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A Comparison Between the Countermeasures Modafinil and Napping for Maintaining Performance and Alertness Using a Quasi-Experimental Analysis

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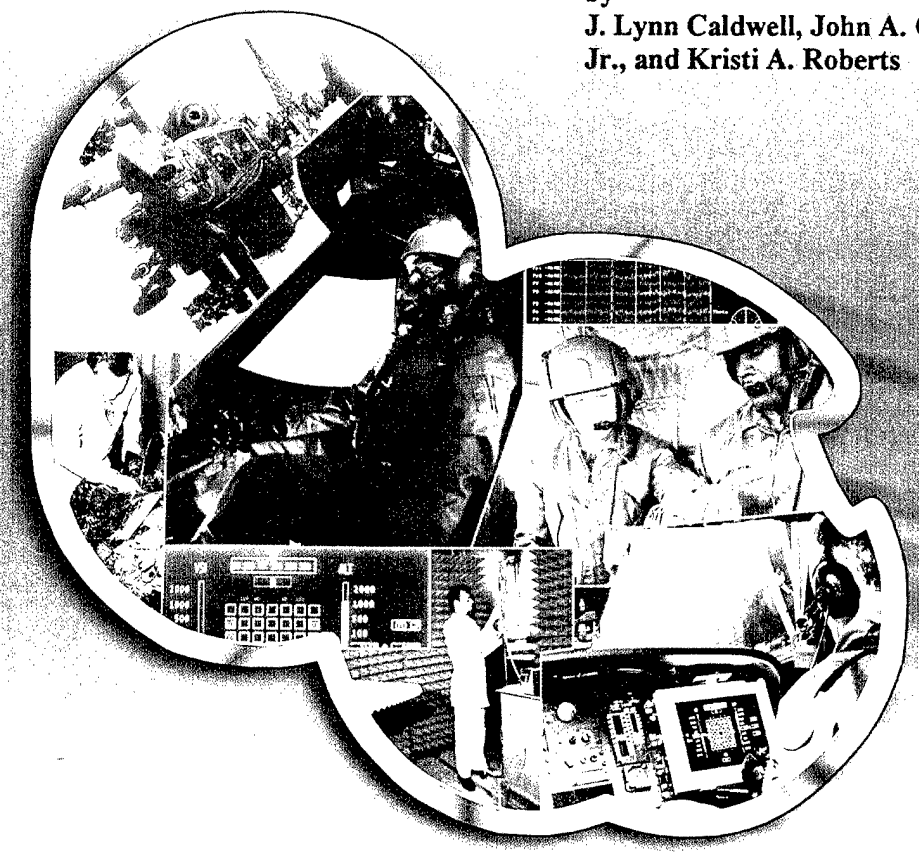

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The data from two separate studies were combined in order to statistically compare the efficacy of the wakefulness-promoting substance modafinil to a 2-hour nap for sustaining cognitive skill and psychological mood in helicopter pilots who have been deprived of sleep (other than the nap). Performance data from the Multiattribute Task Battery (MATB) and mood data from the Profile of Mood States (POMS) were analyzed for this comparison. Eighteen subjects' data from the Napping study were merged with six subjects' data from the Modafinil study (the data were collected at similar testing times). Baseline-adjusted difference scores were analyzed. A three-way mixed factorial analysis of variance (ANOVA) was used with one grouping factor (Modafinil study versus Napping study) and two repeated-measures factors-- Condition (Treatment or No Treatment) and Time (specific to each test).

The two countermeasures were effective in combating the usual decline in cognitive performance and mood during sleep deprivation, but they were not comparable. It appears that modafinil was superior to naps in maintaining alertness. The subjective mood data

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indicated that both countermeasures were successful at decreasing fatigue and confusion, and increasing vigor when compared to no intervention at all. However, when comparing modafinil and a nap, modafinil maintained a higher level of vigor and a lower level of fatigue than the nap, particularly in the early morning hours when the circadian dip in alertness is most problematic. The performance data supported the subjective mood findings by showing that, while both strategies attenuated performance losses during sustained wakefulness, modafinil was more efficacious than a nap. This was especially true of reaction time and errors of omission. As with subjective mood, modafinil's superiority was particularly evident in the early morning hours.

Although napping was not the superior countermeasure, it was nonetheless effective, and may therefore be considered in situations where some sleep (but not a full, consolidated sleep period) is feasible. However, in settings where sleep opportunities are limited or unavailable, napping alone may not adequately offset the majority of fatigue-related decrements. In these cases, a pharmacological fatigue countermeasure such as modafinil may be appropriate for the short-term postponement of sleep until adequate crew rest schedules can be implemented.

Table of contents

Table of contents (continued)

List of tables

List of figures

General objective

The purpose of this analysis was to compare the efficacy of the wakefulness-promoting substance modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) to a 2-hour nap for sustaining cognitive skill and psychological mood in helicopter pilots who have been deprived of sleep (other than the nap). This quasi-experimental analysis combines data from two different studies in order to statistically compare the efficacy of these two countermeasures for minimizing sleep deprivation effects.

Military relevance

This research is important to the Department of Defense because of the increased concern that missions which were once effectively achieved by many soldiers are still required, but few soldiers now are available to accomplish them due to the downsizing of the military over the past 10 years. Individual soldiers are working longer hours, and units remain on alert for longer periods of time. This situation can eventually create significant fatigue-related problems unless work schedules, rest periods, and other factors are adequately managed.

Fatigue in the aviation community can lead to dangerous consequences for all concerned, since aviators are responsible for planning missions, flying aircraft, managing flight personnel, and performing a host of other duties. Appropriate countermeasures are required to ensure that aviators and crew are sufficiently rested to perform their duties effectively. However, in many situations, it is impossible to ensure that adequate sleep and rest will be obtained in the operational environment. Therefore, a variety of countermeasures must be explored in an effort to prevent the attentional lapses, slower reaction times, and increased errors associated with fatigue (Krueger, 1989).

Stimulant medications are possible alternatives in some situations. The newest compound modafinil appears to be efficacious while at the same time manifesting a favorable side-effect profile compared to other stimulants such as dextroamphetamine. In addition, modafinil appears to have a lower abuse potential than dextroamphetamine. Another possible countermeasure is napping whenever the aviator or crew member has a short period of time in which to sleep. Research suggests that well-placed naps can sustain performance, but the efficacy and feasibility of napping depend on many factors.

Questions have arisen in the aviation community about which fatigue countermeasures are most effective. Both modafinil and napping have been evaluated separately in an aviation setting, but not in the same study. In order to obtain an indication of how modafinil and naps compare in the ability to sustain performance and mood during long hours without sleep, the data from the two studies were merged and analyzed.

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.

There are difficulties inherent in maintaining effective round-the-clock operations, particularly in situations where there are insufficient numbers of personnel to staff the day and night shifts with different well-rested 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, 1988). 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 can receive a continuous block of sleep, this may not be sufficient to ensure appropriate levels of vigilance during long periods of overnight duty without some fatigue countermeasure (Pascoe, Nicholson, and Turner, 1994). In settings where some "down time" is possible, a short nap might be very beneficial. At other times, the only viable alternative may be to sustain performance through pharmacological means (i.e., stimulants). A discussion of both these countermeasures follows.

