantage by optimizing the element of surprise and reducing the probability of enemy detection. Combining an efficient night-fighting capacity with normal daytime operations exerts a significant strain on enemy resources by requiring a sustained response throughout successive 24-hour periods.

Unfortunately, however, there are difficulties inherent in maintaining effective round-the-clock operations. This is particularly the case in situations where there are insufficient numbers of personnel to staff the day and night shifts with separate crew members. Although the aircraft and equipment can be expected to function for extended periods without adverse effects, the same cannot be said for the human operators. Humans need sleep for the restitution of both the body and the brain following periods of wakefulness (Horne, 1978), and while the exact mechanisms for the restorative value of adequate rest have not been established, there is

substantial evidence that humans who are required to work long periods without proper sleep experience a number of problems.

Krueger (1989) reviewed numerous studies on the effects of sustained work and sleep loss, and indicated that sleep deprivation: 1) increases mental "lapses" which have an impact on the speed and accuracy of responses; 2) reduces ability to acquire and recall information in complex tasks; 3) produces changes in brain activity associated with decreased alertness; and 4) slows cognitive ability in which task performance declines in conjunction with mood and motivation. Furthermore, humans cannot overcome the effects of sleep loss through any training mechanism, such as by gaining experience with performing under sleep-deprived conditions.

There has been much research conducted on potential strategies for improving the sustainment of aviator performance in situations where sleep deprivation may be a factor. Some of the current strategies include: 1) manipulating the timing and duration of sleep periods via sleep management programs or the administration of hypnotics (Babkoff and Krueger, 1992), or 2) ensuring mandatory rest periods between flight missions (Department of the Army, 1988a). However, these countermeasures can only work in situations where there exists some flexibility in terms of personnel staffing and scheduling--flexibility that often does not exist in a combat scenario.

In combat, the mission demands are both intense and unpredictable, and the operational setting is not conducive to sleep even when opportunities arise. Thus, it is virtually impossible to ensure that aircrews will not become sleep deprived. Evidence obtained from Army personnel deployed during Operation Desert Storm confirmed the difficulties associated with operational fatigue by indicating that sleep deprivation was a problem for a small number of personnel even though the actual combat period was short (Caldwell, 1992). Cornum (1994) further highlighted the problem in his report on Air Force F-15C pilots who were flying air combat patrol missions during Desert Storm. He indicated that pilots suffered significant circadian rhythm disruptions and fatigue because of the necessity for continuous and sustained operations, and that effective crew-rest or sleep management strategies could not have been implemented due to operational constraints.

Thus, during times of intense aviation operations, it appears that administrative and behavioral interventions will not be sufficient to satisfactorily preserve the performance of aviators in every deployed unit. Even in situations where aviators do receive enough sleep, they may not be able to maintain appropriate levels of vigilance during long periods of overnight duty without some form of assistance (Pascoe, Nicholson, and Turner, 1994). Therefore, there may be times when the only viable alternative is to sustain performance through pharmacological means (i.e., stimulants).

## Stimulants and military performance

Stimulants (primarily amphetamines) have been used by the military for some time to reduce fatigue and increase the performance of soldiers assigned to special duties such as long-range reconnaissance and extended transport flights (Babkoff and Krueger, 1992). Grinspoon and

Hedblom (1975) report that an estimated 200 million amphetamine tablets were supplied to American troops during World War II alone. Although such stimulant use has not been well-studied in a field setting, occasional reports have substantiated the operational utility of drugs such as benzedrine given to ground forces (Tyler, 1947) and, more recently, Dexedrine administered to EF-111A pilots (Senechal, 1988) and F-15C pilots (Cornum, 1992). Emonson and Vanderbeek (1993) provided anecdotal information that Air Force pilots effectively used dextroamphetamine during Operation Desert Storm to counteract the effects of fatigue during sustained missions. In each of these cases, dextroamphetamine minimized the fatigue of the missions themselves and any associated sleep deprivation without producing any noteworthy adverse effects. These findings have recently been confirmed in controlled laboratory investigations (Newhouse et al., 1989; Pigeau et al., 1995; Caldwell, et al., 1995; Caldwell, Caldwell, and Crowley, 1997; Caldwell and Caldwell, 1997; Caldwell et al., 1998).

There are other stimulant compounds (besides dextroamphetamine) that have shown potential for sustaining the performance of sleep-deprived individuals as well. However, a variety of factors have affected the degree to which any of these have been used. Methamphetamine may be slightly more effective than dextroamphetamine (Shappel, Neri, and DeJohn, 1992; Stanny, McCardie, and Neri, 1993), but it has not been the stimulant of choice due to its higher abuse potential. Caffeine, although easy to acquire and socially acceptable, is less effective than most other stimulants including dextroamphetamine (Penetar et al., 1993). Caffeine appears suitable for sustaining alertness only in relatively short (i.e, 37-hour) rather than long (i.e., 64-hour) periods of continuous wakefulness (Lagarde and Batejat, 1995). Pemoline appears to be an effective means for promoting alertness without significant side effects, but its onset of action is slower than other stimulants (Babkoff et al., 1992). Methylphenidate has known stimulant effects, and may be a good choice to promote wakefulness for brief periods. However, its pharmacological effects are relatively short (only 4-6 hours) (Sonsalla, 1995).

Modafinil, a new psychostimulant, shows promise for sustaining the performance of sleep-deprived personnel (Lagarde and Batejat, 1995); but controlled studies in nonpatient populations are lacking because the compound was only recently approved for use in the United States (as of December, 1998). However, because modafinil appears to significantly reduce sleepiness without producing serious side effects, there is substantial interest in testing the efficacy of this compound for maintaining the performance of personnel in sustained operations.

## Modafinil

### General

Modafinil (Cephalon, Inc.) is 2-[(diphenylmethyl)sulfinyl]acetamide which is supplied in 100 mg tablets. Although the exact mechanism by which modafinil exerts its effects are unknown, the compound has been shown to affect serotonergic and gamma-aminobutyric acid (GABA) sites in the CNS (Cephalon, 1998). Modafinil apparently reduces the amount of GABA release in several areas of the brain including the cerebral cortex and the nucleus accumbens (Fuxe et al., 1996). The action of this compound depends upon an intact $\alpha_1$-adrenergic system. Modafinil has been shown to produce highly selective CNS stimulation with minimal effects on the

peripheral nervous system (Lin, Hou and Jouvet, 1996; Cephalon, 1998), it has a relatively low abuse potential (Lyons and French, 1991) and does not appear to affect normal sleep (Saletu et al., 1989a). The most frequently used dosage range is 50-400 mg per day (usually administered as a single dose); however, there is evidence indicating the safety of up to 600 mg per day (Cephalon, 1998; Lagarde and Batejat, 1995). For instance, 5 pharmacodynamic studies with a total of 67 nonsleep-deprived adults indicated only mild increases in nervousness with doses of over 400 mg per day and no significant cardiovascular changes with doses of up to 1400 mg per day. Ten other studies with a total of 114 nonsleep-deprived adults suggested that doses ranging from 50-600 mg per day produced elevations in alertness without significant side effects. Another investigation with 12 volunteers (given 50-800 mg per day) revealed increased CNS side effects (nervousness) with 600 to 800 mg per day; however, there were no cardiovascular changes with up to 600 mg per day, and the CNS changes were not of a magnitude to create concerns over participant safety. It was originally thought that modafinil was a central $\alpha_1$-adrenergic agonist, but more recent evidence suggests this may not be the case. It reaches peak blood concentration in approximately 2-4 hours and has a half life of approximately 8-13 hours (Moachon et al., 1996). The kinetics of doses from 50-600 mg are linear and appear to be unchanged by the administration of food. Modafinil is biotransformed into an inactive acid metabolite in the liver. Urinary secretion of unchanged modafinil is relatively low.

Typical effects

Modafinil exerts significant CNS effects with few peripheral effects (Drugs of the Future, 1990). A review of the earlier literature on modafinil indicated that it increases wakefulness, decreases electroencephalographic (EEG) indications of fatigue, improves concentration, enhances mood, and facilitates cognitive performance without elevating psychomotor activity or disrupting the architecture of recovery sleep (Lyons and French, 1991). These general findings have been reiterated in a more recent paper as well (Akerstedt and Ficca, 1997). In monkeys, it has been reported that modafinil is able to produce prolonged wakefulness across 4 days and nights with no behavioral side effects and no residual effects on sleep architecture (Lagarde and Milhaud, 1990)--a finding that, in terms of side effects, was later confirmed by Hermant, Rambert, and Duteil (1991) after administration of the drug to monkeys over 5 consecutive days. Although modafinil was only recently approved for use in the United States, the drug was approved in France over 2 years ago for the treatment of narcolepsy after 4 years of testing in over 1,000 European patients (Drug News Perspective, 1993). In narcoleptics, modafinil has been shown to reduce the frequency of daytime sleep attacks while improving performance on cognitive tests (Boivin et al., 1993; Besset, et al., 1993). Besset et al. (1996) indicated modafinil effectively reduced excessive daytime sleepiness in 140 narcolepsy-cataplexy patients as evidenced by the fact that 64 percent rated the medication either "good" or "excellent" for this purpose. These results have been supported by Phase III clinical studies conducted in the U.S. in which modafinil significantly improved wakefulness and reduced disease severity among narcoleptic patients (Cephalon, 1996).

Adverse reactions and toxicity

The most commonly observed adverse reactions to this medication (at 200 mg and 400 mg per day in narcoleptic patients) are headache and nausea (Cephalon, 1998). Modafinil has relatively low toxicity as evidenced by the fact that doses of up to 1400 mg per day have not produced significant peripheral effects in patients with decreased motivation, and although blood pressure was found to be elevated in elderly patients receiving 1000 mg per day, these effects were not clinically significant. Furthermore, Bastuji and Jouvet (1988) reported that a female hypersomniac who attempted suicide via the acute ingestion of 4500 mg modafinil suffered only tachycardia and 24 hours of nervousness, nausea, and insomnia prior to a full recovery. Laffont (1996) reported modafinil has been proven safe in 530 patients receiving 50-600 mg per day. The most frequently-reported adverse events were dose-related increases in nervousness and excitability (33 cases), and the second most frequently-reported events were headache, digestive disturbances, skin rash, excessive sweating, or salivary changes (18 cases). There is no evidence that either tolerance or dependence develops even in patients who have received modafinil for 2-3 years (Bastuji and Jouvet, 1988). In terms of abuse potential, Cephalon (1998) reports that in normal young adults, modafinil produces subjective effects closer to those of placebo and caffeine than to those of amphetamine. Warot et al. (1993) concurred with these findings and subsequently concluded that modafinil probably does not pose the abuse liability associated with amphetamine.

Vigilance and performance effects

Because modafinil has only recently become available, performance studies are scarce. However, there are indications that modafinil has significant vigilance-enhancing properties with few side effects. Goldenberg and Weil (1986) examined the impact of a single 200-mg dose on EEG activity and digit symbol substitution in nonsleep-deprived volunteers. Modafinil prevented significant reductions in alertness (measured by theta/alpha ratios) for up to 6 hours postdose. Digit symbol substitution was not differentially affected by placebo versus modafinil, but this was probably because the subjects were not sleep deprived. The EEG findings are consistent with those of Saletu et al. (1986) who found that Modafinil (200, 400, and 600 mg) administered to elderly subjects produced reductions in delta and theta activity concurrent with increases in alpha and fast beta.

In terms of the effects of modafinil in sleep deprived individuals, initial results have been encouraging. Lagarde et al. (1995) studied the efficacy of 200-mg doses of modafinil, given at 8-hour intervals (for a total of 600 mg per day), for maintaining the alertness of eight normal volunteers throughout a 60-hour sleep-deprivation period. The findings showed that modafinil reduced episodes of microsleeps and permitted subjects to maintain more normal (i.e., rested) mental states than placebo without inducing the anxiety that is sometimes associated with psychostimulant administration. Lagarde and Batejat (1995) further reported that the modafinil, given to these same subjects, effectively maintained cognitive performance at non-sleep-deprived levels. Bensimon et al. (1991) examined the efficacy of a single 200-mg dose of modafinil for sustaining the performance of normal sleep-deprived subjects. On the sleep-deprivation nights,

the participants were given drug or placebo at 2200 hours and then tested at 0400 and 1600 on critical flicker fusion (an indicator of CNS activation), choice reaction time, and memory. The results showed that in comparison to placebo, modafinil significantly sustained alertness, reaction time, and short-term (but not long-term) memory at 0400, while the majority of these effects dissipated by 1600. These findings partially confirm an earlier study by Benoit et al. (1987) in which a single 200-mg dose of modafinil was found to improve subjective ratings of alertness and, to some extent, performance on a search and memory task in normal subjects during 24 hours of sleep deprivation. Although this dose of modafinil did not sustain post-deprivation alertness at predeprivation levels, the perceived effects on activation persisted throughout the testing period.

Numerous questions remain about how modafinil compares to more traditional stimulants (i.e., amphetamines) in terms of sustaining performance, but a recent report by Pigeau et al. (1995) suggests that modafinil may offer a safe and efficacious alternative to dextroamphetamine. Based upon evaluations of subjective mood reports and the results of cognitive tests from 41 subjects undergoing 64 hours of sleep deprivation, it was concluded that both 300 mg modafinil and 20 mg dextroamphetamine (3 separate doses of each) were effective for maintaining mood, alertness, and performance in comparison to placebo. However, modafinil was considered to be superior to dextroamphetamine in terms of the reported side effects. Specifically, 45 percent of the side effects were reported by subjects in the amphetamine group as opposed to 35 percent and 20 percent reported by subjects in the modafinil and placebo groups, respectively. In addition, it was noted that dextroamphetamine was more likely than modafinil to produce euphoriant effects (a factor associated with abuse potential).

Other reports suggest that modafinil may be preferable to dextroamphetamine in terms of its effects (or lack of effects) on sleep. Saletu et al. (1989a) administered single doses of modafinil (100 and 200 mg), dextroamphetamine (10 and 20 mg), and placebo to normal young volunteers 30 minutes prior to bedtime and studied the subsequent effects on sleep quality and postsleep alertness and performance. It was found that dextroamphetamine (particularly the 20-mg dose) significantly reduced sleep quality while modafinil produced no adverse effects. None of the drug conditions produced changes in cognitive performance; however, next-day alertness (measured by critical flicker fusion) and muscle strength were found to have been improved by 20 mg dextroamphetamine. Saletu et al. (1989b) later replicated this study on a group of older subjects (mean age of 68 years) and demonstrated that the differential effects of dextroamphetamine and modafinil on sleep quality are not age dependent.

Taken together, the results from these investigations indicate that modafinil possesses vigilance-promoting qualities similar to those of dextroamphetamine without the potential for serious adverse side effects and/or abuse often associated with amphetamines. However, while modafinil appears to hold promise for the sustainment of sleep-deprived military personnel, actual "real-world" performance studies are nonexistent. Modafinil has not been adequately tested in field situations (Akerstedt and Ficca, 1997). To determine the general effects of repeated daily doses and the effectiveness of modafinil for the sustainment of real-world complex tasks, particularly in the aviation environment, additional work is necessary. Specifically, before

this drug can be used in tactical aviation operations, the effects of modafinil on actual pilot performance must be evaluated.

## Objectives

The present investigation examined the efficacy of modafinil for safely sustaining the alertness and performance of helicopter pilots despite sleep loss. The study evaluated 1) flight performance (accuracy of heading, altitude, airspeed, and other control parameters) during a standardized flight profile in a UH-60 helicopter simulator; 2) central nervous system activation in terms of EEG power in the delta, theta, alpha, and beta ranges; 3) cognitive performance--the speed and accuracy of completing simulated aviation tasks; 4) subjective psychological mood states in terms of depression-dejection, anger-hostility, confusion-bewilderment, fatigue-inertia, vigor-activity, and several similar measures on visual analog scales; and 5) sleep quality in terms of duration and architecture of recovery sleep.

