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ORIGINAL INVESTIGATION

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A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study

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Abstract *Rationale:* In 1998, the FDA approved modafinil for treating excessive daytime sleepiness in narcoleptics, and this has raised questions about the appropriateness of this compound for enhancing alertness in sleep-deprived controls. This study explored the efficacy of modafinil for maintaining the performance of volunteers required to accomplish highly demanding tasks despite sleep loss. *Objective:* The principal objective was to determine whether prophylactic doses of modafinil would attenuate decrements in aviator performance and arousal throughout 2 days and 1 night without sleep. *Methods:* Six pilots were exposed to two 40-h periods of continuous wakefulness. In one, three 200-mg doses of modafinil were given and in the other, matching placebos were administered. Helicopter simulator flights, resting EEGs, and Profile of Mood States (POMS) questionnaires were evaluated. *Results:* Modafinil attenuated sleep deprivation effects on four of six flight maneuvers, reduced slow-wave EEG activity, and lessened self-reported problems with mood and alertness in comparison to placebo. The most noticeable benefits occurred between 0330 and 1130 hours, when the combined impact of sleep loss and the circadian trough was most severe. The most frequently observed drug side effects were vertigo, nausea, and dizziness. These could have been related to: 1) the motion-based testing, 2) the use of a simulator rather than an actual aircraft (i.e., "simulator sickness"), and/or 3) the administration of more than 400 mg modafinil. *Conclusions:* Modafinil is a promising countermeasure for sleep loss in normals; however, additional studies aimed at reducing side effects are needed before it should be used in aviators.

Key words Modafinil · Alertness · Efficacy · Aviators · Simulator

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Introduction

Emergency workers and military personnel frequently confront situations in which they must perform for extended periods without adequate recovery sleep. This places them at risk for a host of problems associated with sleep deprivation. Humans need sleep for restitution of the body and brain (Horne 1978), and insufficient sleep has been associated with increased mental lapses, impaired information processing, decreased central nervous system arousal, and degraded mood and motivation (Dinges et al. 1997). These problems generally constitute what has come to be referred to as "fatigue", a term that "is widely used throughout government, industry, labor, and the public to indicate the effects of working too long, or following too little rest, and being unable to sustain a certain level of performance on a task" (p. 4, Dinges 1995).

Although several strategies for overcoming fatigue-related degradations have been explored, few are feasible for non-standard work environments. Well-planned work/rest schedules may minimize the amount of sleep loss in some settings, but they are impossible to implement successfully in unpredictable circumstances. Rigorous training may make simple tasks resistant to fatigue, but the ability to respond to novel demands remains impaired (Johnson 1982). Behavioral countermeasures, such as exercise, may temporarily improve alertness (Angus and Heslegrave 1985), but will probably produce detrimental aftereffects (LeDuc et al. 1998).

Stimulants are effective for maintaining performance, especially in monitoring and vigilance tasks which tend to unmask sleepiness in fatigued individuals. Dextroamphetamine is reliably efficacious (Caldwell et al. 1995, 1997, 1998), but its history of abuse makes it unpopular. Modafinil (Provigil), a new psychostimulant which shows promise for sustaining performance in sleepy personnel (Lagarde and Batejat 1995), is a more palatable alternative, but controlled studies in non-patients are scarce. However, because modafinil apparently reduces sleepiness without significant side effects or abuse potential, there is substantial interest in this compound.

The precise actions of modafinil, 2-[(diphenylmethyl)sulfinyl]acetamide, are unknown, but it appears to affect serotonergic and gamma-aminobutyric acid (GABA) sites in the central nervous system (CNS) (Cephalon 1998). Modafinil reduces GABA release in several areas of the brain including the cerebral cortex and the nucleus accumbens (Fuxe et al. 1996). It produces highly selective CNS stimulation with minimal effects on the peripheral nervous system (Lin et al. 1996), has a relatively low abuse potential (Lyons and French 1991), and exerts a minimal negative impact on sleep (Saletu et al. 1989). The most frequently used dosage range is 200–400 mg per day (usually administered as a single dose), but up to 600 mg per day is safe (Lagarde and Batejat 1995; Cephalon 1998). Peak blood concentration occurs in approximately 2–4 h and the half-life is approximately 8–13 h (Moachon et al 1996).

In narcoleptics, modafinil has been found to reduce daytime sleepiness while improving cognitive performance (Besset et al 1993; Boivin et al 1993; Cephalon 1998). In normals, it sustains alertness, as measured by the electroencephalogram (EEG), in younger (Goldenberg and Weil 1986) and older (Saletu et al. 1986) subjects. Compared to placebo, 200 mg curtails microsleeps and maintains more normal (i.e., rested) mental states without the anxiety sometimes associated with psychostimulants (Lagarde et al. 1995). Cognitive performance is reportedly maintained at non-sleep-deprived levels (Lagarde and Batejat 1995).