Modafinil

General

Modafinil (Cephalon, Inc.) is 2-[(diphenylmethyl)sulfinyl]acetamide which is supplied in 100 and 200 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 central nervous system (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 a_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). Modafinil 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 literature on modafinil indicate 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; Akerstedt and Ficca, 1997). In monkeys, it has been reported that modafinil is able to produce prolonged wakefulness across four 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, has been confirmed by Hermant, Rambert, and Duteil (1991) after administration of the drug to monkeys over five consecutive days. 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 Agood≡ or Aexcellent≡ for this purpose. These results have been supported by Phase III clinical studies 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, 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 nonsleep-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 were 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., caffeine and amphetamines) in terms of sustaining performance, but recent reports suggest that modafinil may offer an efficacious alternative to other better-known compounds. Based upon evaluations of subjective mood reports and the results of cognitive tests from 41 subjects undergoing 64 hours of sleep deprivation, Pigeau et al. (1995) 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 and its reduced tendency to produce euphoriant effects (a factor associated with abuse potential).

In addition, modafinil appears more satisfactory than older stimulants because of its lack of sleep-disturbing effects. 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. 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 were not age dependent.

An evaluation of modafinil and caffeine was conducted by Wesensten et al. (2002) to compare 100, 200, or 400mg of modafinil to 600 mg of caffeine. After being awake for 41.5 h, subjects were administered either placebo, 100 mg modafinil, 200 mg modafinil, 400 mg modafinil, or 600 mg of caffeine. Hourly tests of performance and alertness (for the next 13 hours) indicated improvements in the subjects who received 200 and 400 mg modafinil compared to placebo. These doses were comparable to 600 mg caffeine. The authors concluded that modafinil was similar to caffeine in the ability to sustain performance and alertness during periods of prolonged wakefulness. However, the subjects in this study were not heavy caffeine users; only subjects with reported daily caffeine consumption of 400 mg or less were included in the study. Therefore, whether caffeine and modafinil are similarly effective in people who consume moderate to heavy doses of caffeine has yet to be determined.

Taken together, the results from these investigations indicate that modafinil possesses vigilance-promoting qualities similar to those of dextroamphetamine and caffeine. However, it does not have the potential for serious adverse side effects and/or abuse often associated with amphetamines, and, since it is not readily available, tolerance to modafinil is not as likely as it is with caffeine.

Naps and performance

There is an abundance of evidence indicating that a nap taken during long periods of otherwise continuous wakefulness is extremely beneficial for improving alertness and performance (Akerstedt and Torsvall, 1985; Bonnet, 1990; Bonnet, 1991; Dinges et al., 1987; Dinges et al., 1988; Haslam, 1985; Lumley et al, 1986; Matsumoto and Harada, 1994; Mullaney et al., 1983; Naitoh and Angus, 1989; Naitoh, Englund, and Ryman, 1982; Rogers et al., 1989; Rosa, 1993; Webb, 1987). Reviews of the literature indicate that napping is beneficial for maintaining mood and performance over a continuous wakefulness period. A nap may be taken before a long wakefulness period (prophylactic nap) or after one has been awake for a while, but will need to remain awake for a longer period (replacement nap).

A review of the literature indicates that a prophylactic nap taken during the day before an all-night work shift results in better performance than continuous wakefulness. Although naps taken later in the sleep-deprivation period also are beneficial, these naps probably should be longer than prophylactic naps in order to derive the same performance benefit. Schweitzer, Muehlback, and Walsh (1992) measured performance and alertness in subjects who received a 2- to 3-hour nap before a night work shift (with concurrent sleep loss). Although the usual circadian trough was seen in the early morning, the nap attenuated the decline in performance compared to a night where no nap was taken prior to the shift.

In a study conducted by Bonnet (1991), some subjects napped before a 52-hour continuous performance period while others remained awake. The nap was beneficial in sustaining performance and alertness for up to 24 hours as compared to the no-nap condition. However, by the second night of sleep loss, the benefit of the naps could not be reliably measured. In a study by Naitoh, Englund and Ryman (1982), subjects were given a 3-hour nap after being awake for approximately 24 hours. After the nap, they were required to stay awake an additional 20 hours. Results indicated that this 3-hour nap reduced the decline in performance during the additional work period. Other studies have found similar results using 24 hours of sleep deprivation (Dinges et al., 1987; Gillberg, 1984; Nicholson et al., 1985; Bonnet, 1990). In each case, prophylactic naps taken prior to extended periods of sleep loss considerably attenuated the decrease in performance. The naps do not totally eliminate the circadian dip seen in the early morning (around 0500), but the degradation in both cognitive performance and alertness is attenuated compared to no napping conditions (Bonnet, 1990). These conclusions have received significant support elsewhere (Gillberg, 1984; Nicholson et al., 1985; Carskadon and Dement, 1982; Haslam, 1985).

The length of the nap appears to be important as indicated by several studies. It is difficult to compare many of the nap studies due to variations in methodology; however, most indicate that naps from 1 hour to 8 hours will improve performance and alertness during continuous operations. A relationship between nap length and performance was reported by Bonnet (1991) based on a study in which subjects were allowed either a 2, 4, or 8-hour nap before 52 hours of continuous operations. The results indicated a dose-response relationship between the length of the nap and performance during the first 24 hours of sleep deprivation. Bonnet concluded that the nap before an all-night shift should be as long as possible to produce maximum performance benefits. The importance of nap length was further highlighted in an investigation by Lumley et al. (1986), in which subjects were deprived of sleep for 24 hours and then permitted naps of either 15, 30, 60, or 120 minutes. The results indicated that alertness increased as a function of increased nap length, with the highest level of alertness occurring after the 60-minute nap. There was, however, no difference between the 60-minute nap and the 120-minute nap, possibly due to sleep fragmentation in the longer period.

The timing of naps with regard to circadian phase is important, but complex. Nap timing should take into account the ease of falling asleep at various times, the quality of sleep as a function of the body's internal clock, and the effects on performance both immediately after awakening and later in the work period. It has been established that sleep tendency is highest when core body temperature is in its trough, and lowest when core body temperature is in its peak (Dinges, 1986). Thus, there may be significant problems initiating and/or maintaining a nap during times when core temperature is high. In part because of the potential impact of the temperature rhythm on sleep, Lavie (1986) considers the period from around 2000 to 2200 a "forbidden zone" for sleep, meaning that sleep initiation and maintenance are difficult during this time period (even in sleep-deprived personnel).

Naps which are placed during the circadian troughs are the easiest to maintain, and they show beneficial effects on later performance. A study by Naitoh, Englund and Ryman (1982) indicated that a 3-hour nap taken between 0400 and 0700 (circadian trough) after 20 hours of continuous wakefulness reduced the amount of performance degradation seen upon awakening when compared to a no-nap group. When naps placed in the circadian trough are compared to naps placed in the circadian peak, the effects on performance are different. Gillberg (1984) examined the effects of a 1-hour nap placed either at 2100 or 0430 after 24 hours of sleep deprivation. Both naps improved performance the following morning when compared to a no-nap group, but the nap taken at 0430 (in the circadian trough) showed the most benefit. These findings, that early morning naps are most beneficial in restoring alertness and performance, have been supported by others (Matsumoto, 1981; Naitoh, Englund and Ryman, 1982).

Dinges et al. (1988) found that a nap taken anywhere in the circadian cycle before sleep deprivation will be beneficial in maintaining performance across the sleep loss period. However, there can be a high cost to napping during the circadian trough. Although naps during the circadian trough may be more effective for performance sustainment (and they are easier to initiate and maintain), they also are more difficult from which to awaken. In fact, failure to account for the difficulty in awakening from these naps has caused some authors to initially conclude that naps during the circadian trough were inferior to naps placed elsewhere. For instance, Dinges, Orne, and Orne (1985) indicated that naps taken during the circadian trough are likely to be associated with lower performance than naps taken during circadian peaks--results which appear contrary to the general findings of other researchers. However, these conclusions were a result of the fact that Dinges, Orne and Orne (1985) tested subjects immediately upon awakening, whereas other investigators allowed longer intervals of time to pass prior to task performance. Generally, studies have shown that post-nap sleepiness, termed "sleep inertia," is higher and performance is lower immediately upon awakening from a nap taken during the circadian trough as compared to naps taken during the circadian peak (Dinges, Orne and Orne, 1985). Lavie and Weler (1989) found that after 32 hours of sleep deprivation, a 2-hour nap taken at 1500 produced less sleep inertia than a 2-hour nap taken at 1900. However, the later nap was more successful in reducing early morning (2300 to 0400) sleepiness. Regardless of the time of the nap, sleep inertia will occur, and work requirements should be delayed accordingly.