## Methods

### Modafinil dosage

The divided dosage of 600 mg within a 24-hour period was chosen to *prevent* performance decrements associated with sleep deprivation and to *maintain* acceptable performance throughout a night of sleep deprivation and for an additional 12-13 hours after the last dose. Although there have been only a few studies of sleep deprived normals, there is evidence that a 200 mg dose of modafinil would not accomplish this purpose. For instance, Benoit et al. (1987) have shown that while a 200 mg dose did improve nighttime alertness, it did not maintain alertness at pre-deprivation levels. Also, Bensimon et al. (1991) showed that a single 200 mg dose given at 2200 was not effective for maintaining alertness throughout the day following sleep loss despite the fact there were positive modafinil effects earlier during the night. The adequacy of 600 mg modafinil has not been fully established, but it seems likely that a divided dose of 600 mg would be necessary to accomplish the objectives of this research. Lagarde and Batejat (1995) reported that 600 mg of modafinil maintained the performance of sleep-deprived subjects at near predeprivation levels apparently without inducing unwanted side effects.

### General overview

A double-blind, within-subjects, counterbalanced, placebo-controlled design was employed in which 6 aviators participated for a period of 1 week each. Each subject remained in the U.S. Army Aeromedical Research Laboratory (USAARL) from Sunday evening until the following Saturday morning (however, subjects were permitted to walk around both inside and outside of the Laboratory between test sessions). Testing required that each aviator be exposed to two, 40-hour sleep deprivation periods. During one of these, 3 doses of modafinil (200 mg each) were administered, and during the other, 3 doses of a matching placebo were administered (see table 1). Note that in this study, the drug doses were administered approximately 1 hour before the completion of the test sessions rather than at the end of the test sessions as was the case in our

Table 1.

Testing schedule.

| Time | Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|---|
| 0000 | | Sleep | Sleep | | Sleep | | Sleep |
| | | ^ | ^ | Simulator | ^ | Simulator | ^ |
| | | ^ | ^ | EEG | ^ | EEG | ^ |
| | | ^ | ^ | **DRUG** | ^ | **PBO** | ^ |
| | | ^ | ^ | MiniSim | ^ | MiniSim | ^ |
| | | ^ | ^ | POMS | ^ | POMS | ^ |
| | | ^ | ^ | MATB | ^ | MATB | ^ |
| 0400 | | ^ | ^ | | ^ | | ^ |
| | | ^ | ^ | Simulator | ^ | Simulator | ^ |
| | | ^ | ^ | EEG | ^ | EEG | ^ |
| | | ^ | ^ | **DRUG** | ^ | **PBO** | ^ |
| | | ^ | ^ | MiniSim | ^ | Minisim | ^ |
| | | ^ | ^ | POMS | ^ | POMS | ^ |
| | | Wakeup | Wakeup | MATB | Wakeup | MATB | Wakeup |
| 0800 | | | | | | | |
| | | Training | Simulator | Simulator | Simulator | Simulator | Electrode |
| | | | EEG | EEG | EEG | EEG | removal |
| | | | ---- | ---- | ---- | ---- | |
| | | | MiniSim | MiniSim | MiniSim | MiniSim | |
| | | | POMS | POMS | POMS | POMS | |
| | | | MATB | MATB | MATB | MATB | |
| 1200 | | | | | | | |
| | | Training | Simulator | Simulator | Simulator | Simulator | |
| | | | EEG | EEG | EEG | EEG | |
| | | | ---- | ---- | ---- | ---- | |
| | | | MiniSim | MiniSim | MiniSim | MiniSim | |
| | | | POMS | POMS | POMS | POMS | |
| | | | MATB | MATB | MATB | MATB | |
| 1600 | Start | | | | | | |
| | | Training | Simulator | Simulator | Simulator | Simulator | |
| | | | EEG | EEG | EEG | EEG | |
| | | | ---- | ---- | ---- | ---- | |
| | | | MiniSim | MiniSim | MiniSim | MiniSim | |
| | EEG | | POMS | POMS | POMS | POMS | |
| | hookup | | MATB | MATB | MATB | MATB | |
| 2000 | | | | | | | |
| | | Exercise | Exercise | Exercise | Exercise | Exercise | |
| | | | | | | | |
| | | POMS | | POMS | | POMS | |
| | Bedtime | Bedtime | **DRUG** | Bedtime | **PBO** | Bedtime | |
| 2400 | | | POMS | | POMS | | |

Note: DRUG= 200 mg. modafinil; PBO= matching placebo tablets.
POMS= Profile of Mood States
MATB=Multi Attribute Task Battery

earlier work with dextroamphetamine. This was done because modafinil takes approximately 1 hour longer to peak than dextroamphetamine. Also, modafinil has a longer half life. Using earlier dose times enhanced the comparability between this study and our earlier work on dextroamphetamine. The orders of drug/placebo administration were counterbalanced, and specific orders were assigned to subjects randomly upon arrival to the Laboratory (see table 2). Drug or placebo doses were given orally with approximately 8 oz water. Testing sessions were conducted around the clock during deprivation periods.

Table 2.
Dose orders.

| Subject | First deprivation period | Second deprivation period |
|---|---|---|
| 1 | Modafinil | Placebo |
| 2 | Placebo | Modafinil |
| 3 | Placebo | Modafinil |
| 4 | Modafinil | Placebo |
| 5 | Placebo | Modafinil |
| 6 | Modafinil | Placebo |

## Subjects

Eight UH-60 qualified male helicopter pilots were enrolled in the study. The first volunteer was unable to complete the study due to severe nausea and headache which occurred early during his first deprivation period (he was on placebo at the time). In the medical monitor's opinion, the reason for this subject's discomfort was possible mild gastroenteritis. The sixth volunteer was replaced because, despite his successful completion of the investigation, his flight data were confounded by an exceptionally steep training curve (he had not flown either a simulator or an aircraft in over 6 months, and as a result, his data were not comparable to those of the other aviators who were "current" in the UH-60). The subject numbers noted in table 2 are actually the case numbers of individuals who successfully completed the project and whose data were used in the final analysis. The six aviators who made up the final sample were aged 37.3 years (ranging from 29-46 years), and possessed 2173.3 total hours of flight experience (ranging from 900-5500 hours). An average of 492.5 flight-hours were obtained in the UH-60. The average body weight of the sample was 193 pounds (ranging from 145-217 pounds). Each was individually tested during a 1-week stay in the USAARL test facility. Males were used exclusively 1) to ensure comparability with the majority of earlier Dexedrine subjects, and 2) for safety reasons since reproductive toxicologic and other potentially gender-specific effects have not been studied adequately. Subjects signed consent forms and passed a medical evaluation conducted by a USAARL flight surgeon prior to admission into the protocol. None of the subjects who volunteered were found to have evidence of past psychiatric or cardiac disorder, a history of sleep disturbances, or current significant illness. All participants refrained from consuming alcoholic and caffeinated beverages and any type of medication (other than acetaminophen or ibuprofen) throughout the protocol.

## Apparatus

### Drug doses

The white, oblong, drug and placebo tablets were supplied by Cephalon, Inc. (West Chester, Pennsylvania).* Active tablets contained 100 mg modafinil. In one deprivation period, two active tablets (200 mg) were administered at each dose interval (there were three dose intervals

* See manufacturers' list

per subject). In the other deprivation period, two matching placebo tablets were administered at each dose interval.

Vital signs data

Oral temperatures, pulse, and blood pressure data were collected with an IVAC vital signs monitor (Model number 4200).

Simulator flights

Simulator flights were conducted on site using the UH-60 flight simulator which includes computer-generated visual display (set for standard daytime flight) and a multi-channel data acquisition system for analyzing various aspects of simulator control such as heading, airspeed, and altitude control. Digitized flight performance data were collected and stored on a VAX computer system for subsequent statistical evaluation.

EEG evaluations

EEG evaluations were performed with a Cadwell Spectrum 32, Neurometric Analyzer which recorded spontaneous EEG data on optical disk for analysis. The low filter was set at 0.53 Hz, the high filter was set at 70 Hz, and the 60 Hz notch filter was used. In order to accomplish topographic mapping of brain electrical activity, 21 active EEG channels (referenced to linked mastoids) were collected with Grass silver-cup electrodes, but for the present report, only the data from midline electrodes (Fz, Cz, and Pz) will be presented. All test sessions were conducted in a dimly-illuminated, sound-attenuated chamber.

Desktop flight simulator

The desktop flight simulation task consisted of the Microsoft Flight Simulator 4.0®, combined with a custom-designed, timed flight course (Microsoft Aircraft and Scenery Designer®). This task was run on an IBM 486 computer with VGA graphics. Flight control was via a Virtual Pilot flight yoke (CH Products®), with system interface using either mouse or keyboard. During each flight, there was an additional secondary task which required subjects to perform auditory monitoring of high and low tones presented over a small speaker.

POMS and Visual Analog Scales (VAS)

The mood questionnaire was a 65-item, computerized version of the POMS which measures affect or mood on 6 scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment (McNair, Lorr, and Droppleman, 1981). Visual analog scales in which subjects indicated how they felt in terms of "alert/able to concentrate," "anxious," "energetic," "feel confident," "irritable," "jittery/nervous," "sleepy," and "talkative" were administered in conjunction with the POMS. Each of the above adjectives were centered over 100 mm lines. At the extremes of each line, "not at all" and "extremely" were printed respectively. Subjects were asked to indicate how they felt by placing

a mark along each of the lines. Scores consisted of the distance of the mark from the left end of the line (in mm).

MATB

The MATB, which consisted of visual monitoring, simulated fuel management, simulated radio communications, and target tracking, was administered via a Pentium computer equipped with a Soundblaster audio card, a joystick, and a 15-inch color monitor. Scores for each subtest were automatically computed at the end of each session.

Polysomnography

Polysomnographic data on baseline and recovery sleep nights were collected using a Nihon Khoden electroencephalograph. The EEG data were collected using a subset of the same electrodes attached for the recording of the waking EEG (C3, C4, O1, and O2, referenced to contralateral mastoids, A1/A2). Four additional electrodes (SensorMedics), affixed with adhesive collars immediately prior to each sleep period, were used to collect electrooculographic (EOG) and electromyographic (EMG) data. The time constant for the EEG channels was set at 0.3, and the high filter was set at 35 Hz. For EOG (recorded from the outer canthus of each eye), the time constant was 5.0 and the high filter was set at 10 Hz. For EMG (recorded with submental electrodes), a time constant of 0.003 and a high filter setting of 120 Hz was used. The chart speed was 10 mm per second. The sleep data were hand-scored using guidelines set forth by Rechtschaffen and Kales (1968).

## Procedure

Simulator flight performance

The simulator flight performance evaluations required subjects to perform a variety of precision maneuvers (see table 3). There were actually three parts to each simulator flight, but only the nontactical, upper-airwork maneuvers which subjects were required to fly based upon instrument information only (the windscreen was an opaque gray during this part) will be presented here. The same sequence of maneuvers was used for every subject during each of the simulator flights. These maneuvers were of the type typically flown in a UH-60 aircraft and are fully described in the Aircrew Training Manual (Department of the Army, 1988b). All maneuvers were performed under simulated instument conditions which remained constant during each flight. These conditions included no winds or turbulence and a scene illumination level equivalent to 12:00 o'clock noon. The first group of maneuvers was flown with the automatic flight control system (AFCS) trim engaged (the normal mode when flying the UH-60), and the second group was flown with the AFCS trim turned off (thus, increasing the aviators' workload). There are 15 maneuvers in the upper-airwork profile. These consist of four straight-and-levels (one with AFCS off), two left standard-rate turns (one with AFCS off), three right standard-rate turns (one with AFCS off), two standard-rate climbs (with AFCS on), three standard-rate descents (all with AFCS off), and one left descending turn (with AFCS off). The subject pilot was seated in the right seat of the simulator in each case.

Table 3.

Status of the automatic trim system during each upper-airwork maneuver.

| Maneuver | AFCS On/Off |
|---|---|
| Straight and level number 1 | On |
| Left standard-rate turn number 1 | On |
| Straight and level number 2 | On |
| Climb number 1 | On |
| Right standard-rate turn number 1 | On |
| Straight and level number 3 | On |
| Right standard-rate turn number 2 | On |
| Climb number 2 | On |
| Descent number 1 | Off |
| Left descending turn | Off |
| Descent number 2 | Off |
| Left standard-rate turn number 2 | Off |
| Straight and level number 4 | Off |
| Right standard-rate turn number 3 | Off |
| Descent number 3 | Off |

For each of these maneuvers, the subjects were required to maintain a constant airspeed of 120 knots, but the specific targets for other parameters such as heading, altitude, roll, slip, etc., change depending upon which maneuver is being flown. However, subjects always attempt to maintain appropriate ideal flight parameters during each maneuver. All turns were made at a standard rate of 3 degrees per second, and all climbs and descents were made at a standard rate of 500 feet per minute.

Flight scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated for a variety of measures. These scores, based upon the extent to which subjects deviated from target values, expressed how well subjects maintained headings, altitudes, airspeeds, and other parameters. The scoring bands for each parameter are listed in table 4. Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver.

Table 4.

Scoring bands for flight performance data.

| | Maximum deviations for scores of: | | | | | |
|---|---|---|---|---|---|---|
| Measure (units) | 100.0 | 80.0 | 60.0 | 40.0 | 20.0 | 0 |
| Heading (degrees) | 1.0 | 2.0 | 4.0 | 8.0 | 16.0 > | 16.0 |
| Altitude (feet) | 8.8 | 17.5 | 35.0 | 70.0 | 140.0 > | 140.0 |
| Airspeed (knots) | 1.3 | 2.5 | 5.0 | 10.0 | 20.0 > | 20.0 |
| Slip (ball widths) | 0.0 | 0.1 | 0.2 | 0.4 | 0.8 > | 0.8 |
| Roll (degrees) | 0.8 | 1.5 | 3.0 | 6.0 | 12.0 > | 12.0 |
| Vertical speed (feet/m) | 10.0 | 20.0 | 40.0 | 80.0 | 160.0 > | 160.0 |
| Turn rate (degrees/s) | 0.3 | 0.5 | 1.0 | 2.0 | 4.0 > | 4.0 |

This strategy avoided the necessity of performing analyses on multiple measures from each maneuver which would have been required if root mean square (RMS) errors or some other type of deviation metric had been used. The reason is that, while performance scores (all normalized to a scale from 0-100) can be averaged, there is no straightforward method for making composite deviation scores for airspeed (expressed in knots), heading (expressed in degrees), altitude (expressed in feet), and other parameters because each is evaluated in different units.

The entire profile lasted approximately 55 minutes, and during each profile, performance was measured using the simulator's computerized performance monitoring system. During each simulator flight, a UH-60 pilot was present to instruct the subject and ensure the proper sequencing and timing of all flight maneuvers.

EEG evaluations

Each EEG session began with a check to ensure electrode impedances were 5000 ohms or less. Any impedance problems were corrected before continuing with the test. Subjects then were instructed to sit quietly with eyes open for 2 m followed by 2 m of eyes closed, while data are recorded. The EEGs were visually scanned for three relatively artifact-free 2.5-second epochs on which absolute power values were calculated for each of four bands. The results were averaged together to produce one set of power values for each electrode site under eyes closed and eyes open. The activity bands were defined as follows: delta (1.0-3.5 Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

Desktop flight simulation task

Following the EEG, subjects completed a 20-minute session on the desktop flight simulation task. This task required subjects to "fly" a timed course consisting of 21 "gates" positioned at various altitudes and headings. The first 15 gates were flown under nonturbulent conditions while gates 16-21 were made more difficult by the addition of 20-knot winds emanating from various directions. This task produced a summary score at the conclusion of each "flight" which was calculated automatically from the elapsed time it took to fly the course, the number of gates missed, and the precision with which the subjects flew through each of the gates.