Performance generally will be lowest during the first 5 minutes after awakening, but it usually recovers after 15 to 30 minutes (Dinges, Orne and Orfe, 1985). Generally, sleep inertia will be extended in situations where the timing of the nap is misplaced and/or the amount of sleep deprivation is extensive before the nap occurs. Thus, Dinges, Orne and Orne (1985) suggest that during continuous operations, naps in the circadian trough should be avoided, and naps should be taken before a person's sleep loss extends beyond 36 hours. However, it should be possible to take advantage of the improved quality of naps in the circadian trough while avoiding the sleep-inertia effects if napping personnel can be awakened about 1 hour prior to their work shifts.

In summary, the research concerning naps indicates that properly-implemented naps are beneficial for reducing sleepiness and performance decrements normally observed during sleep-deprivation periods. A nap is most beneficial if taken before significant sleep loss occurs (a prophylactic nap). This nap should be as long as possible, but even short naps can be beneficial. The timing of the nap should be planned in relation to the timing of work requirements. Sleep occurs most readily and performance is sustained most effectively when naps are placed in the circadian troughs; however, care must be taken to minimize the sleep inertia which is greatest when awakening from these naps.

Methods

As was stated at the outset, the purpose of this paper is to compare a napping strategy (prophylactic naps) to a stimulant (modafinil). To accomplish this, data from two separate studies will be combined and analyzed. Prior to a presentation of the analysis strategy, each study will be presented so the reader may gain an appreciation for the protocol under which the data were originally collected.

Review of modafinil study

Methods

A double-blind, within-subjects, placebo-controlled design was employed in which six aviators participated for a period of one 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 2 separate 40-hour continuous wakefulness 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). The orders of drug/placebo administration were counterbalanced, and specific orders were assigned to subjects randomly upon arrival to the Laboratory. Drug or placebo doses were given orally with approximately 8 oz water. Testing sessions were conducted around the clock during deprivation periods. For the current data analysis, only the

Profile of Mood States (POMS) and Multiattribute Task Battery (MATB) were used since the timing of these tests were comparable to the timing of the tests during the napping study (to be discussed later). A full description of this study is published in a technical report (Caldwell et al., 1999).

Subjects

Eight UH-60 qualified male helicopter pilots were enrolled in the study, but only six were included in the data analysis. One 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). The sixth volunteer was replaced because, despite his successful completion of the investigation, his flight data were confounded by an exceptionally steep training curve which was different from the other volunteers. The six aviators who made up the final sample averaged 37.3 years of age (ranging from 29-46 years) and possessed 2173.3 total hours of flight experience (ranging from 900-5500 hours), 492.5 hours of which 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 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 modafinil, 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 per subject). In the other deprivation period, two matching placebo tablets were administered at each dose interval.

* See manufacturers' list in the Appendix

Table 1.
Modafinil study testing schedule.

Time	Sunday	Monday Training	Tuesday Baseline	Wednesday Test	Thursday Recovery	Friday Test	Saturday Recovery
0100				Simulator		Simulator	
0200				EEG MiniSim		EEG MiniSim	
0300				*DRUG* **POMS/MATB**		*PLACEBO* **POMS/MATB**	
0400							
0500				Simulator		Simulator	
0600				EEG MiniSim		EEG MiniSim	
0700		Wakeup	Wakeup	*DRUG* **POMS/MATB**	Wakeup	*PLACEBO* **POMS/MATB**	Wakeup Breakfast
0800		Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Electrode Removal
0900		Simulator	Simulator	Simulator	Simulator	Simulator	Release
1000		EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	
1100		**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	
1200		Lunch	Lunch	Lunch	Lunch	Lunch	
1300		Simulator	Simulator	Simulator	Simulator	Simulator	
1400		EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	
1500	Arrive/ Inservice	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	
1600	Medical Screening						
1700	Electrode Hook-up	Simulator	Simulator	Simulator	Simulator	Simulator	
1800		EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	EEG MiniSim	
1900		**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	**POMS/MATB**	
2000	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	
2100	PT	PT	PT	PT	PT	PT	
2200							
2300	Lights Out	POMS Lights Out	*DRUG* POMS	POMS Lights Out	*PLACEBO* POMS	POMS Lights Out	
2400							

Note: DRUG= 200 mg. modafinil; Placebo= matching placebo tablets, counter-balanced
POMS= Profile of Mood States; MATB=Multi Attribute Task Battery; PT=Physical Training

POMS

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 Aalert/able to concentrate,≅ Aanxious,≅ Aenergetic,≅ Afeel confident,≅ Airritable,≅ Ajittery/nervous,≅ Asleepy,≅ and Atalkative≅ were administered in conjunction with the POMS. Each of the above adjectives were centered over 100 mm lines. At the extremes of each line, Anot at al≅ and Aextremely≅ 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 voice synthesizer card (Soundblaster 16, Creative Lab*), stereo speakers (Altec Lansing*), a joystick (Advance Gravis Computer Tech. LTD*), and a standard keyboard and 15-inch color monitor. Scores for each subtest were automatically computed at the end of each session.

Procedure

POMS

The POMS was given at 1125, 1525, 1925, and 2335 on baseline days and at 0325, 0725, 1125, 1525, 1925, and 2335 on test days. Subjects were presented with a series of 65 words which described mood states, and for each "mood state" the subject indicated on a computer 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.

MATB

Following the POMS, subjects completed the MATB at 0330, 0730, and 1130 on baseline days, and at 0330, 0730, 1130, 1530, and 1930 on test days. This test was designed to simulate a subset of 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 bottom right quadrant, a *resource management task* required the subjects to maintain 2500 units of "fuel" in two tanks by monitoring and controlling the status of 8 "pumps." In the lower left quadrant, a *communications task* required subjects to monitor and respond to verbal instructions about radio-frequency changes presented via headphones. In the upper left quadrant, a *systems monitoring task* required subjects to attend to two warning lights and four dials and to press specific keys either to terminate the onset of a specific light, note the extinguishing of another light, or to reset a dial deviating more than two tick marks from center.

In the upper right quadrant, a *tracking task* required subjects to center an unstable target in the middle of a grid pattern through the use of joystick manipulations. Scores on accuracy and speed were recorded automatically by computer.

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 training sessions for all the tests. 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), 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. Test sessions began on *Wednesday* two 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. 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 at 0100 and ending with a recovery sleep period in the evening. On *Saturday*, the aviator was medically evaluated and released. Although many tests were administered during each test session, only the MATB and POMS data will be analyzed for this comparison.

Review of napping study

Methods

A double-blind, within-subjects, placebo-controlled design was employed in which 18 subjects participated for a period of 10 days each. Each subject remained in the USAARL from Sunday evening until the following Tuesday 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 3 separate 38-hour continuous wakefulness periods (with the exception of a 2-hour nap). During one of these, 10 mg zolpidem tartrate was administered before a 2-hour nap; during another, a placebo was administered before a 2-hour nap; and during the other, a 2-hour rest period was allowed (no sleep permitted) (see Table 2). The orders of the drug/placebo/rest were counterbalanced, and specific orders were assigned to subjects randomly upon arrival to the Laboratory. Drug or placebo doses were given orally with approximately 8 oz water. Testing sessions were conducted around the clock during deprivation periods. For the current data analysis, only the POMS and MATB data from the placebo nap condition and the rest condition were used. The objective of the analysis was to compare a standard, natural nap to the stimulant modafinil. The rest period served as the placebo condition for the napping study. The full report of this study is published in a technical report (Caldwell et al., 1997).

Subjects

Eighteen subjects between the ages of 22 and 31 (mean=24.4) were recruited from Fort Rucker and other Army installations. Subjects were males (no females volunteered) who weighed between 145 and 205 pounds (mean=177.6 pounds). Fourteen of the subjects were flight students, and four were rated helicopter pilots. All subjects gave informed consent and were medically evaluated prior to testing. Subjects were healthy, nonsmokers who used only small amounts of caffeine (no more than three 8-ounce cups caffeinated coffee or five 12-ounce caffeinated soft drinks per day) and who reported no problems sleeping. Potential subjects were screened for current significant medical problems (including sleep abnormalities), use of tobacco products, current use of medications (other than sodium naproxin, ibuprophen, acetaminophen, or aspirin) that could not be discontinued, or excessive use of caffeine. Subjects were instructed to abstain from drug and alcohol use for 48 hours prior to the beginning of the study, and no drug or alcohol use was permitted during participation. Subjects remained inside of the USAARL at Fort Rucker, Alabama, for the duration of testing (10 consecutive days and 9 nights).

Apparatus

POMS

The POMS (McNair, Lorr and Droppleman, 1981) was used to assess subjective reports of mood at various times throughout the day. This questionnaire is the same one used in the modafinil study and is described above.

MATB

The MATB, a computerized aviation simulation test, was used to assess cognitive performance on a variety of measures. It is the same test used in the modafinil study and is described above.

Procedure

POMS

The POMS was administered every 2 hours beginning at 0900 on training and control days and at 0100 on sleep deprivation days. The last administration occurred at 1900 on each day. The test was administered using the standard POMS answer sheet on which subjects indicated how well each of 65 adjectives described the way they were feeling at the time. The test took approximately 5 minutes.

MATB

Subjects completed the MATB every 4 hours from 0910 to 1710 on training and control days, and from 0110 to 1710 on test days. The test followed the completion of the POMS and was 30 minutes in length. Subjects were required to simultaneously monitor and respond to four different tasks throughout the testing period. As described earlier, there was a resource

management task (monitoring fuel levels), a communications task (adjusting radio frequencies in response to verbal commands), a systems monitoring task (monitoring lights and dials), and an unstable tracking task.

Testing schedule

Each subject reported to the Laboratory on *Sunday* afternoon and signed the informed consent prior to medical records review. Attachment of electrodes followed. Initial training was then conducted on several of the tests prior to the adaptation sleep period which began at 2200 on Sunday night. On *Monday*, there were three training sessions (at 0900, 1300, and 1700) during which subjects completed all tests in the sequence to be used for the remaining 8 days. Subjects slept from 2200-0800 on Monday night. On *Tuesday* (a control day), the schedule was the same except the subject was not permitted to sleep at night. Instead, he received the first of one of three interventions: 1) a 2-hour nap with 10 mg zolpidem tartrate 2) a 2-hour nap with placebo, or 3) a 2-hour rest period during which no sleep occurred. Only the placebo-nap condition and the resting condition were used for this analysis. Each intervention began at 2100 and ended at 2300. In the nap condition, electrode attachments for the muscle (EMG) and eye (EOG) measurements were completed and subjects were escorted to a bedroom for the 2-hour nap. In the rest condition, subjects spent their time watching television and conversing with staff members (they were monitored at all times to ensure that no sleep occurred during the rest period). On *Wednesday* (a test day), the first post-intervention test session began at 0100 (2 hours after the nap or rest period) and subsequent sessions occurred every 4 hours (sessions started at 0100, 0500, 0900, 1300, and 1700). Subjects were allowed to sleep Wednesday night from 2200 to 0800. The schedule on *Thursday* and *Saturday* (control days) was the same as the one on Tuesday, and the schedule on *Friday* and *Sunday* (test days) was the same as the one on Wednesday. The *second Monday* of each subject's participation was a recovery day in which the control-day schedule (i.e., the one for Tuesday, Thursday, and Saturday) was followed. On the morning of the *second Tuesday*, subjects were evaluated and released. See Table 2 for a full schedule of each day's test sessions.

Results of present 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.

Table 2.
Napping study testing schedule.

Time	Sunday In Process	Monday Training	Tuesday Baseline	Wednesday Test	Thursday Recovery	Friday Test	Saturday Recovery	Sunday Test	Monday Recovery	Tuesday Release
0100				VAS/**POMS/ MATB**		VAS/**POMS/ MATB**		VAS/**POMS/ MATB**		
0200				VAS/RTSW EEG/EP		VAS/RTSW EEG/EP		VAS/RTSW EEG/EP		
0300				VAS/POMS/ SYNWORK MiniSim		VAS/POMS/ SYNWORK MiniSim		VAS/POMS/ SYNWORK MiniSim		
0400				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0500				VAS/**POMS/ MATB**		VAS/**POMS/ MATB**		VAS/**POMS/ MATB**		
0600				VAS/RTSW EEG/EP		VAS/RTSW EEG/EP		VAS/RTSW EEG/EP		
0700				VAS/POMS/ SYNWORK MiniSim		VAS/POMS/ SYNWORK MiniSim		VAS/POMS/ SYNWORK MiniSim		
0800		Wakeup Breakfast	Wakeup Breakfast	VAS Breakfast	Wakeup Breakfast	VAS Breakfast	Wakeup Breakfast	VAS Breakfast	Wakeup Breakfast	Wakeup Breakfast
0900		VAS/POMS/ MATB	VAS/POMS/ MATB	VAS/POMS/ MATB	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	Debrief
1000		VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	Release
1100		VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	
1200		VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	VAS/RTSW Lunch	
1300		VAS/POMS/ MATB	VAS/POMS/ MATB	VAS/POMS/ MATB	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	
1400		VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	
1500	Arrive/ Inservice	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	
1600	Medical Screening	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1700	Electrode Hook-up	VAS/POMS/ MATB	VAS/POMS /MATB	VAS/POMS/ MATB	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	VAS/**POMS/ MATB**	
1800		VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	VAS/RTSW EEG/EP	
1900	Dinner	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	VAS/POMS/ SYNWORK MiniSim	
2000		VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	VAS/RTSW Dinner	
2100	Vitals	PT	Drug Lights out	PT	Placebo Lights out	PT	Rest	PT	PT	
2200	Lights Out	Lights Out		Lights Out		Lights Out		Lights Out	Lights Out	
2300			Wakeup VAS		Wakeup VAS		Wakeup VAS			
2400										

Note: Drug=10 mg zolpidem; Placebo=matching placebo tablets; Rest -- counter-balanced. Only looked at the placebo nap and rest days

POMS= Profile of Mood States; MATB=Multi Attribute Task Battery; PT=Physical Training

Eighteen subjects' data from the Napping study were merged with six subjects' data from the Modafinil study (at five similar testing times) to create one data file. Because of differences between the groups during baseline, the 3 baseline sessions at 1100, 1500, and 1900 were averaged for each subject (in each study). These averaged scores were subtracted from each subject's test session scores, creating a difference score for each session (difference score = raw score – averaged baseline score). Therefore, a positive difference score indicated a higher score than baseline, whereas a negative score indicated a lower score than baseline. A three-way mixed factorial analysis of variance (ANOVA) was used for each set of data, with one grouping factor Group (Modafinil study or Napping study), and two repeated-measures factors Condition (Treatment or No Treatment) and Time (specific to each test). For the Condition factor, treatment was modafinil for the Modafinil group and a 2-hour nap for the Napping group. No treatment was placebo for the Modafinil study group and rest for the Napping study group.