POMS and VAS

The POMS was given after each desktop flight simulation test. Subjects were presented with a series of 65 words which described mood states, and for each "mood state" the subject indicated on a standardized, computerized answer sheet how well it described the way he was presently feeling. This test took approximately 5 minutes to administer and yielded scores on the factors of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The VAS was given after the POMS. Subjects were presented with eight adjective/descriptors and asked to indicate how each represented how they were currently feeling. This test took approximately 2 minutes to administer and yielded scores on the scales described earlier.

MATB

Following the POMS, subjects completed the MATB which was designed to simulate tasks that an aviator would perform during a normal flight. It required subjects to simultaneously monitor and respond to four tasks which were presented on four quadrants of the computer screen. In the upper left quadrant, there is a "lights and dials" monitoring task that required the subject to make keyboard entries in order to extinguish warning lights and maintain specific dial positions. In the lower left quadrant, there is a communications task that required the subject to adjust "radio frequencies" in response to instructions given periodically through the wall-mounted speaker. In the upper right quadrant, there is a tracking box in which a cursor was maintained over a centered target through the use of joystick manipulations. In the bottom right quadrant, there is a "fuel management" task that required subjects to make keyboard entries in order to adjust fuel levels in two main tanks. The MATB yielded a variety of speed and accuracy scores for each task.

Polysomnography

The sleep recordings were made while the aviator was sleeping in a darkened, private bedroom. Each night on which sleep is allowed, EOG and submental electrodes were placed, and the subject was escorted into his bedroom at the proper time. Lights out occurred at 2300, after which the subject was permitted to sleep while electrophysiological data were recorded. There were 3 nights during which polysomnographic data were collected. The first was the baseline night that occurred on Monday (following a Sunday adaptation night). The second was the recovery night on Wednesday, and the third was the recovery night on Friday. Data from each of these nights were recorded on a standard paper trace at 10 mm per second for analysis according to the rules set forth by Rechtschaffen and Kales (1968). The number of minutes from lights out to the appearance of stage 2 sleep, the percentage of time subjects spent in stages 1-4 and Rapid Eye Movement (REM) sleep, the latency to the first REM sleep period, the percentage of movement time, and the percentage of time subjects were awake during the night were calculated.

Testing schedule

The subject reported to the Laboratory on *Sunday* for medical examination, EEG electrode attachment, and an adaptation sleep period. On *Monday,* he completed three simulator training flights each of which was followed by EEG, performance, and mood testing. He then exercised for 1 hour after which he retired for the day (at 2300). Following a 0700 wakeup on *Tuesday,* there were three more test sessions (baseline tests for the simulator flights, EEG, performance, and mood scales), but the aviator was not allowed to go to sleep in the evening. Instead, he was given his first drug/placebo dose at 2300 and a subsequent dose was given at 0300 and at 0700 on Wednesday. On *Wednesday,* test sessions began with a simulator flight 2 hours after each drug/placebo administration (for the first three sessions) and there were two additional non-drug sessions as well for a total of five equally-spaced test periods (at 0100, 0500, 0900, 1300, and 1700). Afterwards, the aviator completed about an hour of physical exercise and then retired for

the day (his sleep was recorded). On *Thursday,* the participant repeated the same schedule which was used on Tuesday--there were three test sessions during the day, and, as was the case on Tuesday night, he was not allowed to go to sleep. Instead he was given the first dose in his second series of drug/placebo doses at 2300. On *Friday,* the subject repeated the Wednesday schedule, beginning with his first simulator flight at 0100, and ending with a recovery sleep period in the evening. On *Saturday*, the aviator was medically evaluated and released (the entire schedule was depicted earlier in table 1).

### Data analysis

All data were analyzed with BMDP4V, repeated measures analysis of variance. Significant interactions were followed by analyses of simple effects and appropriate contrasts. Main effects which occurred in the absence of higher-order interactions were examined using either pairwise contrasts or trend analysis. All results were checked for sphericity violations, and where these were found, Huynh-Feldt adjusted degrees of freedom were utilized.

The analyses of variance (ANOVAs) consisted of at least the two within-subjects factors of **drug** (modafinil, placebo) and **session** (sessions 1-5). The flight performance analyses included an additional factor called **iteration** for maneuvers which were flown multiple times during each flight profile.

Flight performance data consisted of scores which represented the average control accuracy across all of the parameters (i.e., heading, airspeed, altitude, slip, roll, and vertical speed control) important to each individual maneuver. EEG data consisted of absolute power within each of four activity bands. The desktop flight simulator data consisted of one composite score per flight. The MATB results included both speed and accuracy scores from each of the four tasks. The POMS data consisted of scores from each of six test scales, and the VAS data consisted of scores from eight questions. Polysomnographic results included various measures of sleep quality such as the percentage of time spent in each sleep stage, total sleep time, and sleep latency from each night during which sleep was permitted.

## Results

### Flight performance data

The flight performance scores from three baseline flights (at 0900, 1300, and 1700) and five deprivation flights (0100, 0500, 0900, 1300, and 1700) under the influence of placebo versus modafinil were analyzed with a 3-way ANOVA for drug, session, and (in most cases, iteration). The iteration factor was added to include each instance of maneuvers that were conducted more than once during the flight profile. This was the case with every maneuver with the exception of the left descending turn.

Straight and levels (SLs)

Analysis of the composite scores based on how well subjects controlled heading, altitude, airspeed, and roll during the four iterations of straight-and-level flight (the last of which was flown without the benefit of the AFCS trim system) revealed a drug-by-session interaction and a iteration main effect. The interaction ($F(7,35)=3.24$, $p=.0093$) was found (by analysis of simple effects) to be due to the fact that there were no differences across the flights under modafinil, while there were noticeable decrements in sleep-deprived performance under placebo ($F(7,35)=4.48$, $p=.0012$). Examined in another way, the modafinil and placebo conditions did not differ at any of the three baseline sessions (predrug) or the first two deprivation sessions (at 0100 and 0500), but performance under placebo suffered significantly relative to performance under modafinil at 0900 ($F(1,5)=8.51$, $p=.0331$).

There were no drug-related effects in the later flights (at 1300 and 1700). This interaction is depicted in figure 1.The iteration main effect ($F(3,15)=15.59$, $p=.0001$) occurred because performance on SL1 was substantially better than performance on the remaining SLs, and performance on SL4 was poorer than performance on the other SLs ($p<.05$). The means for the four SLs were 87.4, 82.7, 83.6, and 77.8, respectively.

Climbs

Analysis of the composite scores based on heading, airspeed, slip, roll, and vertical speed control during both iterations of this maneuver (one was a 500-foot climb and the other was a 1000-foot climb) indicated there were no drug-related effects. However, there was a difference between the two iterations of the climb ($F(1,5)=8.78$, $p=.0314$) which was due to the fact that performance on the first climb (the shorter of the two) was better than performance on the second climb. The means were 69.5 and 68.1, respectively.

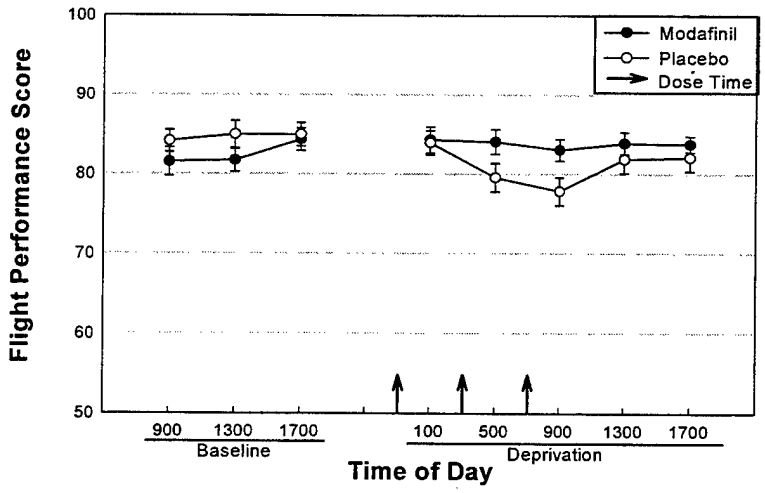


Figure 1. The effects of modafinil versus placebo on flight scores during the straight-and-level maneuver.

Descents

Analysis of the composite of heading, airspeed, slip, roll, and vertical speed scores from the three descents (two were 500-foot descents and one was a 1000-foot descent, all flown without the aid of the AFCS trim system) revealed drug-by-session interaction ($F(7,35)=4.13$, $p=.0021$) and an iteration main effect ($F(2,10)=4.91$, $p=.0327$). Simple effects indicated there were small differences across the flights under the modafinil condition ($F(7,35)=2.24$, $p=.0542$) and larger differences under the placebo condition ($F(6.36,31.81)=4.06$, $p=.0034$). Furthermore, there was an unexplained baseline effect (placebo better than modafinil, $p<.05$) at the 1300 baseline session which was followed by a statistically significant reversal (poorer performance under placebo than modafinil) at the 1300 flight on the sleep-deprivation day ($p<.05$). There were no other drug-related session effects (see figure 2).

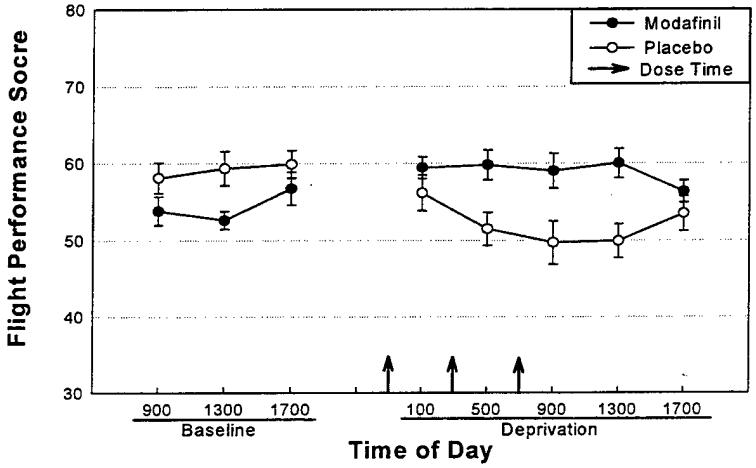


Figure 2. The effects of drug condition on flight performance during the descents.

Although it appeared there were differences at 0500 and 0900, these were not significant (the p levels were .08 and .23, respectively). The iteration main effect was because performance on the second descent was significantly better than the third descent ($p<.05$) and tended to be better than the first descent ($p=.06$). The means were 54.2, 58.3, and 55.5, respectively.

Left standard-rate turns (LSRTs)

Analysis of the composite scores based upon how well subjects maintained turn rate, airspeed, slip, roll, and vertical speed during the two LSRTs (one was a 360-degree turn with the AFCS trim system on and the other was a 180-degree turn with the trim system off) showed several effects. There was a drug-by-session interaction ($F(7,35)=2.23$, $p=.0548$). Analysis of simple effects indicated this was due to the absence of drug-related differences on the baseline day or at 0100 in the deprivation period, but significant performance reductions under placebo versus modafinil at the 0500, 0900, and 1700 flights on the sleep-deprivation day (see figure 3, left panel). A drug-by-iteration interaction ($F(1,5)=8.35$, $p=.0342$) was because of drug-related

differences during the second LSRT (flown with the AFCS off), but not the first. As can be seen in figure 3 (right panel), there was little difference between the two drug conditions until the second left turn.

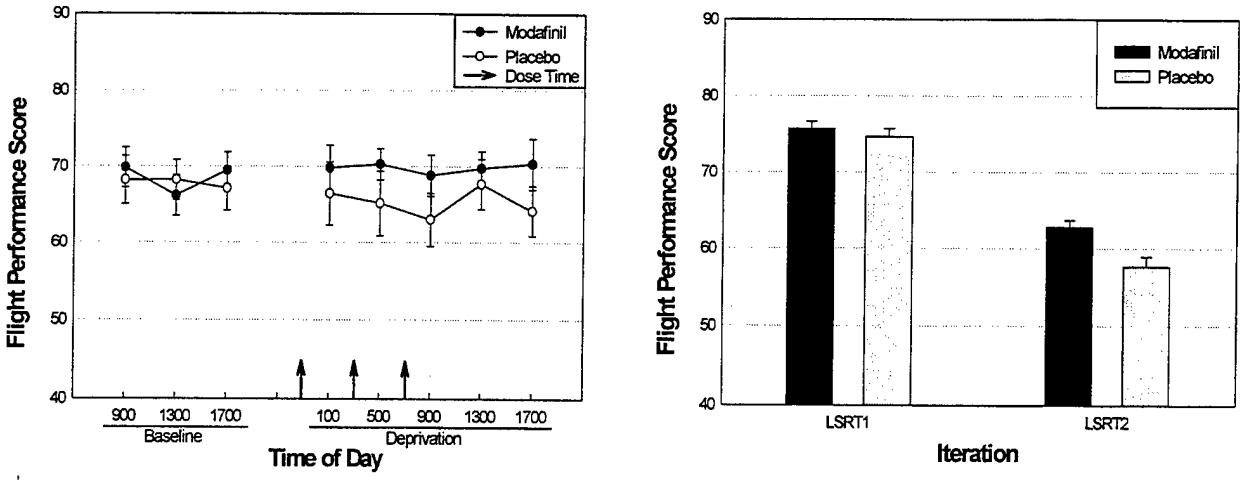


Figure 3. The effects of modafinil versus placebo on flight scores during the left standard-rate turns.

In addition to these interactions, there were main effects on the drug factor ($F(1,5)=8.65$, $p=.0322$) and the iteration factor ($F(1,5)=37.98$, $p=.0016$). Performance under modafinil was better overall than performance under placebo (the means were 69.3 versus 66.2, respectively). The iteration effect was due to overall superior performance on the first versus the second LSRT (the means were 75.2 versus 60.3, respectively). This is not surprising given that the first LSRT was flown with the aid of the AFCS trim system, whereas the second LSRT was not.

Right standard-rate turns (RSRTs)

The composite scores for the RSRTs (two were 180-degree turns flown with the AFCS trim system off and one was a 360-degree turn flown with the trim system engaged) were based on the average of turn rate, altitude, airspeed, slip, and roll scores. The ANOVA on these data indicated there were no drug-related or time-related effects; however, there was a tendency toward a drug main effect in which modafinil appeared to be slightly better than placebo ($p=.0658$), but this was not significant (see figure 4). There was a difference in performance across the three iterations of the RSRT ($F(2,10)=5.49$, $p=.0246$). Contrasts revealed this was due to higher flight scores in the second RSRT than in the third, probably a result of the fact that the third iteration was flown without the benefit of the AFCS trim system. The means for the three RSRTS were 70.9, 72.9, and 67.1, respectively.

Left descending turn (LDT)

The composite score on the LDT was an average of scores for turn rate, airspeed, slip, roll, and vertical speed. ANOVA indicated there was a drug main effect ($F(1,5)=6.47$, $p=.0516$) on

these data which was due to poorer performance under placebo than under modafinil. The means for the two conditions were 48.2 and 51.7, respectively.

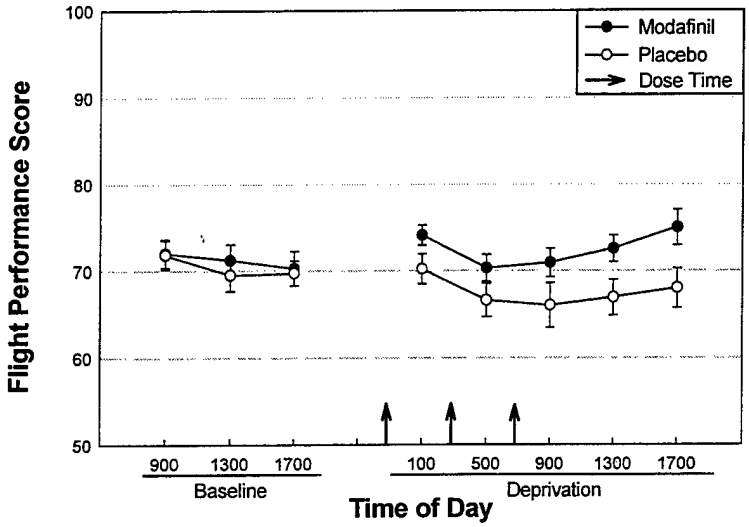


Figure 4. The tendency toward better performance under modafinil than placebo in the right standard-rate turns.