POMS

Analyses for the POMS data were conducted using data collected from the Napping study at 0300, 0700, 1100, 1500, and 1900 and for the Modafinil study at 0325, 0725, 1125, 1525, and 1925. Several interactions occurred among the variables. A *condition by time by group* interaction occurred for Vigor ($F(4,88)=2.91$, $p=0.0258$) and Fatigue ($F(4,88)=2.59$, $p=0.0418$). The interactions were due to a larger difference between the two conditions (treatment versus no treatment) in the Modafinil group compared to the Napping group at the 0300, 0700, and 1100 sessions only (Figure 1).

A two-way interaction occurred between *time and group* for Tension ($F(4,88)=3.34$, $p=0.0135$). In the Modafinil group (with both treatment and no-treatment collapsed), scores significantly increased from 0300 to 0700, then decreased the remainder of the day. In the Napping group (with both treatment conditions collapsed), scores increased until 1100, after which they decreased before rising again at 1900 (Figure 2).

A *condition by time* interaction for Fatigue ($F(4,88)=3.25$, $p=0.0155$) was due to increased Fatigue under the No-treatment condition compared to the Treatment condition at 0300, 0700, and 1100, but not at 1500 and 1900. The relationship is depicted in Figure 3.

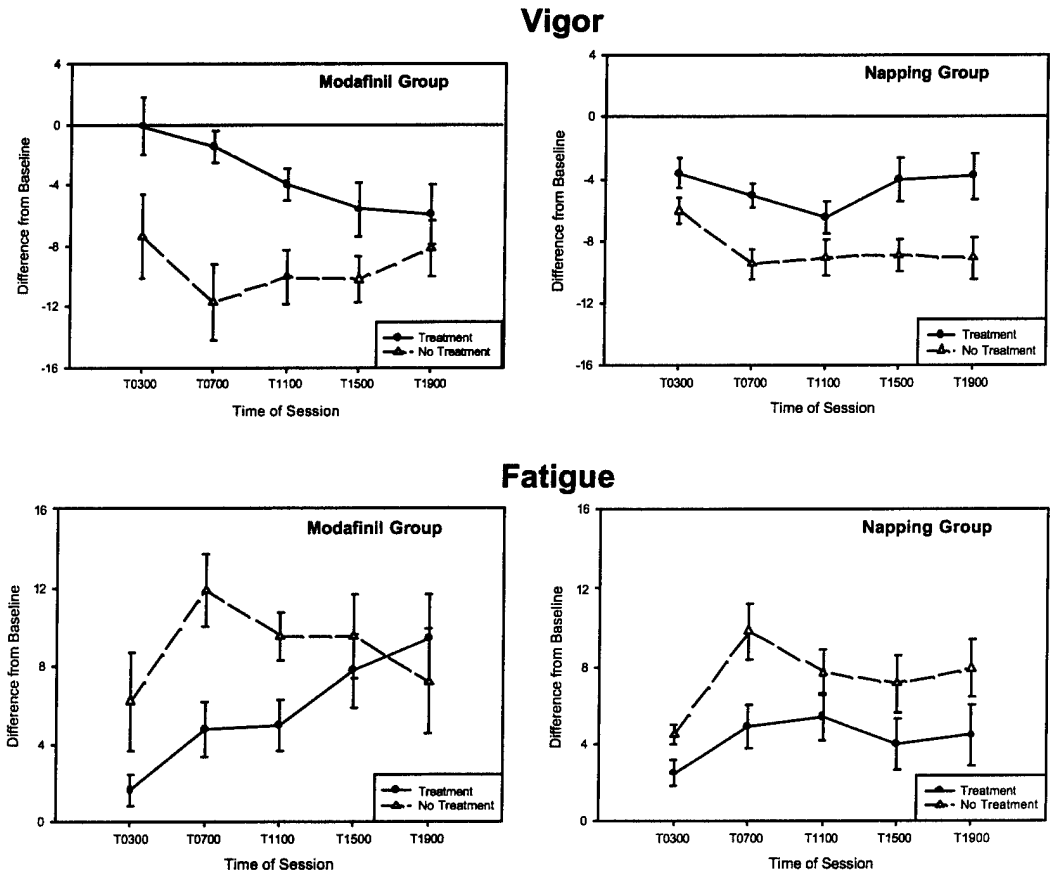

Figure 1. A *condition x time x group* interaction for POMS Vigor and Fatigue. A larger effect is shown from modafinil (versus placebo) than from napping (versus rest only) at 0300, 0700, and 1100.

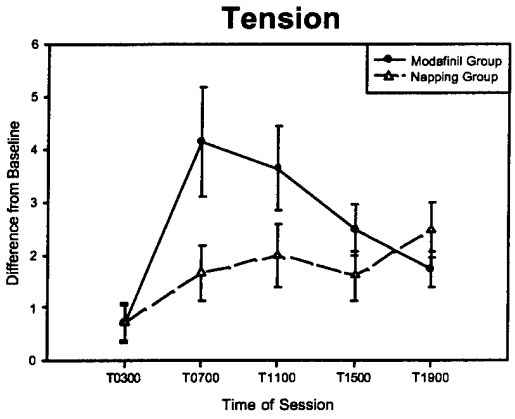

Figure 2. A *time by group* interaction for POMS Tension. This graph shows a marked initial increase in tension in the Modafinil study as opposed to a less pronounced effect in the Napping study.

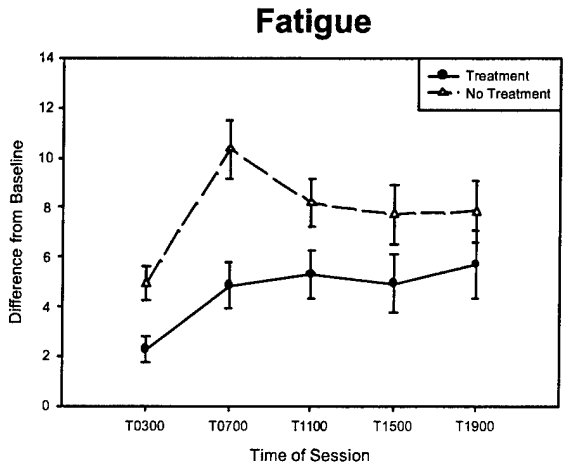

Figure 3. A *condition by time* interaction for POMS Fatigue. The benefits of modafinil and napping (collapsed across groups) can be seen at sessions 0300, 0700, and 1100.

Results indicated a *condition* main effect for Vigor ($F(1,22)=19.90$, $p=0.0002$), Fatigue ($F(1,22)=12.15$, $p=0.0021$), and Confusion ($F(1,22)=14.57$, $p=0.0009$). Vigor scores were lower while Fatigue and Confusion scores were higher under the No-treatment condition compared to the Treatment condition (Modafinil and Napping groups averaged together). The means and standard errors are depicted in Table 3.

Table 3.
Means and standard errors of difference scores from the POMS for the *condition* effect.

	Vigor		Fatigue		Confusion	
	Mean	SE	Mean	SE	Mean	SE
Treatment	-4.33	0.44	4.61	0.46	1.18	0.16
No Treatment	-8.77	0.44	7.81	0.50	2.21	0.17

A *time* main effect showed a significant difference among the sessions for Tension ($F(4,88)=6.27$, $p=0.0002$), Vigor ($F(4,88)=4.20$, $p=0.0037$), Fatigue ($F(4,88)=5.64$, $p=0.0004$), and Confusion ($F(4,88)=6.12$, $p=0.0002$). All but Vigor were significantly lower at 0300 compared to the all other sessions, and Confusion scores also were lower at 1900 compared to 0700 and 1100 and 1500 ($p=.06$) (see Table 4). With regard to Vigor, the scores were higher at 0300 than elsewhere. Data from all scales show the increasing departure from baseline (well-rested levels) as sleep deprivation increased.

Table 4.
Means and standard errors of difference scores from the POMS factors for the *time* effect.

	Tension		Vigor		Fatigue		Confusion	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0300	0.72	0.30	-4.56	0.68	3.60	0.48	1.07	0.24
0700	2.28	0.49	-7.10	0.71	7.60	0.82	2.28	0.27
1100	2.40	0.49	-7.58	0.69	6.73	0.70	2.01	0.27
1500	1.82	0.37	-6.85	0.79	6.33	0.85	1.67	0.25
1900	2.28	0.41	-6.63	0.87	6.77	0.94	1.44	0.28

MATB

Analyses were conducted using MATB data collected from the Napping study at 0110, 0510, 0910, 1310, and 1710 and from the Modafinil study at 0330, 0730, 1130, 1530, and 1930. Although the sessions are approximately 2 hours apart for the two studies, it was determined that the times were close enough for this particular quasi-experimental comparison of the two treatments since one objective was to establish the relative efficacy of both strategies for sustaining *overall* alertness and performance. Four MATB sub-tasks (Communications, System Monitoring, Resource Management, and Tracking) were analyzed separately with three-way ANOVAs for Group (modafinil or napping), Condition (treatment, no-treatment), and Time (see session times above).

Communications

The data for the communications task included the mean reaction time (RT) for correct responses, the standard deviation of reaction times (SDRT) for correct responses, and the number of time-out (TO) errors. The ANOVA indicated only a *group* main effect for TO errors ($F(1,22)=5.16$, $p=0.0333$). The Modafinil group (with both active medication and placebo collapsed) showed higher reaction times overall compared to the Napping group (with both napping and rest conditions collapsed). The difference-from-baseline means are 0.31 and –0.05, respectively.

Another main effect occurred for *time* for the number of TO errors ($F(4,88)=2.37$, $p=.0587$). Contrasts among the means indicated a significant increase in TO errors between 0300 and 0700, and between 0300 and 1500. The TO errors dropped significantly from 1500 to 1900 ($p<.05$). The difference-from-baseline means for each of the five sessions are 0.82, 1.90, 3.00, 2.41, and 1.34.

System monitoring

Data for systems monitoring included RT for responding to lights, RT for responding to dial deviations, SDRT for lights, SDRT for dials, TO errors for lights, and TO for dials. A *condition by time by group* interaction was found for SDRT for lights ($F(4,88)=2.81$, $p=0.0300$). Analysis of simple effects indicated a difference between the groups at the Treatment condition at 1100 and 1500, and at the No-Treatment condition at 0700 (see Figure 4).

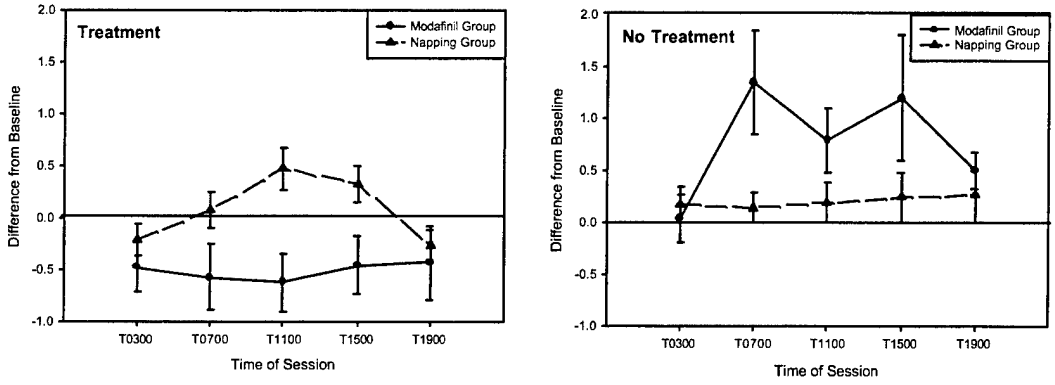

Figure 4. A *condition x time x group* interaction from the MATB Systems Monitoring subtask for SDRT for lights. Increased variability is apparent after napping versus modafinil at 1100 and 1500 (left panel) despite some apparent tendency for modafinil subjects to have been more variable at 0700 under placebo (right panel).

A *condition by group* interaction occurred for RT for lights ($F(1,22)=8.56$, $p=0.0078$), SDRT for lights ($F(1,22)=8.35$ $p = 0.0085$), TO errors for lights ($F(1,22)=5.26$, $p=0.0317$), and TO errors for dials ($F(1,22)=9.30$, $p=0.0059$). A significant difference between Treatment and No-Treatment occurred in the Modafinil group, with lower RTs, less variability, and lower TO errors to both lights ($p=.07$) and dials during the Treatment condition than during the No-Treatment condition. There were no differences between the two conditions in the Napping group (see Figure 5).

A *time by group* interaction occurred for RT for lights ($F(4,88)=2.39$, $p=0.0570$) and SDRT for lights ($F(4,88)=2.81$, $p=0.0301$). A significant difference among the times occurred in the Napping group, but not in the Modafinil group. Analysis of simple effects indicated a significant increase in RT and SDRT from 0300 to 0700, 1100, then a decrease at 1500 and 1900. RT and SDRT peaked at 1100. A graph of this interaction is shown in Figure 6. Note that in each of these, the treatment and no-treatment conditions, are collapsed (averaged together).