## EEG

The absolute power data from the resting eyes open/eyes closed EEG were analyzed in four parts using a series of three-way ANOVAs (one each for delta, theta, alpha, and beta activity). A subset of the initial twenty-one electrode sites were analyzed because of the presence of recording artifacts, usually from muscle activity. Visual inspection of data from all sites indicated that EEG activity from Fz, Cz, and Pz was of sufficient quality to warrant further analysis. The ANOVAs consisted of three factors: condition (modafinil versus placebo), session (1015, 1415, and 1815 on the baseline day, and 0215, 0615, 1015, 1415, and 1815 on the deprivation day), and eyes (eyes open/eyes closed).

### Delta activity

Analysis of delta activity (1.5-3.0 Hz), the slowest-wave EEG indicative of fatigue or sedation in awake subjects, revealed several effects. A drug-by-eyes interaction at Fz ($F(1,5)=8.53$, $p=.0330$) was due to the presence of much less delta under modafinil versus placebo at eyes closed but no difference at eyes open. At Cz, a similar effect ($F(1,5)=10.30$, $p=.0237$) was due to the fact that, while there were drug-related differences both at eyes open and eyes closed, the difference was substantially larger when subjects closed their eyes (i.e., the amount of delta was much lower under modafinil versus placebo). A similar trend occurred for the electrode site Pz, although it did not reach statistical significance ($p=.0683$). These are depicted in figure 5. No other interactions occurred.

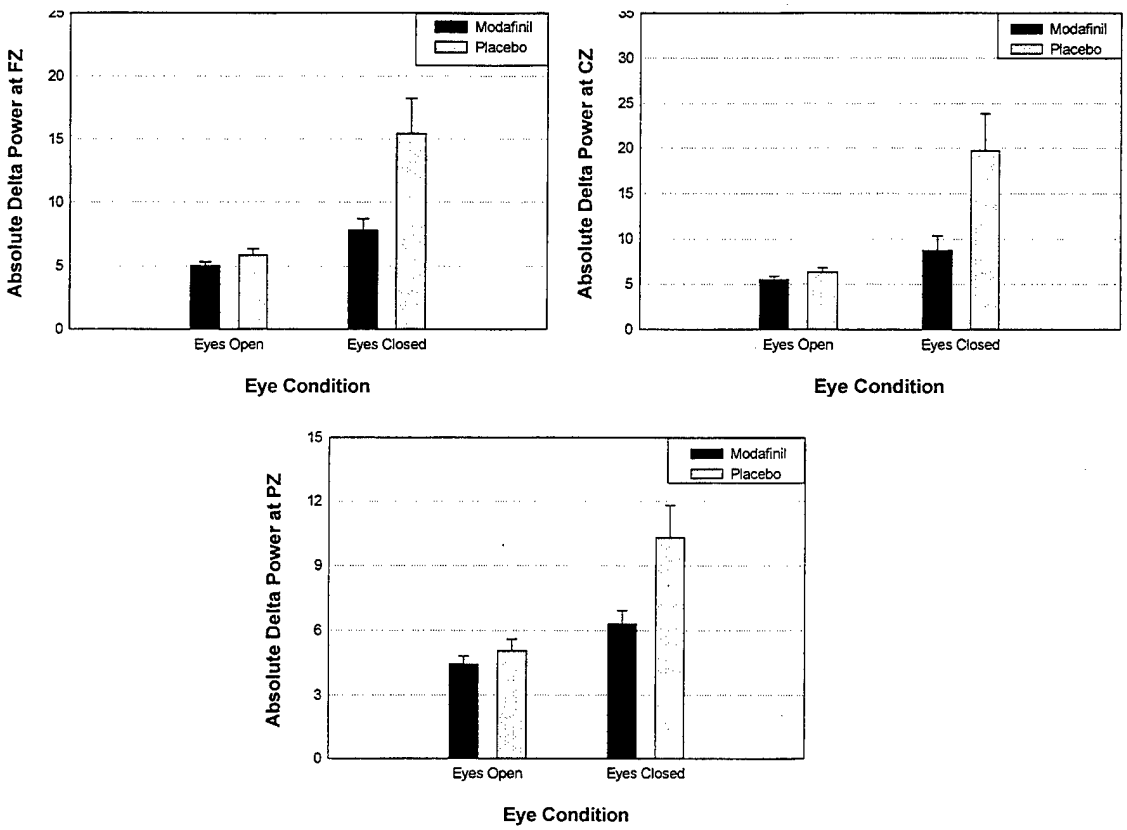


Figure 5. The interaction between eye closure and drug condition showing the differences between modafinil and placebo are greatest with eyes closed.

There was a main effect for drug at sites Fz ($F(1,5)=21.90$, $p=.0054$), Cz ($F(1,5)=12.15$, $p=.0175$), and Pz ($F(1,5)=10.45$, $p=.0231$), all of which were due to higher delta power during the placebo condition than during the modafinil condition. A main effect for eyes occurred at sites Fz ($F(1,5)=11.60$, $p=.0191$), Cz ($F(1,5)=10.54$, $p=.0228$), and Pz ($F(1,5)=14.13$, $p=.0132$) due to higher delta power during eyes closed than during eyes open.

Theta activity

Analysis of theta activity (3.0-8.0 Hz), which is faster than delta but still considered to be slow-wave EEG known to increase with sleep deprivation, showed several effects. A drug-by-session interaction occurred at Fz ($F(7,35)=2.56$, $p=.0305$), Cz ($F(7,35)=3.00$, $p=.0141$), and Pz ($F(7,35)=2.41$, $p=.0402$). No differences between the sessions were observed during baseline, but during the deprivation period, there was less theta at Fz during the modafinil versus the placebo condition at 0615 and 1415 (see figure 6) .During deprivation at Cz, there was less theta during the modafinil than the placebo condition at 0215 and 1415, with a similar tendency at 1015 ($p=.06$). At Pz, there was a difference at 1015 and a tendency at 1415 ($p=.06$). A condition-by-eyes interaction occurred at Fz ($F(1,5)=36.20$,$p=.0018$), Cz ($F(1,5)=13.54$, $p=.0143$), and Pz ($F(1,5)=6.94$, $p=.0463$). For all electrode sites, there was much less theta

under modafinil than placebo at eyes closed versus eyes open. At Cz there was a statistically significant condition effect at eyes open as well, but the magnitude of the difference between

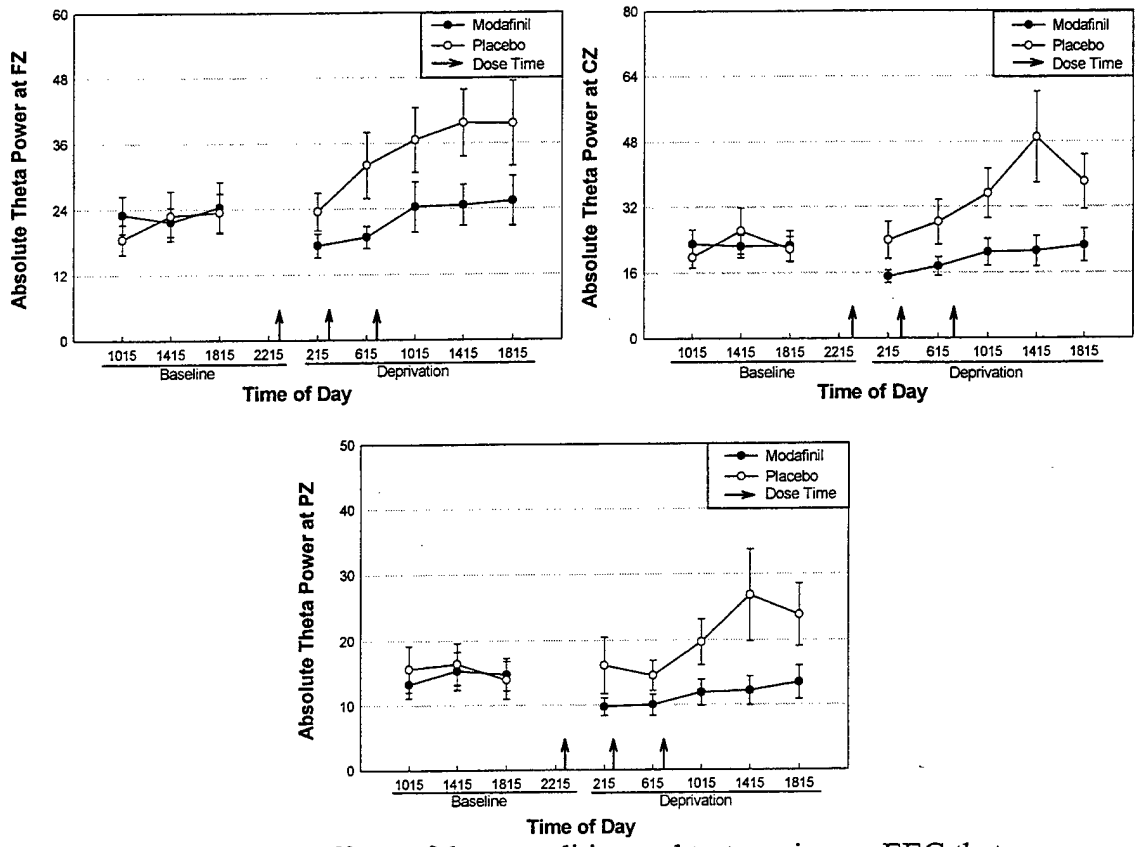


Figure 6. The combined effects of drug condition and test session on EEG theta activity.

modafinil and placebo was smaller than it was with eyes closed . Effects for each electrode site are shown in figure 7. A session-by-eyes interaction occurred at electrode site Cz ($F(7,35)=2.61$, $p=.0281$) due to more theta activity at eyes closed than eyes open at each session except the 1015 session on the baseline day

A drug main effect occurred at Fz ($F(1,5)=16.26$, $p=.0100$), Cz ($F(1,5)=18.06$, $p=.0081$), and Pz ($F(1,5)=6.76$, $p=.0482$) due to less theta activity during the modafinil condition than during the placebo condition. A main effect also occurred for session at sites Fz ($7,35)=8.97$, $p<.0001$), Cz ($F(7,35)=6.97$, $p<.0001$), and Pz ($F(7,35)=3.60$, $p=.0051$).

There was a significant linear trend at each site showing a general increase in theta activity as the day progressed, as well as a significant quadratic trend at Cz and Pz due to increased theta at 1415 on baseline, a decrease at 1815, and then a steady increase in activity from 0215 until 1415 on the deprivation day (see table 5). Significant main effects for eyes occurred at Fz ($F(1,5)=63.32$, $p=.0005$), Cz ($F(1,5)=69.81$, $p=.0004$), and Pz ($F(1,5)=44.92$, $p=.0011$), all of which were due to higher theta activity during eyes closed than during eyes open.

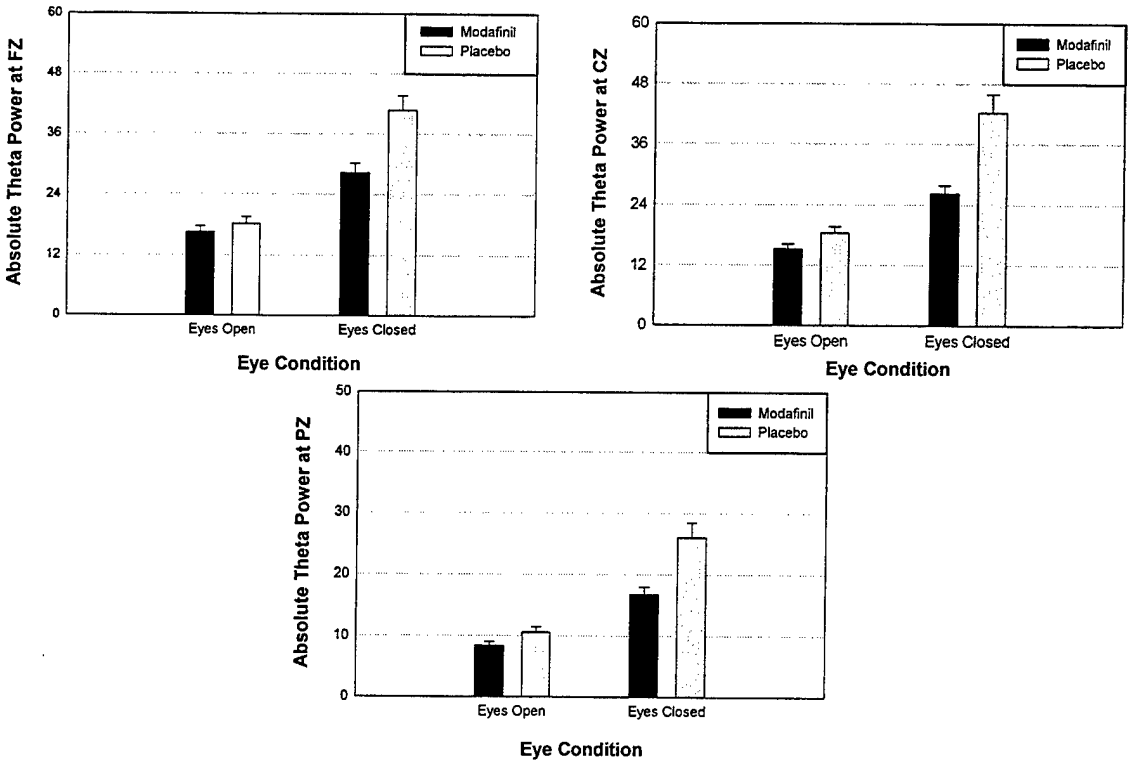


Figure 7. The effect of eye closure on EEG theta activity as a function of drug, showing that the difference between modafinil and placebo is larger with eyes closed.

Table 5.
Means for the session main effects for theta activity.

| Time | Fz | Cz | Pz |
|---|---|---|---|
| BL-1015 | 20.751 | 21.440 | 14.425 |
| BL-1415 | 22.250 | 24.347 | 15.869 |
| BL-1815 | 23.845 | 22.193 | 14.365 |
| SD-0215 | 20.412 | 19.485 | 12.928 |
| SD-0615 | 25.362 | 22.931 | 12.299 |
| SD-1015 | 30.456 | 28.089 | 15.764 |
| SD-1415 | 32.195 | 35.154 | 19.489 |
| SD-1815 | 32.531 | 30.327 | 18.643 |

Alpha activity

Analysis of alpha activity (8.0-13.0 Hz), which is predominant during relaxed wakefulness under eyes closed, but is suppressed during sleep, showed several effects, none of which were

related to modafinil or placebo. Session-by-eyes interaction occurred at Fz ($F(7,35)=4.14$, $p=.0021$) and Cz ($F(7,35)=2.54$, $p=.0320$). The effect at Fz was due to more alpha under eyes closed than eyes open at baseline times 1015 and 1815, and again at deprivation times 0215 and 0615. At Cz, there was more alpha activity under eyes closed than eyes open at every session, but the magnitude decreased as the amount of sleep deprivation increased (see figure 8).

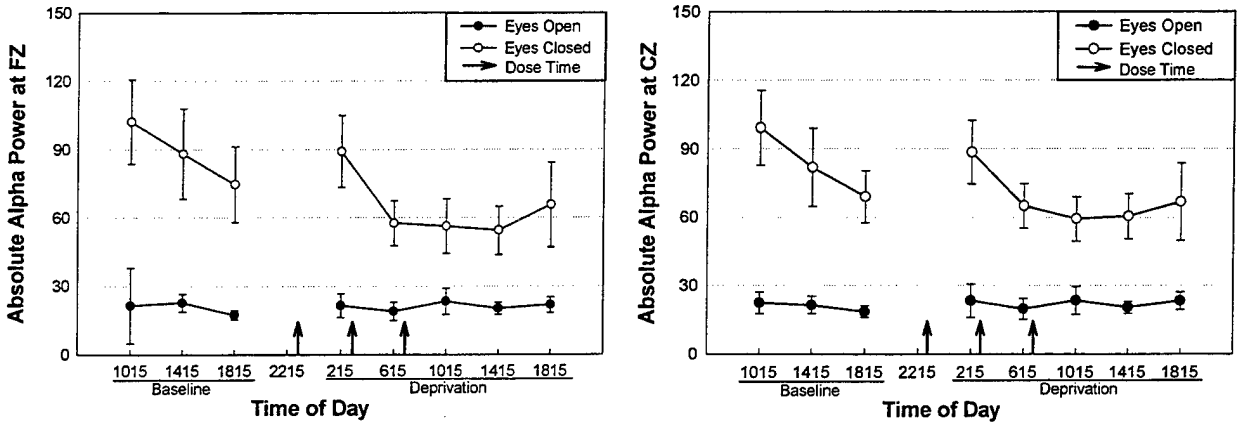


Figure 8: The combined effects of eye closure and test session on EEG alpha activity.

A main effect for session occurred at Fz ($F(7,35)=5.68$, $p=.0002$) and Cz ($F(7,35)=3.85$, $p=.0033$). Both were due to significant linear decreases in alpha power as testing progressed ($p<.05$). A significant quadratic trend occurred at Fz because of a decrease in alpha activity throughout all testing with the exception of the last session of the deprivation day, in which there was an increase (see table 6). Eyes main effects occurred at Fz ($F(1,5)=7.56$, $p=.0403$), Cz ($F(1,5)=10.96$, $p=.0212$), and Pz ($F(1,5)=13.81$, $p=.0138$) due to increased alpha activity during eyes closed compared to eyes open.

Table 6.
Means for the session main effects for alpha activity.

| Time | Fz | Cz | Pz |
|---|---|---|---|
| BL-1015 | 61.794 | 60.774 | 60.814 |
| BL-1415 | 55.287 | 51.598 | 55.381 |
| BL-1815 | 45.972 | 43.658 | 51.972 |
| SD-0215 | 55.245 | 55.883 | 57.933 |
| SD-0615 | 38.147 | 42.325 | 45.814 |
| SD-1015 | 39.695 | 41.243 | 45.566 |
| SD-1415 | 37.202 | 40.279 | 48.345 |
| SD-1815 | 43.616 | 44.916 | 46.211 |

Beta activity

Analysis of beta activity (13.0-20.0 Hz), which is the fastest type of EEG activity typically analyzed (it occurs during increased mental concentration and sometimes appears to be

increased when contaminated by muscle tension), revealed a significant session-by-eyes interaction at Pz ($F(7,35)=2.50$, $p=.0342$. This was due to less beta activity during eyes closed than eyes open at all the baseline sessions and two of the deprivation sessions (0215 and 0615), whereas there were no effects elsewhere. Main effects on the eyes factor occurred at Fz ($F(1,5)=13.86$, $p=.0137$), Cz ($F(1,5)=19.13$, $p=.0072$), and Pz ($F(1,5)=12.97$, $p=.0155$) due to less beta activity during eyes open than during eyes closed.

## Desktop flight simulator

There was a "flight" portion of this task that yielded a score based on the accuracy and speed with which subjects flew the course, and there was a reaction-time portion that yielded the percentage of target tones to which the subject failed to respond (percent misses) and the reaction time (RT) to the target tones hit. Both components were analyzed using 2-way ANOVA for drug (placebo versus modafinil) and session (1101, 1501, and 1901 on the baseline day, and 0301, 0701, 1101, 1501, and 1901 on the deprivation day).

The ANOVA on the "flight" scores indicated there were no significant interactions or main effects. An examination of the means showed there was little difference between performance under modafinil versus placebo. There was one drug-related main effect on the secondary task for the percentage of missed tones ($F(1,5)= 7.81$, $p=.0383$). Additionally, there were session effects on both the percent missed ($F(7,35)=6.01$, $p=.0001$) and RTs ($F(7,35)=5.92$, $p=.0001$). Trend analysis indicated there were both linear and quadratic trends in the percentage of target tones missed ($p<.05$). This was due to a generalized increase in misses from baseline throughout deprivation with especially poor performance at 0701 and 1101 on the deprivation day. For the mean RT data, a significant linear trend ($p<.05$) was attributable to an overall increase in RTs throughout the testing sessions (see table 7).

Table 7.
Means for the session main effects for minisim secondary task.

| Times | Percentage of missed tones | RT to target tones (msec.) |
|---|---|---|
| BL-1101 | 7.4 | 816.8 |
| BL-1501 | 10.1 | 888.0 |
| BL-1901 | 7.7 | 839.1 |
| SD-0301 | 9.3 | 866.5 |
| SD-0701 | 15.5 | 932.0 |
| SD-1101 | 15.4 | 929.7 |
| SD-1501 | 14.3 | 927.8 |
| SD-1901 | 12.9 | 919.1 |

## POMS

The factor scores collected during four baseline sessions (1125, 1525, 1925, and 2335) and six deprivation sessions (0325, 0725, 1125, 1525, 1925, and 2335) under the influence of placebo versus modafinil were analyzed in a series of 2-way ANOVAs for drug and session. Each of the

factors (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) was analyzed separately.

Tension-anxiety scale

The 2-way ANOVA on the tension-anxiety scale, which reflects heightened musculoskeletal tension, indicated no drug-related effects. However, there was a session main effect ($F(9,45)=8.83$, $p<.0001$) which was to a linear increase in tension levels from baseline in to the deprivation period ($p<.05$). The means for this effect in the baseline (BL) and sleep-deprivation (SD) sessions are presented in table 8.

Depression-dejection scale

The scores on the depression-dejection scale, which measures despondence and sadness, also indicated only a session main effect ($F(9,45)=2.11$, $p=.0487$). None of the subsequent trend analyses were significant; however, an examination of the means suggest that depression ratings tended to increase slightly throughout the deprivation period (see table 8).

Table 8.
Means for the session main effects from the POMS.

| Time | Tension | Depression | Vigor | Fatigue | Confusion |
|---|---|---|---|---|---|
| BL-1135 | 2.1 | 0.6 | 19.5 | 1.1 | 1.8 |
| BL-1535 | 2.4 | 0.7 | 14.8 | 2.8 | 2.2 |
| BL-1935 | 2.3 | 0.7 | 13.9 | 3.2 | 2.7 |
| BL-2335 | 2.2 | 0.6 | 12.3 | 4.5 | 3.3 |
| SD-0335 | 3.0 | 0.8 | 12.3 | 6.3 | 3.1 |
| SD-0735 | 6.4 | 1.6 | 9.5 | 10.7 | 4.7 |
| SD-1135 | 5.9 | 1.2 | 9.1 | 9.6 | 5.0 |
| SD-1535 | 4.8 | 1.1 | 8.2 | 11.0 | 4.4 |
| SD-1935 | 4.0 | 0.8 | 9.0 | 10.9 | 3.7 |
| SD-2225 | 2.8 | 0.4 | 8.9 | 10.8 | 3.4 |

Anger-hostility scale

The 2-way analysis of variance on anger-hostility scores, which reflect anger and antipathy towards others, indicated that there were no drug or session effects on this scale.

Vigor-activity scale

The ANOVA on vigor-activity scores, which reflect energy levels, revealed a drug-by-session interaction ($F(9,45)=3.19$, $p=.0046$) and a session main effect ($F(9,45)=10.08$, $p<.0001$). The interaction was due to significantly lower vigor ratings under placebo than modafinil at both the 0735 and the 1135 testing times while no differences existed at baseline or elsewhere during sleep deprivation (see figure 9).

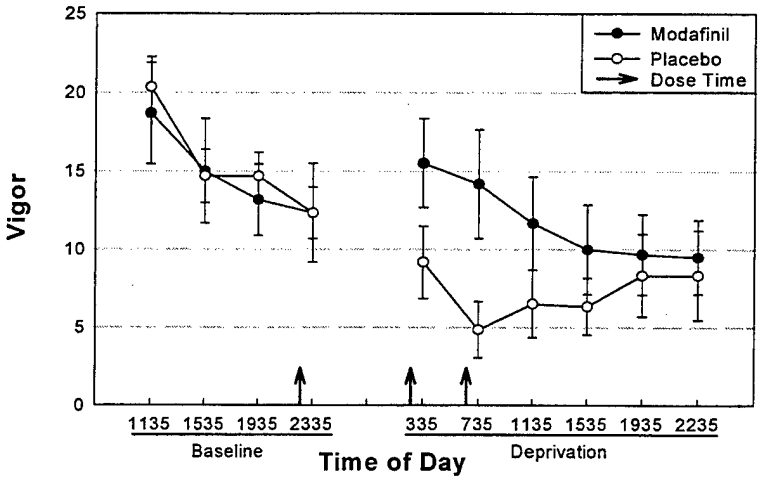


Figure 9. The combined effects of drug condition and session on POMS vigor ratings.

The session main effect resulted from the presence of linear, quadratic, and cubic trends in the data ($p<.05$). As can be seen in table 8, vigor ratings declined sharply from the first to the second baseline session, then leveled off somewhat before declining once again as a result of sleep deprivation between 0335 and 0735. The ratings fell to the lowest point at 1535 before recovering slightly during the last two sessions of the day.

Fatigue-inertia scale

The 2-way ANOVA on fatigue-inertia scores, which signify weariness and tiredness, revealed a drug-by-session interaction ($F(9,45)=5.04$, $p=.0001$), a session main effect ($F(9,45)=11.57$, $p<.0001$), and a drug main effect ($F(1,5)=12.84$, $p=.0158$). Analysis of simple effects indicated that the interaction was due to the fact that fatigue ratings substantially greater under the placebo relative to the modafinil condition at 0335, 0735, 1135, and 1535 ($p<.05$) while there were no differences at the final two testing times of the day. There also were some unexplained baseline differences at 1935 and 2235, but the magnitude of these was about half of the effect size observed during the sleep-deprivation period (see figure 10).

The session main effect was due to significant linear and quadratic trends ($p<.05$). Fatigue ratings increased as a function of continuous wakefulness throughout the test. However, as can be seen in table 8, fatigue levels peaked at 0735, recovered slightly 4 hours later, and then increased again for the remainder of the day.The drug main effect was due to an overall increase in fatigue levels under placebo that was attenuated by modafinil. The means were 9.4 and 4.8, respectively.

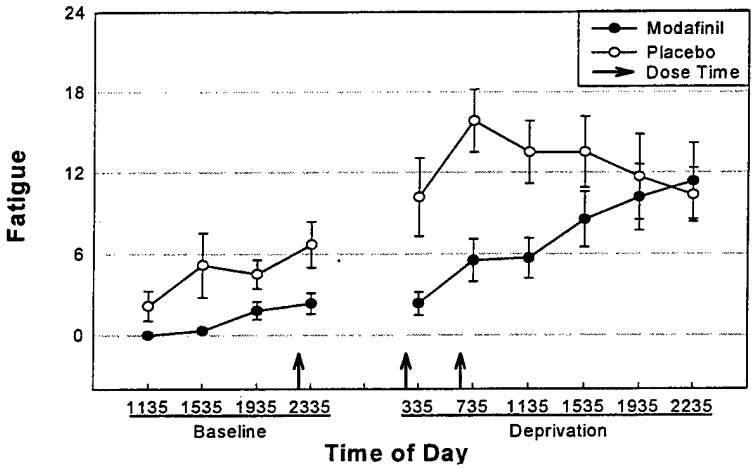


Figure 10. The combined effects of drug condition and session on POMS fatigue ratings.

Confusion-bewilderment scale

Analysis of the confusion-bewilderment scores, which reflect difficulties in mental abilities, showed session ($F(9,45)=7.42$, $p<.0001$) and drug ($F(1,5)=7.67$, $p=.0394$) main effects. The session effect was due to linear and quadratic trends in the data ($p<.05$) which resulted from a gradual deprivation-related increase in confusion ratings that was punctuated by a peak in confusion scores at 0735 and 1135. This tended to subside by the end of the day (see table 8). The drug effect was due to an elevation in confusion scores under placebo versus modafinil (the means were 4.1 and 2.8, respectively). As shown in figure 11, confusion increased under the placebo versus the modafinil condition during the deprivation period (especially at 0735 and 1135 in the morning) while there were no effects during baseline. Although the drug-by-session effect did not attain statistical significance ($p=.0875$), a tendency was present in the data.

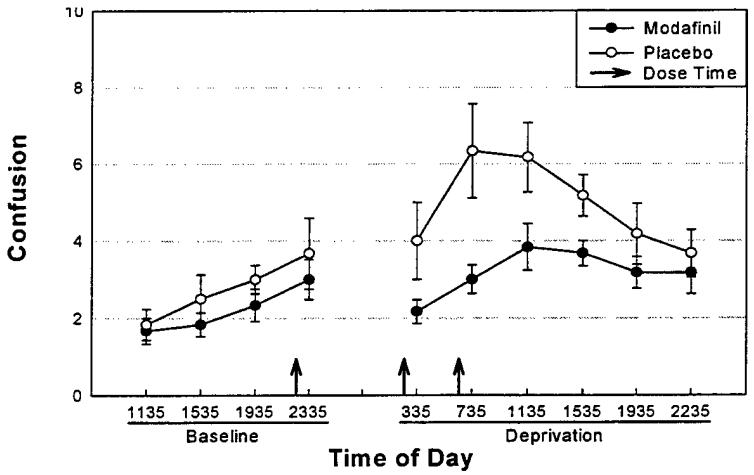


Figure 11. Drug main effect on POMS confusion ratings, largely due to differences under deprivation.

## VAS

VAS ratings collected during four baseline sessions (1125, 1525, 1925, and 2335) and six deprivation sessions (0325, 0725, 1125, 1525, 1925, and 2335 on the deprivation day) under the influence of placebo versus modafinil were analyzed in a series of 2-way ANOVAs for drug and session. Each of the ratings (alertness, anxiety, energy, confidence, irritability, nervousness, sleepiness, and talkativeness) was analyzed separately.

There were drug-by-session interactions on four of the five scales associated with general arousal. Specifically, effects were found on energy ($F(9,45)=4.73$, $p=.0002$), confidence ($F(9,45)=3.06$, $p=.0061$), sleepiness ($F(9,45)=5.77$, $p<.0001$), and talkativeness ($F(9,45)=4.64$, $p=.0002$). Analysis of simple effects indicated there was no baseline difference on any of the scales with the exception of talkativeness at the 1535 testing time. However, there were predictable effects across all four scales at 0335 and 0735 (there was marginal significance on confidence at 0350, and the others were variably affected from 1135 to 1935 (see table 9). As can be seen in figure 12, modafinil attenuated the sleep deprivation effects most noticeably in the period from 0335 to 1135.