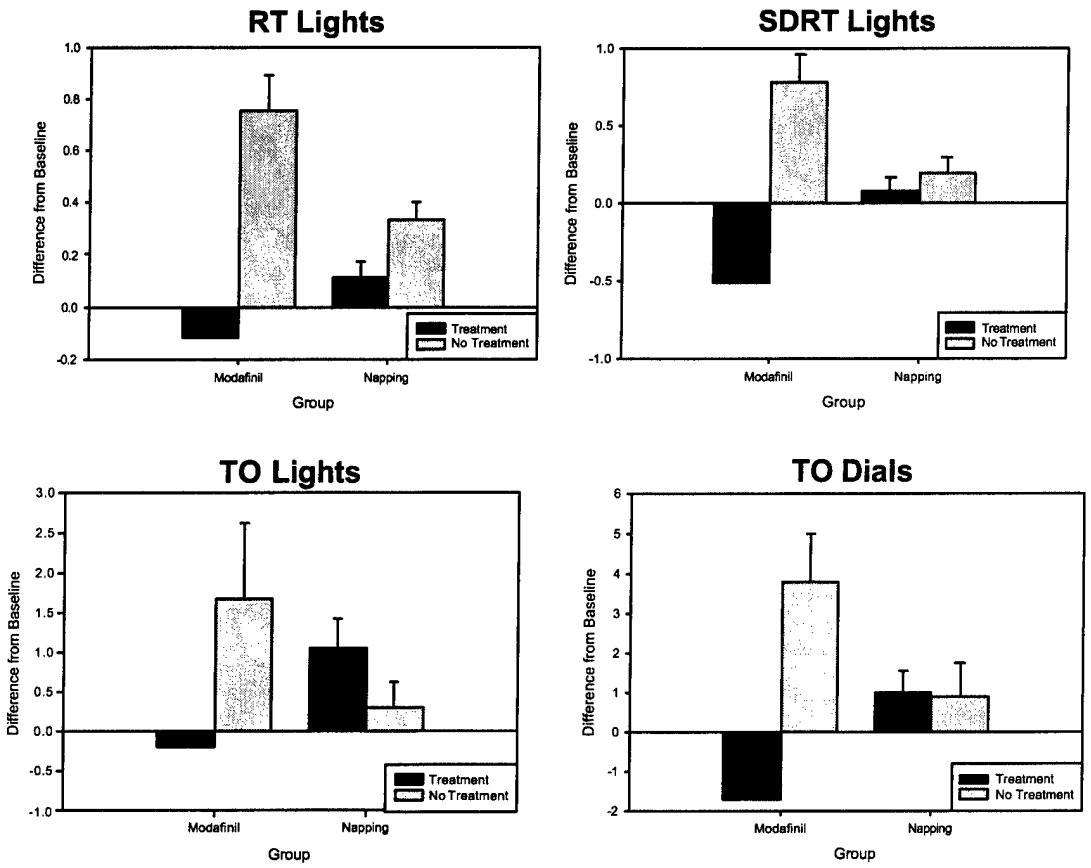

Figure 5. A *condition x group* interaction from the MATB Systems Monitoring subtask for RT for lights, SDRT for lights, TO errors for lights, and TO errors for dials. Lower RTs, TO errors, and less variability to light and dials are apparent during the Treatment condition, but not during the No Treatment condition.

A *condition by time* interaction was found for RT for dials ($F(4,88)=2.77$, $p=0.0322$). Analysis of simple effects indicated a difference between the conditions at all times except 1900. In general, RT was faster under the Treatment condition than under the No-Treatment condition (see Figure 7).

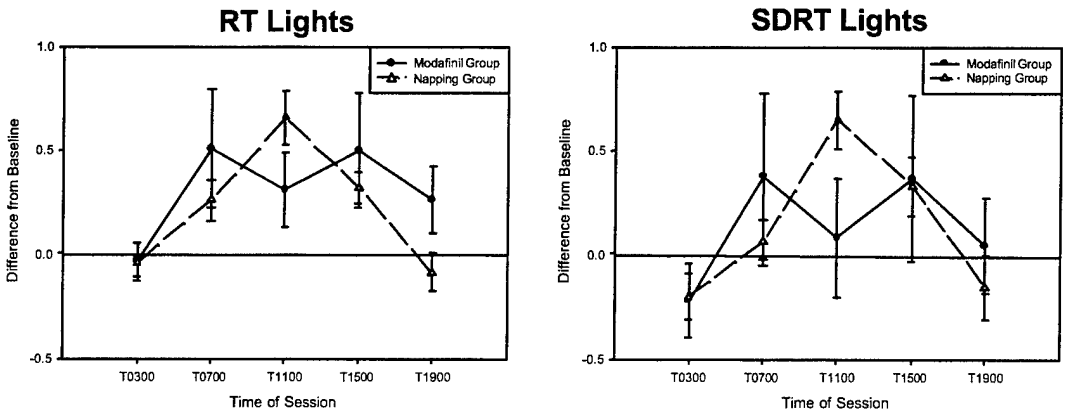

Figure 6. A *time by group* interaction from the MATB Systems Monitoring subtask for RT for lights and SDRT for lights. There were no session differences in the averaged performance (modafinil/placebo) in the Modafinil group while the converse occurred in the Napping group (napping/rest).

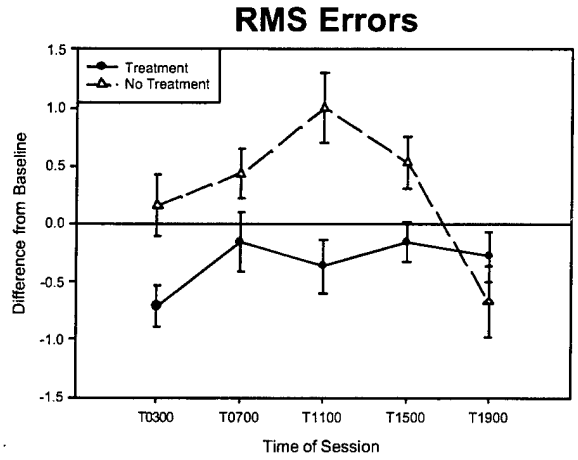

Figure 7. A *condition by time* interaction for the MATB Systems Monitoring subtask for RT for dials. Better overall performance occurred under the treatments (modafinil and napping) compared to the no-treatment condition (placebo and rest).

Condition main effects were found for RT for lights ($F(1,22)=23.47$, $p=0.0001$), RT for dials ($F(1,22)=7.50$, $p=0.0120$), SDRT for lights ($F(1,22)=11.75$, $p=.0024$), and TO errors for lights ($F(1,22)=8.45$, $p=0.0082$). Under the Treatment condition, participants revealed decreased reaction times, variability, and TO errors compared to the No-treatment condition. The means and standard errors are listed in Table 5.

Table 5.
Means and standard errors for Systems Monitoring subtask *condition* effects.

	Treatment Condition		No-Treatment Condition	
	Mean	SE	Mean	SE
RT for Lights	0.06	0.05	0.43	0.07
RT for Dials	-0.33	0.10	0.29	0.13
SDRT for Lights	-0.06	0.07	0.34	0.09
TO Errors for Lights	0.74	0.29	1.61	0.51

A *time* main effect occurred for RT for lights ($F(4,88)=6.62$, $p=.0001$), RT for dials ($F(4,88)=4.43$, $p=.0026$), SDRT for lights ($F(4,88)=6.34$, $p=.0002$), and TO errors for dials ($F(4,88)=4.14$, $p=.0040$). Comparisons among the means indicated lower RT, variability, and errors at 0300 compared to 0700, 1100, and 1500 (not at 0700 for RT for dials), with lower RT, variability, and errors at 1900 compared to 1100 (except TO for dials) and 1500. The means and standard errors for these variables are shown in Table 6.

Table 6.
Means and standard errors for the MATB Systems Monitoring subtask *time* effects.

	RT for Lights		RT for Dials		SDRT for Lights		TO Errors for Lights	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0300	-0.04	0.07	-0.27	0.17	-0.20	0.09	-0.45	0.37
0700	0.32	0.11	0.15	0.17	0.14	0.13	1.72	0.91
1100	0.57	0.11	0.32	0.21	0.51	0.13	3.10	1.02
1500	0.37	0.09	0.19	0.15	0.34	0.14	1.36	0.65
1900	-0.00	0.08	-0.48	0.19	-0.11	0.12	-0.89	0.55

Resource management

The resource management task includes the mean deviation of fuel in tanks A and B from a constant level of 2500. No statistically significant effects were found on any of the measures from this subtask.

Tracking

Tracking data were defined as the root mean square (RMS) deviations of the tracking target from the center of the upper right-hand quadrant of the computer screen.

A *condition by group* interaction ($F(1,22)=24.98$, $p=0.0001$) indicated overall differences in RMS deviations between the two conditions for the Modafinil group, but not for the Napping group. The Modafinil group had significantly lower RMS deviations during the Treatment

condition (modafinil) than during the No-Treatment condition (placebo). The effects for both groups are shown in Figure 8.