Table 9.
Statistically-significant drug effects on the VAS at each testing time.

| Time | Energy | Confidence | Sleepiness | Talkativeness |
|---|---|---|---|---|
| BL-1135 | -- | -- | -- | -- |
| BL-1535 | -- | -- | -- | *p=.04* |
| BL-1935 | -- | -- | -- | -- |
| BL-2335 | -- | -- | -- | -- |
| SD-0335 | *p=.01* | *p=.06* | *p=.01* | *p=.02* |
| SD-0735 | *p=.01* | *p=.01* | *p=.01* | *p=.01* |
| SD-1135 | *p=.03* | -- | *p=.01* | -- |
| SD-1535 | -- | *p=.01* | *p=.03* | -- |
| SD-1935 | -- | *p=.02* | -- | -- |
| SD-2225 | *p=.05* | -- | -- | -- |

There were session main effects (figure 13) on alertness ($F(9,45)=11.94$, $p<.0001$), energy ($F(9,45)=9.32$, $p<.0001$), confidence ($F(9,45)=9.03$, $p<.0001$), nervousness ($F(9,45)=2.99$, $p=.0070$), sleepiness ($F(9,45)=8.93$, $p<.0001$), and talkativeness ($F(9,45)=2.85$, $p=.0096$). Trend analysis indicated there were linear, quadratic, and cubic trends for alertness, energy, and confidence ($p<.05$) basically because of a general deprivation-related decline in all of these scales which was punctuated by sharp drops between 0335 and 0735. Also, there was a slight recovery toward the end of the day. There were both linear and quadratic trends on the sleepiness scale ($p<.05$), and quadratic and cubic trends on the talkativeness scale. Sleepiness ratings rose steadily throughout the study, but ratings increased particularly between

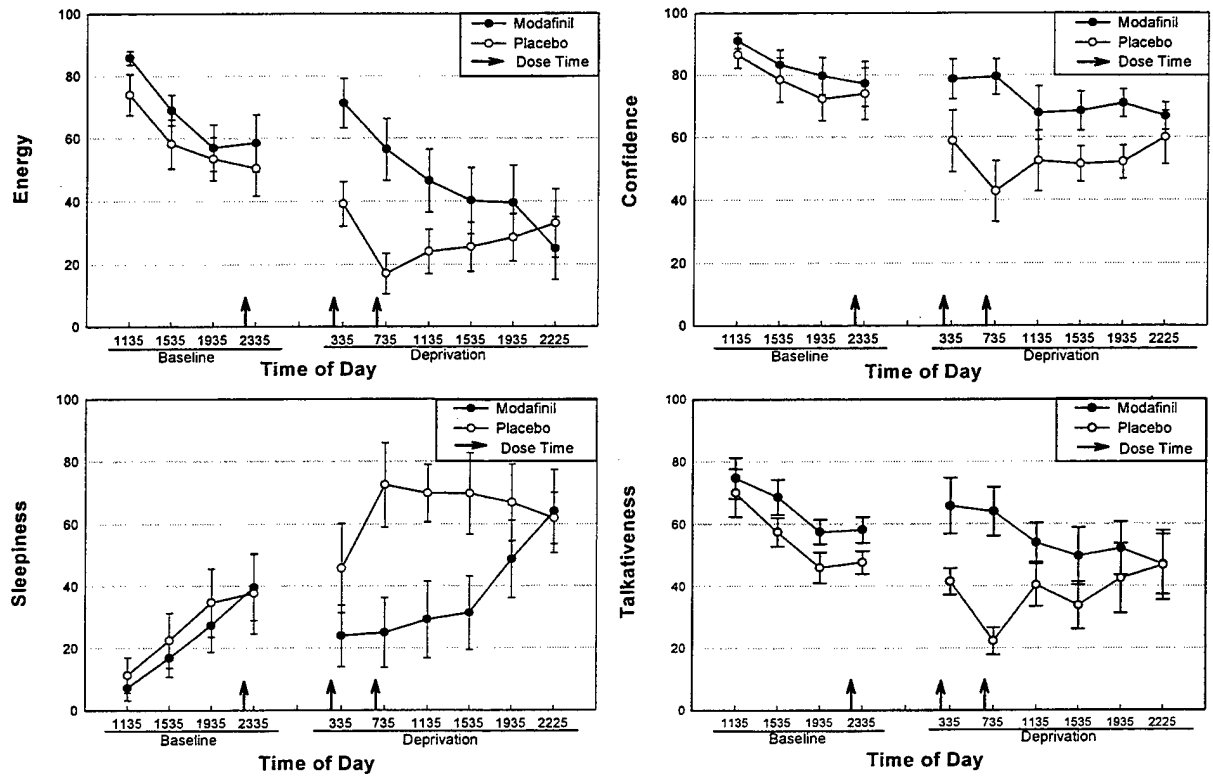


Figure 12. Effects of drug condition and time of day on VAS energy, confidence, sleepiness, and talkativeness.

the 1535 and 2335 sessions on the baseline day after which sleepiness seemed to recede somewhat before increasing further. Talkativeness ratings dropped substantially from the first to the last session on the baseline day, and after a brief plateau, cycled between lower and higher ratings from 0735 until the end of the day. Caution is advised when attempting to interpret main effects which occur in the presence of higher-order interactions; the ratings are often being influenced by the drug as well as the session factor (at least in the case of four of these scales).

There were drug main effects on alertness ($F(1,5)=19.31$, $p=.0071$), confidence ($F(1,5)=8.15$, $p=.0356$), sleepiness ($F(1,5)=13.13$, $p=.0152$), and talkativeness ($F(1,5)=9.25$, $p=.0287$). Subjects were more alert (66 versus 50), more confident (76 versus 63), less sleepy (31 versus 49), and more talkative (59 versus 45) under modafinil than placebo.

## MATB

The speed and accuracy with which subjects completed the MATB at 3 baseline (0330, 0730, and 1130) and 10 deprivation times (0330, 0730, 1130, 1530, and 1930) under the influence of placebo versus modafinil were analyzed with 2-way ANOVAs. Each task (communications, resources management, systems monitoring, and tracking) was analyzed separately.

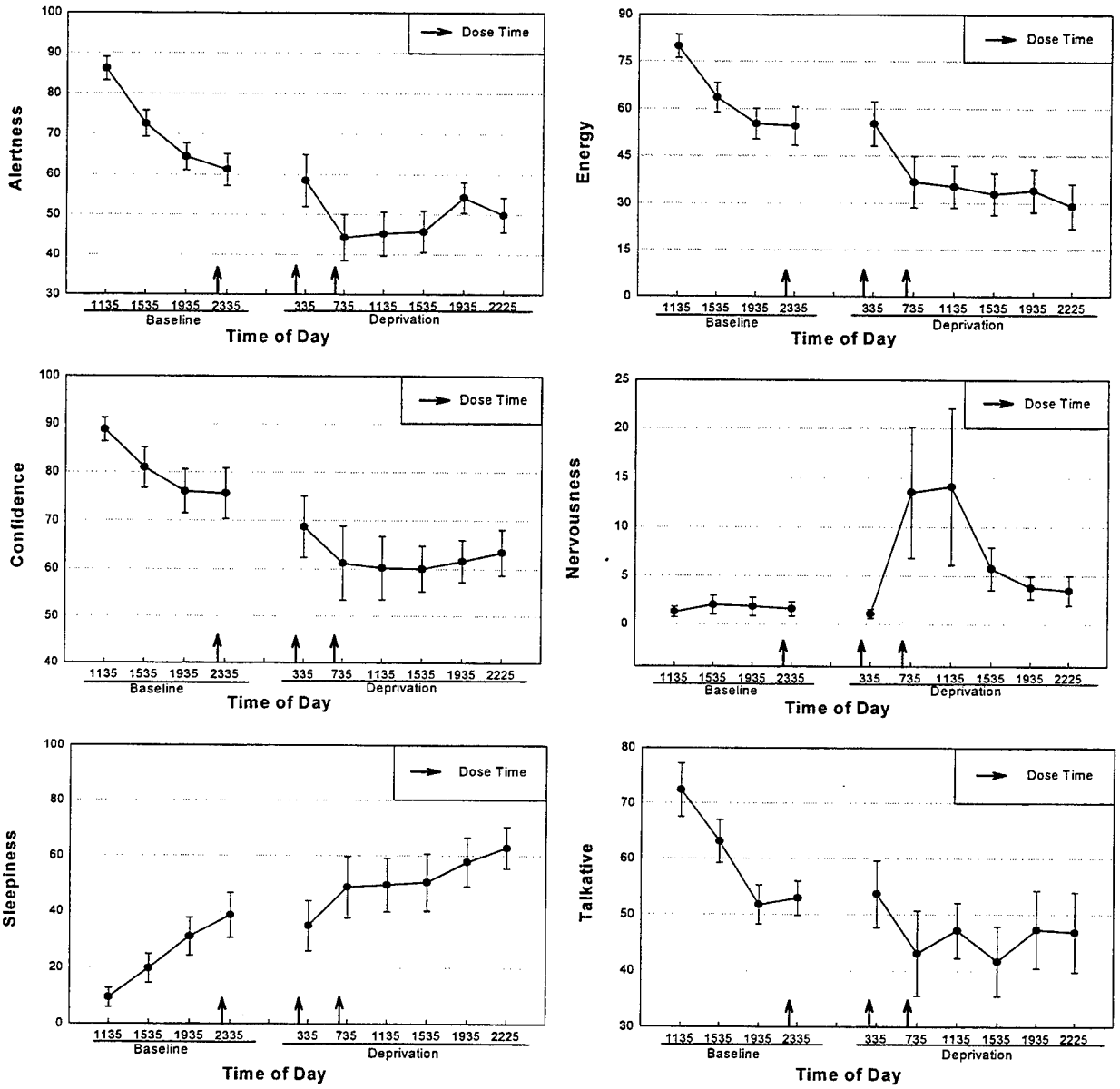


Figure 13. Effects of time of day on VAS alertness, energy, confidence, nervousness, sleepiness, and talkativeness.

Communications

Three variables from this subtask were analyzed. The first was the RT from when subjects were given an instruction to "change a communications radio frequency" until they actually changed the frequency. The second was the standard deviation of these reaction times (SDRT). The third was time out (TO) errors, or the number of times subjects failed to respond to an instruction to change a radio frequency. There were no drug-related effects on any of these variables; however, a single session effect occurred on TO errors ($F(7,35)=2.90$, $p=.0169$). Trend analysis indicated this was due to a linear increase in time outs ($p<.05$) throughout the

study (the lowest number was 0.1 at the 1140 baseline session, and the highest was 1.9 at the 1540 deprivation session). The means are presented in table 10.

Table 10.
Means for the session main effects from the MATB.

| Testing Times | Communications TO errors | Systems monitoring RT to lights | Systems monitoring TO errors for dials | Tracking errors |
|---|---|---|---|---|
| BL-1140 | 0.1 | 1.7 | 5.1 | 29.5 |
| BL-1540 | 0.2 | 1.7 | 3.5 | 31.3 |
| BL-1940 | 0.3 | 1.6 | 3.6 | 30.1 |
| SD-0340 | 0.3 | 1.7 | 2.1 | 35.2 |
| SD-0740 | 2.7 | 2.2 | 7.3 | 52.2 |
| SD-1140 | 1.2 | 2.0 | 5.2 | 46.8 |
| SD-1540 | 1.9 | 2.2 | 6.8 | 51.4 |
| SD-1940 | 0.8 | 2.0 | 4.3 | 42.2 |

Resource management

One variable from this task was analyzed. This was a measure of the accuracy with which subjects were able to maintain "fuel levels in their fuel tanks" at the ideal value of 2500 units (mean deviation of tanks A and B from 2500). The ANOVA on these data revealed no significant interactions or main effects.

Systems monitoring

There were six variables analyzed from this subtask. The first was RT to lights which indicated how long it took subjects to press one key in response to the onset of a warning light, and to press another key when a different light was extinguished. The second was a measure of response variability in this subtask (SDRT for lights). The third was RT to dials which indicated how long it took for subjects to press a key in response to an out-of-limits excursion of any of four dials. The fourth was SDRT for dials. The fifth and sixth variables were TO errors for lights and TO errors for dials. The ANOVA on these data showed there were drug-by-session interactions on both RT measures--RT to lights ($F(7,35)=6.69$, $p<.0001$) and RT to dials ($F(7,35)=2.88$, $p=.0174$)--and on the SDRT for lights ($F(7,35)=5.32$, $p=.0003$) and the TO errors for dials ($F(7,35)=3.68$, $p=.0044$). On each of these measures, performance at 0740 under placebo was significantly poorer than performance at the same time under modafinil. On both RT to lights and SDRT to lights (but not on the other measures), this difference continued through the 1540 session ($p<.05$). These effects are depicted in figure 14.

In addition to the interactions, there were session main effects for RT to lights ($F(7,35)=3.16$, $p=.0107$) and TO errors for dials ($F(7,35)=2.28$, $p=.0506$). Trend analyses indicated no significant session trends in the RT data (although there was a tendency toward a linear effect), but there was a significant cubic trend in the TO errors for dials ($p<.05$). As can be seen in table 8, RTs to lights tended to grow progressively longer throughout testing whereas TO errors for

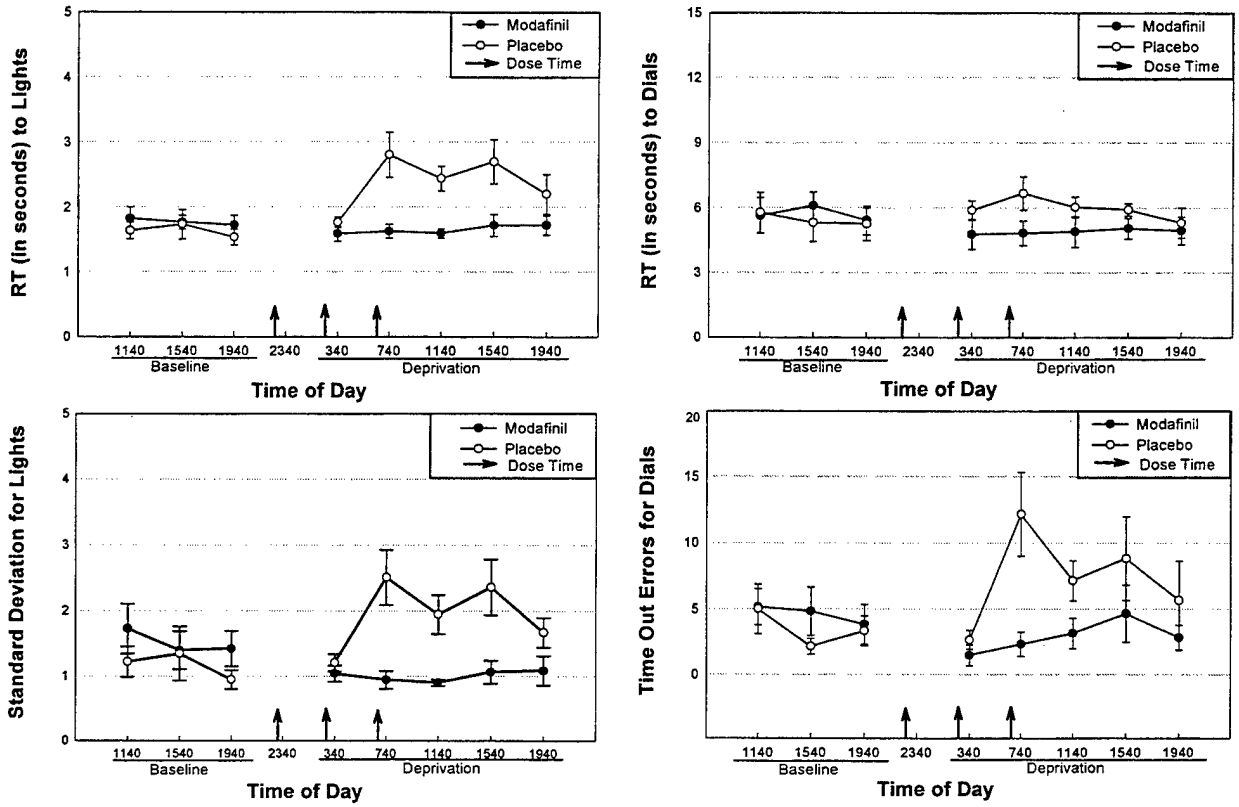


Figure 14. The effects of drug condition and time of day on performance of the MATB systems monitoring task.

dials initially decreased, then sharply increased at 0740, 1140, and 1540 before becoming less nu merous by the end of the deprivation day.

There were drug main effects only on RT to lights ($F(1,5)=8.35$, $p=.0342$). Consistent with what was observed in the earlier drug-by-session interaction on this measure, the RTs were slower under placebo than modafinil (2.1 versus 1.7 seconds, respectively). The reader is cautioned to interpret this main effect as well as the session main effects cautiously since they occurred in the presence of higher-order interactions. The overall session effects were due largely to changes that occurred under placebo rather than modafinil, and the overall drug effect actually resulted from a combination of both drug and session effects.

## Tracking

The root mean square (RMS) tracking error (or the amount of deviation from where the subject was supposed to be holding the cursor on the target to where he/she actually held the cursor) was analyzed. The ANOVA indicated there was a drug-by-session interaction ($F(7,35)=18.87$, $p<.0001$) which analysis of simple effects revealed was due to significantly larger tracking errors under placebo than modafinil at 0740, 1140, 1540, and 1940 ($p<.05$). There were no differences in the predrug baseline sessions (see figure 15).

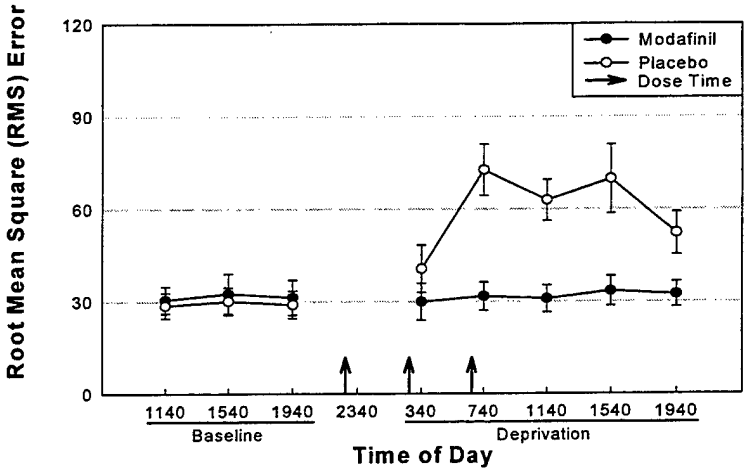


Figure 15. The effects of drug condition and time of day on MATB tracking accuracy.

There was a session main effect ($F(7,35)=12.02$, $p<.0001$) and a drug main effect ($F(1,5)=13.11$, $p=.0152$) as well. The session effect was attributable to significant linear and cubic trends in the data due to the fact that errors increased throughout testing, but were particularly elevated at 0740 and 1540 during sleep deprivation (see table 10). The drug effect was due to lower overall tracking errors under modafinil versus placebo (the means were 31.5 and 48.1, respectively).

Vital signs data

Vital signs (temperature, pulse, and blood pressures) were taken throughout the baseline and deprivation periods. They will be presented here to contribute to the exploration of modafinil and sleep deprivation effects despite the fact that they were collected primarily for safety monitoring. These data were analyzed in a series of 2-way ANOVAs for drug (placebo vs. modafinil) and time (there were 11 baseline times and 16 deprivation times). Some of the oral temperature data were confounded because subjects periodically ate or drank hot/cold substances within 5 minutes of data collection. Steps were taken to minimize this problem, but because of constraints in the testing schedule (sometimes subjects had only 5-10 minutes between tests), it was difficult to avoid some contamination. The other measures were accurate.

Oral temperature

There were no drug-related effects on oral temperature, but there was a session main effect ($F(26,130)=2.91$, $p<.0001$). Trend analyses indicated there were linear, quadratic, and cubic trends in the data, but the most noticeable effect was from a combination of circadian factors (low temperatures in the mornings versus the afternoons) and an activity confound (subjects performed physical exercise and took a hot shower prior to the 2220 evaluation each night). See figure 16 for details. Although there were no significant drug effects, the data are partitioned by modafinil and placebo for informational purposes.

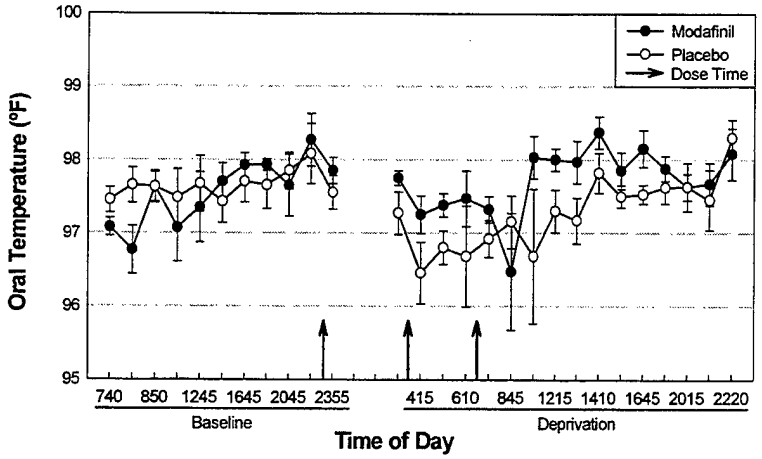


Figure 16. Oral temperature as a function of both drug condition and time of day

Pulse

The ANOVA of pulse data indicated a significant drug-by-time effect ($F(26,130)=2.91$, $p<.0001$) and a time main effect ($F(26,130)=5.42$, $p<.0001$). Analysis of simple effects showed that pulse rate was not different between the two conditions at any of the baseline sessions (pre-drug); however, the beats per minute were higher under modafinil than placebo at 0445, 0845,1010, 1215, 1245, 1615, and 2045 on the deprivation day (see figure 17).

The session main effect was due to significant quadratic and cubic trends ($p<.05$), but these will not be discussed further since they offer little informational value in light of the higher-order interaction already discussed.

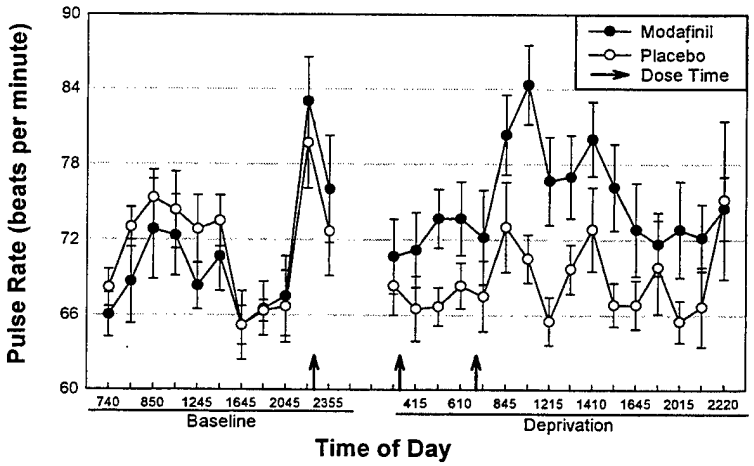


Figure 17. Pulse rate as a function of drug condition and time of day.

Systolic blood pressure

There was a drug-by-time interaction (F(26,130)=1.65, p=.0360) on the systolic blood pressure readings which analysis of simple effects revealed was due to an initial baseline difference (with placebo greater than modafinil at the 0740 and 0850 sessions) which was followed by a general increase under modafinil versus placebo (figure 18, left panel). The baseline effect was probably due to the fact that subjects consistently made efforts to take walks and stand up in order to avoid sleep while on placebo, whereas this was not necessary under modafinil. The apparent later elevations under modafinil during the deprivation sessions only attained statistical significance at 1615 ($p<.05$), but not during the earlier times. In addition to the interaction, there was a session main effect (F(26,130)=1.85, p=.0133) which trend analysis indicated was due to the presence of both quadratic and cubic trends ($p<.05$). However, this was not explored further because it was considered superfluous in the presence of the higher-order interaction already discussed.

Diastolic blood pressure

There was a drug-by-time interaction (F(26,130)=1.88, $p<.0113$) on the diastolic blood pressures. Analysis of simple effects indicated this was due to increased blood pressure at 1010, 2015, and 2045 on the deprivation day ($p<.05$), but no changes elsewhere (see figure 18, right panel). There also was a session main effect (F(26,130)=3.39, $p<.0001$) which was attributable to significant linear, quadratic, and cubic trends in the data ($p<.05$); however, these were not pursued further because the presence of a higher-order interaction indicates that the informational value of main effects is negligible.

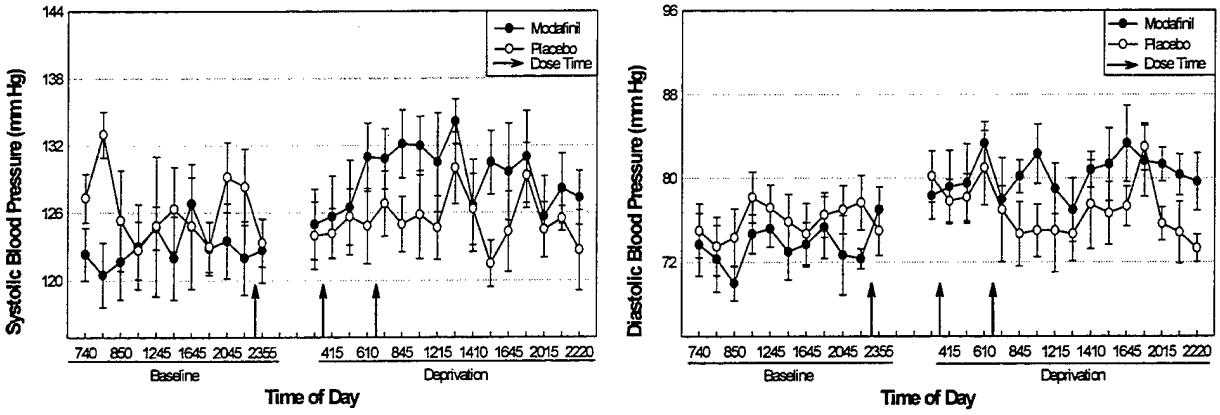


Figure 18. Drug-condition and time-of-day effects on blood pressure.

Polysomnographic data

The data from the baseline sleep night, as well as each recovery night following the modafinil and placebo days, were analyzed with a one-way ANOVA with repeated measures. The number

of minutes from lights out to the appearance of stage 2 sleep (sleep onset); the percentage of time subjects spent in stages 1, 2, 3, 4, and REM sleep; the percentage of time subjects were awake after sleep onset (WASO); sleep efficiency (defined as total sleep time divided by time in bed); number of minutes spent asleep; REM latency (defined as the time from sleep onset to the first REM period of at least 2 minutes in duration); and movement time were the variables of interest. Prior to analysis, percent data were converted using the two arcsine square-root transformation to stabilize the variances (Winer, 1962).

The analysis revealed significant differences among the days for sleep onset ($F(2,10)=7.69$, $p=.0095$) due to a longer sleep onset on the baseline night than on the placebo night ($p<.05$) and a tendency for a longer sleep onset on the baseline night than on the modafinil night ($p=.06$). Sleep efficiency was significantly different among the days ($F(2,10)=17.54$, $p=.0005$) with a lower sleep efficiency on the baseline night than on both the modafinil and placebo recovery nights ($p<.05$). Minutes asleep during the night duplicated the sleep efficiency results with less time asleep during the baseline night than during either recovery night ($F(2,10)=17.69$, $p=.0005$). No differences occurred among the conditions for REM latency. The condition effects for sleep onset and sleep efficiency are depicted in figure 19.

There was a difference among the days for the percentage of time spent in stage 1 sleep ($F(2,10)=5.12$, $p=.0295$), stage 3 sleep ($F(2,10)=5.33$, $p=.0266$), stage 4 sleep ($F(2,10)=6.99$, $p=.0126$), and WASO ($F(2,10)=12.91$, $p=.0017$). Comparisons among the means indicated that

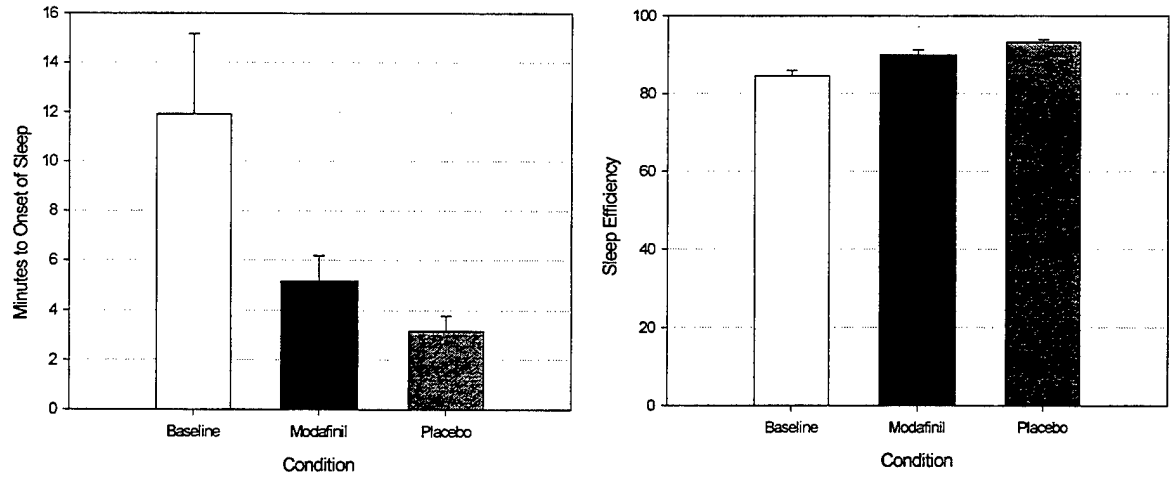


Figure 19. Effect of modafinil and placebo on sleep onset (left) and sleep efficiency (right).

there was more time awake and more stage 1 sleep, with less stage 3 and 4 sleep during the baseline night than during the placebo recovery night. There also was more time awake during the baseline night than during the modafinil recovery night (see figure 20).

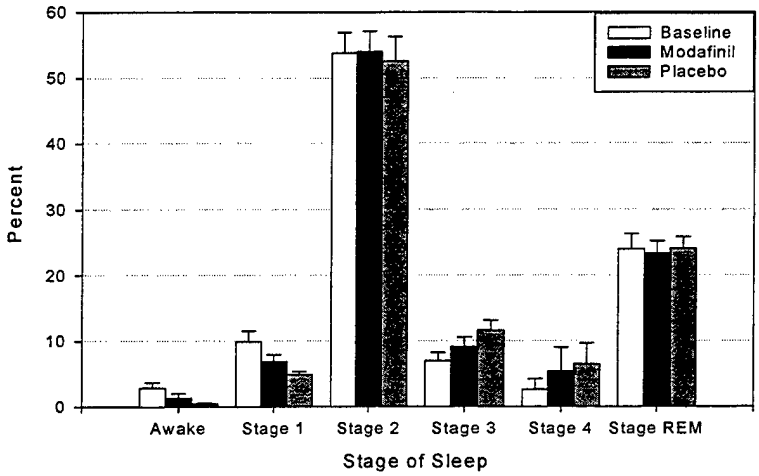


Figure 20. Effects of modafinil and placebo on sleep architecture.

## Discussion

The general finding from this investigation in which six helicopter pilots completed several simulator flights and a variety of other evaluations throughout 40 hours of continuous wakefulness was that modafinil attenuated a number of the problems associated with sleep loss. The benefits of modafinil were especially noticeable from approximately 0330 until noon when the fatigue from sleep deprivation was greatest. However, there were statistically significant differences on some measures in the afternoon as well. The most consistent drug effects (modafinil versus placebo) were observed on self-reported mood (energy, sleepiness, vigor, and fatigue), but a number of performance effects were seen as well.

Although direct comparisons between the results of this investigation (with modafinil) and earlier studies (with dextroamphetamine) have not been accomplished at this point, our subjective impression was that modafinil was not quite as efficacious as Dexedrine®. There was statistical support for this impression in that drug-related effects were fewer in this study than in our previous amphetamine investigations (most notably in the flight performance and EEG results). However, modafinil did improve overall performance and alertness during sleep deprivation, and an accurate comparison between modafinil and dextroamphetamine will necessitate further study. A follow-on report will address this issue via quasi-experimental comparisons between separate Dexedrine/modafinil investigations, and subsequent research will yield a more direct experimental evaluation of the comparability of these two compounds.