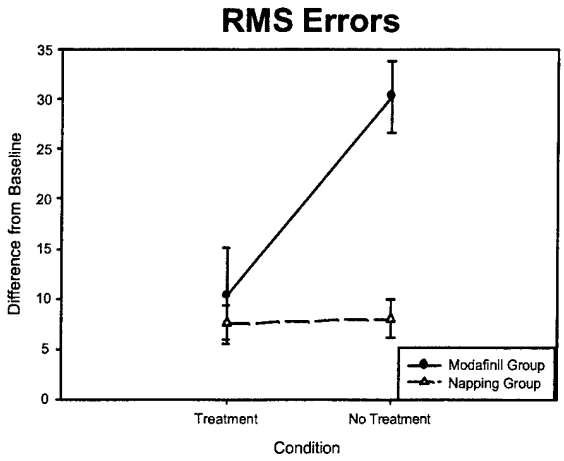

Figure 8. A condition by group interaction for RMS errors from the MATB Tracking subtask.

The ANOVA also indicated a *condition by time* interaction ($F(4,88)=3.85$, $p=0.0062$). This effect was due to increased RMS deviations under the No-Treatment condition (placebo and rest only averaged together) compared to the Treatment condition (modafinil and a nap averaged together) at 0700, 1100, and 1500, but not at 0300 and 1900 (Figure 8).

A *group* main effect occurred ($F(1,22)=4.08$, $p=.0556$) due to more RMS deviations for the Modafinil group than for the Napping group. The difference-from-baseline means were 15.25 and 7.77, respectively.

A *condition* main effect ($F(1,22)=26.48$, $p<.0001$) was due to increased RMS deviations under the No-treatment condition compared to the Treatment condition. The means were 5.70 and 13.58, respectively.

A *time* main effect also was found ($F(4,88)=6.17$, $p=0.0002$). The RMS deviations at 1100 and 1500 were significantly higher than those at 0300 and 1900. The means for the times, beginning at 0300, were 2.19, 10.82, 17.89, 12.49, and 4.79.

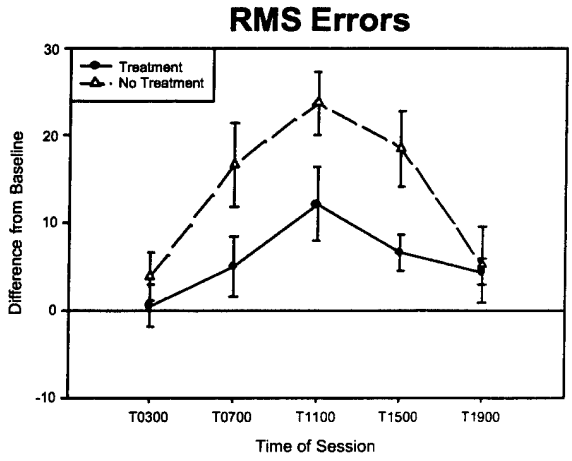

Figure 9. A *condition by time* interaction for RMS errors from the MATB Tracking subtask. While errors increased in both conditions, the treatments (modafinil and napping) attenuated the impact of sleep loss.

Discussion

The comparison of the effects of modafinil and napping on cognitive performance and subjective alertness indicates that the two countermeasures are effective in combating the usual decline in these measures during a period of sleep deprivation, but they are not comparable. Based on this quasi-experimental analysis in which data from two different studies were combined, it appears that modafinil is superior in maintaining alertness in comparison to naps.

The subjective mood data indicated that both countermeasures were successful at decreasing fatigue and confusion, and increasing vigor when compared to no intervention at all. However, when comparing modafinil and a nap, the data indicated that modafinil maintained a higher level of vigor and a lower level of fatigue than the nap, particularly in the early morning hours when the circadian dip in alertness is most problematic (Bonnet, 1990).

The performance data supported the subjective mood findings by showing that while both strategies attenuated performance losses during sustained wakefulness better than no countermeasure, modafinil was more efficacious than a nap. This was especially true of reaction time and errors of omission. As with subjective mood, modafinil's superiority was particularly evident in the early morning hours when performance is at its lowest.

While naps have been shown to improve performance during sustained operations, they do not totally eliminate the circadian dip which occurs in the early morning hours (Bonnet, 1990). This was apparent in the present study in both mood and performance in the Napping group. While naps were better than no countermeasure at all, the short period of sleep obtained during the nap was not enough to overcome the circadian dip in mood and performance. In the present study, subjects slept only an average of 73 minutes during the 120-minute period allotted for the

nap. Had the subjects been able to sleep longer, it is possible that the effects of the nap would have been more pronounced; however, most research indicates that even a 2-to-3- hour nap is not long enough to totally eliminate the circadian dip in performance (Gillberg, 1984; Naitoh, Englund and Ryman, 1982; Nicholson et al., 1985; Schweitzer, Muehlback and Walsh, 1992). In contrast, modafinil's alertness-promoting action and its half-life of approximately 8 to 13 hours was sufficient to overcome the early-morning circadian drive for sleep. These results support past research in which modafinil administered prior to significant sleep deprivation was found to reduce episodes of microsleeps and maintain well-rested levels of performance (Lagarde et al., 1995). In addition, a 400-mg dose of modafinil has been shown to arrest aspects of fatigue-related performance decrements even after 42 to 54 hours of continuous wakefulness (Wesensten et al., 2002). The side effects with modafinil are minimal, but as with any medication, they do occur. The most common events are nervousness and excitability (Laffont, 1996), but nausea and dizziness have been reported as well (Caldwell et al., 1999). It appears that finding an individualized dosing scheme that maximizes efficacy while simultaneously minimizing side effects will require effort. For this reason, and the fact that the long-term consequences of repeated modafinil exposure are currently not known, the choice between modafinil and naps should be made with caution. The doses of modafinil which produce the best effects in sustaining alertness and performance have been associated with problematic side effects in some individuals (Benoit et al., 1987; Caldwell et. al., 1999).

When given a choice between a wakefulness-promoting drug and sleep, one must take into account the feasibility of establishing a napping facility, the existence of sleep opportunities, the amount and quality of sleep one may obtain, the performance requirements of the job at hand, and the likelihood that a pharmacological versus a nonpharmacological approach will be accepted by personnel/managers. If it is possible to sleep well and obtain at least 2 hours of continuous sleep, then napping may be the best choice. However, several factors must be considered before deciding on a napping countermeasure. First, the preexisting sleep debt should not be excessive. Second, there must be opportunities to intersperse several naps within each 24-hour work period. Third, the task to be performed should not be overly tedious, leading to a high degree of boredom which unmasks sleepiness. It is known that the less stimulation a task provides, the more likely it is that sleepiness will disrupt performance (Elsmore et al., 1995; Wilkinson, 1969). Finally, the task should not be too vigilant-dependent because research indicates that reaction time is slower and cues are more frequently missed when sleepiness increases (Bonnet, 1991). If these criteria can be met, napping alone may be sufficient to offset the majority of fatigue-related decrements. However, if a nap is not possible, the length of the nap is short, the chances of obtaining quality sleep are remote (due to environmental or other factors), and the tasks to be performed require a high degree of speed, precision, and vigilance, a pharmaceutical may be considered. In military situations, schedules are often unpredictable, staffing may be limited due to the scope of the mission, sleep facilities may be inadequate or nonexistent, and the performance requirements may be highly error intolerant (Krueger, 1989). In combat military aviation for instance, there often is no choice except to fly a mission regardless of the level of fatigue, and falling asleep while flying has potential disasterous consequences. In these situations, a pharmacological fatigue countermeasure may be an option. However, even when this is the case, drugs should not be used improperly as a substitute for sleep, but only as an emergency measure for postponing sleep until adequate crew rest schedules can be implemented.

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Appendix.

Manufacturers list.

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

Altec Lansing Technologies, Inc.
Milford, PA 18337

Cephalon, Inc
145 Brandywine Parkway
West Chester, PA 19380

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