### Flight performance

Of the six instrument flight maneuvers conducted in the UH-60 simulator, there were drug-by-time effects on three and a drug main effect on one. In these maneuvers, performance under modafinil was maintained at or near baseline levels throughout the deprivation period whereas

performance under placebo suffered. On a fifth maneuver (the right standard-rate turn), there was a tendency toward better overall performance under modafinil versus placebo as well, but this was not significant (p=.0654). Generally speaking, modafinil did not appear quite as efficacious as originally expected, since it exerted a significant positive impact on only four of the six flight maneuvers. In part, this may have been because the pilots in this study possessed a great deal of flight experience, and as a result, may not have been as susceptible to fatigue-related performance decrements as would have been the case with a less-experienced group. In other words, since performance did not deteriorate to more extreme levels under placebo, there was less room for a potential modafinil-related improvement. A future study will explore the impact of flight experience on performance (and sensitivity to stimulant effects) by using analysis of covariance to compare the data from this investigation to the data collected from a different stimulant/sleep-deprivation study in which the subjects had fewer flight hours.

On the maneuvers in this study in which modafinil exerted significant drug-by-time effects, the times during which modafinil most clearly attenuated the problems due to sleep loss (in comparison to placebo) ranged from as early as 0500 to as late as 1700. However, the largest differences between drug and placebo tended to occur at about 0900. There were never differences during the first deprivation session (at 0100), no doubt because subjects were not significantly sleep deprived at that point (it was only two hours past their normal bedtime of 2300). On the left standard-rate turn, there were drug effects at 0500, 0900, and 1700; whereas in the straight and levels and the descents, the differences were at 0900 and 1300, respectively. The fact that modafinil's effects became more pronounced as the amount of sleep deprivation increased (up to around noon after which performance under placebo recovered somewhat) is consistent with the findings of Legarde and Batejat (1995) and Pigeau et al. (1995).

The level of pilot workload exerted some impact on the sensitivity of the different flight maneuvers to drug and fatigue effects. The left standard-rate turn was particularly affected by modafinil versus placebo during the second maneuver in which the automatic trim system was turned off (this increased the amount of effort required to maintain an acceptable flight path). This finding, of improved sensitivity with maneuver difficulty, supports our earlier studies on another stimulant in a sleep-deprivation paradigm (Caldwell et al., 1994; Caldwell et al., 1996).

## EEG

The electroencephalographic findings were consistent with what was observed in the flight performance. A generalized slowing of central nervous system activity (i.e., an increase in EEG delta and theta power) was observed during the sleep deprivation periods, especially under placebo, whereas modafinil significantly attenuated this effect. Sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (Pigeau, Heslegrave, and Angus, 1987), and increased theta activity has been associated with generalized performance decrements on cognitive tasks (Belyavin and Wright, 1987). Also, increased theta power is linked to reduced speed of responding to incoming stimuli (Ogilvie and Simons, 1992). Thus, the elevation in slow-wave EEG (delta and theta) activity, especially under the placebo condition, may explain the fact that flight performance decreased concurrently.

## MATB

Cognitive performance, measured by scores from the MATB systems-monitoring task, indicated that reaction times were slower (for lights and dials) and more variable (for lights), and time-out errors (for dials) were more numerous under placebo than modafinil. In the unstable tracking task, psychomotor tracking performance was also less accurate under the placebo condition in comparison to modafinil. The most pronounced drug-related differences in cognitive performance occurred as early as 0740 and as late as 1940 (from 25 to 36 hours of continuous wakefulness), but the majority of the statistically-significant differences occurred between 0740 and 1540 (the most consistently affected test was the one at 0740). Generally, the cognitive data and the flight scores were similarly influenced by sleep deprivation, and many of the decrements were attenuated by modafinil. Also, it is noteworthy that the times of these performance decrements (under placebo) tended to coincide with the times at which EEG theta activity increased the most (theta decreased under modafinil). The fact that cognitive skill suffered as a function of sleep loss is consistent with earlier reports from this and other laboratories (Caldwell and Ramspott, 1998; Krueger, 1989; Wilkinson, 1969), and the fact that modafinil reduced the level of degradation supports previously-published findings reported by Pigeau et al. (1995) and Lagard and Batejat (1995).

## POMS and VAS

Self-reported vigor, energy, talkativeness, and confidence declined the most under placebo at the 0735 testing time (around the time of the greatest performance decrements), and then recovered somewhat toward the end of the deprivation period. Conversely, ratings of fatigue and sleepiness increased the most at 0735 before improving later in the day. Although wakefulness during deprivation suffered in comparison to baseline under both drug conditions, it was clear that subjects were feeling less sleepy under modafinil than they were under placebo. Visual inspection of the data revealed that modafinil tended to preserve energy, talkativeness, and vigor at baseline levels until approximately 1145 (after almost 29 hours of continuous wakefulness). Meanwhile, feelings of sleepiness and fatigue were substantially attenuated at these and later times. Significant drug-related differences (modafinil better than placebo) were observed as early as 0335 to as late as 1935 (approximately 20-36 hours of continuous wakefulness), but most of the effects were seen between 0735 and 1535. This is consistent with the results reported by Pigeau et al.(1995), who found that modafinil significantly attenuated the circadian- and fatigue-related declines in mood ratings that occurred under placebo. Also, as was the case in the Pigeau et al. (1995) study, the self-reported mood effects found in this investigation were similar to what was found in the cognitive data.

## Polysomnography

All of the significant differences among the three nights on which sleep was permitted (baseline, placebo-recovery, modafinil-recovery) were between the deprivation-recovery nights and the baseline night, no doubt because of the greater sleep pressure following 40-hours of continuous wakefulness. There were no statistically-significant differences between the modafinil and placebo recovery nights on any parameter; however, there were suggestions that

modafinil may have slightly degraded sleep quality in comparison to placebo. This observation is made because of the distribution of effects between the placebo-baseline comparisons and the placebo-modafinil comparisons. Of the seven sleep measures on which there were condition-related effects (sleep onset; sleep efficiency; total sleep; stages 1, 3, and 4 sleep; and time awake after sleep onset), there were differences between the baseline and placebo nights on all seven, whereas there were differences between baseline and modafinil on only two (sleep efficiency and total sleep time). This implies a tendency toward disrupted postdeprivation recovery sleep under modafinil because had modafinil not exerted any impact, there would have been the same number of modafinil-baseline differences as there were placebo-baseline differences. Furthermore, there were tendencies (p=.07-.09) for modafinil to have been associated with longer sleep onset, lower sleep efficiency, less total sleep time, less deep (stage 3) sleep, and a greater percentage of time awake after sleep onset than was the case with placebo. Thus, a divided, 600-mg dose of modafinil (with the last dose 16 hours prior to bedtime) seems to make recovery sleep slightly less restful despite the fact that, in a rigid statistical sense, the present data support earlier conclusions that modafinil has little impact on polysomnographic parameters (Buguet et al., 1995). This deserves further exploration in the future. However, it should be noted that even if statistically-significant differences are found, the magnitude of these effects makes it unlikely that any of the changes in sleep architecture would markedly interfere with recovery from the amount of sleep deprivation used here.

## Vital signs and side effects

Modafinil in comparison to placebo significantly increased the heart rates of the volunteers in this study (at one point, there was a 14 beat per minute difference); however, only one volunteer specifically complained of feeling his heart was "racing," and only one other stated that he could feel his heart beating under the influence of modafinil. The effect of modafinil on blood pressure was minimal. Visual inspection of the systolic blood pressure data, averaged across the 6 participants who were included in the final sample, indicated that the pressure was 6-9 mmHg higher under modafinil than placebo between 0610 and 1645 on the deprivation day; however, only 1 significant difference was found across the 16 deprivation times (at 1615). Inspection of the diastolic data revealed a 6-7 mmHg increase under modafinil versus placebo which was significant at three of the deprivation times (1010, 2015, and 2045). These blood pressure changes may have prompted the minor subjective complaints from two volunteers that they felt "flushed" on the modafinil day.

The most common side effect reported by participants under the modafinil condition was nausea or related symptoms. On the modafinil day, 18 incidences were reported by 4 participants, while on the placebo day, only 4 incidences were reported by 1 participant who also reported nausea on his modafinil day (this excludes the first subject who was released from the study because of excessive nausea on his first deprivation period, in which he received placebo). Ten instances of vertigo were reported by four participants during the sleep-deprivation period in which modafinil was administered, and one instance was reported during the period in which placebo was administered (also reported during his modafinil day). Jitteriness or nervousness was another common complaint that was made seven times by three participants on the modafinil day, but was not mentioned on the placebo day. Dizziness was reported on five occasions by

three participants on the modafinil day, and only once on the placebo day (he also reported this symptom on his modafinil day).** Other less common side effects were heartburn (one on modafinil, zero on placebo) and headache (two on modafinil by one participant, and two on placebo by two participants). When symptoms of vertigo, including dizziness (apparently related to modafinil), were reported, they most often occurred around the times at which the simulator flights were conducted while nausea usually occurred during the flight and/or immediately afterward. Of the total of 33 incidences of nausea, vertigo, and dizziness reported under modafinil, 56 percent occurred between 0600 and 1500.

The lack of clinically-significant effects on vital signs is consistent with what would be expected based upon the existing modafinil literature (Cephalon, 1998). However, some of the other modafinil-related side effects were more pronounced than might have been expected based upon previous reports. Batéjat and Lagarde (1999) for instance, recently stated that "modafinil...combines wakening and stimulating properties without any known side effects" (p 493). Our data do not support this observation, particularly with regard to the vertigo, dizziness, and/or nausea (especially problematic around the simulator flights) experienced by some of the participants in the present study.

One reason that these difficulties, which are quite disconcerting for pilots, were more numerous than expected might have been that a relatively high dosage of modafinil was used in this investigation (Batéjat and Lagarde used only a 200 mg dose to enhance the alertness of their volunteers). For our study, a 600-mg divided dose was chosen because it appeared that more than 200 or 400 mg of the drug (the amount commonly used in clinical settings) would be necessary to *sustain* the alertness and performance of aviators who were being subjected to total sleep deprivation. There was reason to believe that this would be an acceptable dosage level based on an earlier study (Lagarde et al., 1995) in which 600 mg daily (administered in 3, 200-mg doses, each separated by 8 hours) had proven efficacious for overcoming the impact of sleep loss. However, while the stimulant effect of the 600 mg dose used in our study (given in 3, 200-mg increments, spaced 4 hours apart) probably was greater than the effect of the smaller doses used elsewhere, the associated problems related to side effects were less favorable and may have exerted a negative impact on performance. It is certainly the case that vestibular side effects and/or nausea would rule out the use of this medication in aviators, unless a dosage reduction eliminated these problems. A follow-on study of the efficacy of a divided 400-mg dose of modafinil may determine whether the vertigo, nausea, and dizziness will subside without overly reducing the stimulant effect.

Another reason for the higher-than-expected number of side effects may have been related to the fact that the subjects tested in this protocol were being required to perform in a multi-axis, moving platform with computer-generated visual scenery, rather than in a static laboratory

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** The two preliminary subjects, who were tested only under the modafinil condition, are not included here. These individuals were essentially asymptomatic under modafinil; however, their stay in the laboratory was of a much shorter duration than that of the other volunteers (who were exposed to both dose conditions), making it difficult to compare the results.

situation. Past studies (not with stimulants or sleep deprivation) have shown that some aviators tend to develop nausea in the simulation environment despite the fact they do not experience similar problems under actual in-flight conditions (Gower, 1989). Although this would not in-and-of-itself explain the increase in nausea/vertigo symptoms under modafinil versus placebo (since subjects flew the same flight profile in the simulator under both drug conditions), it does raise the issue of whether these problematic side effects would be encountered in the in-flight environment. If modafinil does in fact increase dizziness and vertigo in all flight situations, this obviously would prohibit the use of this drug in aviation operations; however, if modafinil simply lowers the threshold for simulator sickness without producing motion sickness or vertigo in the actual in-flight environment, modafinil could be a useful fatigue countermeasure in real-world aviation operations. If this is the case, the drug should not be discounted because it does have a number of desirable characteristics (low abuse potential, low toxicity, etc). A study in which the 600-mg dose of modafinil is tested in sleep-deprived volunteers flying an actual aircraft (as opposed to a simulator) would resolve this issue, and should be performed in the near future, and certainly before any final decisions are made regarding the suitability of this compound for aviators.

## Summary and conclusions

The results of this study, in which six helicopter pilots flew a flight simulator and completed other tests throughout 40-hour periods of continuous wakefulness, showed that modafinil was moderately effective for sustaining both performance and alertness. On four of the six "instrument maneuvers" in the UH-60 flight simulator, modafinil significantly attenuated the sleep-deprivation problems which were observed under placebo. Similar modafinil-related benefits were seen in the cognitive performance data. Both EEG activity and self-reports indicated that alertness was better under modafinil than placebo. The greatest drug-related effects occurred between 0330 and 1200 when the impact of fatigue was most profound. Recovery sleep following the period of sustained wakefulness in which modafinil was used did not evidence disrupted sleep architecture. Therefore, modafinil would not be expected to prolong recovery time when used to maintain performance in sustained operations.

Despite the fact that modafinil effectively maintained many aspects of alertness and performance in sleep-deprived pilots, there were side effects that must be further explored before this compound can be recommended for use in aviation operations. Most problematic were the vertigo and nausea symptoms which were apparently associated with modafinil administration. These problems would be cause for serious concern in the actual operational environment. However, it is possible that the side effects were at least exacerbated by the motion-base simulator, and that they may not occur to a great extent in the actual in-flight environment. Also, the nausea and vertigo might have been dose-related, and a simple reduction in the amount of modafinil from 600 mg to 400 mg may alleviate the problem. A dose-response relationship in the incidence of adverse events has been reported with doses ranging from 200 to 800 mg (Wong et al., 1999), although most of the problems were headache, insomnia, anxiety, and palpitations rather than the nausea or vestibular symptoms found in the present study. Future investigations will address the relationship between dosage levels and side effects as well as the potential contribution of "simulator sickness" to modafinil-related nausea and vertigo.

Subjectively, it did not appear that modafinil (as tested in this study) was as effective as dextroamphetamine (evaluated in previous investigations) for sustaining performance without producing side effects. However, all six volunteers in this study were able to determine when they were on modafinil versus placebo, and five of the six thought modafinil helped their performance. Thus, modafinil holds promise for its alerting effects, and follow-on comparisons between dextroamphetamine and modafinil are warranted to specifically address the costs and benefits of each compound.

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## Appendix

### Manufacturer's list.

Advanced Gravis Computer Tech., Ltd.
1790 Midway Lane
Bellingham, WA 98226

Altec Lansing Technologies, Inc.
Milford, PA 18337

Cadwell Laboratories
909 North Kellogg Street
Kennewick, WA 99336

C. H. Products
970 Park Center Drive
Vista, CA 92083

Cephalon, Inc
145 Brandywine Parkway
West Chester, PA 19380

Coulbourn Instruments, Inc.
Box 2551
Lehigh Valley, PA 18001

Creative Labs, Inc.
1901 McCarthy Blvd.
Milpitas, CA 95035

Digital Equipment Corp.
P.O. Box C52008
Nashua, NH 03061-2008

Elexor Associates
P.O. Box 246
Morris Plains, NJ 07950

Grass Instrument Co.
101 Old Colony Ave.
Quincy, MA 02169

IVAC Corp.
10300 Campus Point Dr.
San Diego, CA 92121

MicroSoft
1 Microsoft Way
Redmond, WA 98052

Nihon Kohden
17112 Armstrong Ave.
Irvine, CA 92714

SensorMedics
22705 Savi Ranch Parkway
Yorba Linda, CA 92678