Modafinil may offer a safer alternative to traditional stimulants (i.e., amphetamines), despite some anecdotal reports suggesting that it may be less effective. Additional studies on this issue are required. A laboratory study by Pigeau et al. (1995) suggests that 300 mg modafinil equates to 20 mg dextroamphetamine at least in terms of maintaining mood and cognitive performance close to non-sleep-deprived levels. Unfortunately, actual "real-world" performance studies on this compound are nonexistent. To date, modafinil has not been adequately tested in field situations (Akerstedt and Ficca 1997) or in high-fidelty work simulations, and because of this, additional research is required to assess its utility for preventing performance decrements in sleep-deprived workers engaged in tasks such as operating complex machinery (e.g., automobiles, aircraft, flight simulators).

Materials and methods

Objectives

The primary objective of the present study was to determine the efficacy of the stimulant modafinil, 600 mg, for overcoming the effects of sleep deprivation in pilots. Specifically, the study sought to 1) determine whether the simulator flight performance of sleep-deprived aviators was maintained at more normal levels by modafinil than placebo; 2) establish whether modafinil in comparison to placebo significantly attenuated physiological indicators of fatigue in sleep-deprived pilots; and 3) determine whether the subjective mood ratings of sleep-deprived volunteers were sustained more closely to pre-deprivation levels by modafinil than placebo. In addition, the study explored the utility of using modafinil to improve the alertness and performance of fatigued aviators without producing unwanted side effects.

Methods

This investigation was approved by the US Army Aeromedical Research Laboratory's (USAARL) Scientific Review and Human Use Committees prior to execution. In addition, it was approved by the Human Use Committee of the US Army Medical Research and Material Command. Informed consent was obtained from each participant prior to testing, and none of the volunteers were paid for their assistance with this research.

Subjects

Eight male helicopter pilots were enrolled in the study. The first volunteer was unable to complete the study due to severe nausea and headache that 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 proficient in the UH-60). The six aviators who made up the final sample were aged 37.3 years (ranging from 29 to 46 years), and possessed 2173.3 total hours of flight experience (ranging from 900 to 5500 h). An average of 492.5 flight hours had been accrued in the UH-60 helicopter.

Each volunteer was individually tested during a 1-week stay in the laboratory. Males were used exclusively 1) to facilitate comparability with the majority of earlier sleep-deprivation studies in which Dexedrine was evaluated, and 2) for safety reasons since reproductive toxicological and other potentially gender-specific effects of modafinil had not been studied adequately. Subjects passed a medical evaluation prior to admission. None of the volunteers was found to have evidence of past psychiatric or cardiac disorder, a history of sleep disturbances, or current significant illness. All refrained from consuming alcoholic and caffeinated beverages and any type of medication (other than acetaminophen or ibuprofen) throughout the protocol. Each volunteer was instructed to discontinue consumption of caffeinated beverages several days prior to arriving at the laboratory.

Apparatus

Drug and placebo tablets

These were supplied by Cephalon, Inc. (West Chester, Penn., USA). Active tablets contained 100 mg modafinil. In one deprivation period, two active tablets (200 mg) were administered at each dose interval (three per sleep-deprivation period). In the other deprivation period, two matching placebo tablets were administered at each dose interval. The testing sequence (placebo/modafinil or modafinil/placebo) was fully counterbalanced. The 600-mg dose level was administered to each volunteer because, based upon published literature, it was felt that this would be necessary to sustain performance at normal levels.

Vital signs

Oral temperatures, pulse, and blood pressures were collected with an IVAC Model number 4200.

Simulator flight testing

This was conducted in a UH-60 helicopter simulator equipped with computer-generated visual display (set for standard daytime flight) and a computer system for analyzing aspects of simulator control such as heading, airspeed, and altitude control.

EEG data

EEG data were recorded from the midline electrodes Fz, Cz, and Pz (referenced to linked mastoids) via Grass silver-cup electrodes filled with SigmaGel electrolyte. These sites were chosen in an effort to explore generalized EEG changes that occurred during the waking periods without focusing on hemispheric differences. 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. Electrodes were applied on the first day of the study and worn until the participant was released. Electrode impedances were kept at 5000 ohm or less.

POMS questionnaires

POMS questionnaires consisted of 65-item tests, measured mood on six scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment (McNair et al. 1981).

Procedure

Simulator flights

During each flight, subjects flew precision maneuvers such as straight-and-levels, climbs, descents, and turns of the types typically flown in a UH-60 aircraft (Department of the Army 1988). The same sequence of maneuvers was used for every subject, and all were performed under simulated instrument conditions; in other words, the views of the terrain outside of the cockpit were obscured by white/grey "clouds" requiring the pilots to fly by instrument references only. No wind or turbulence was included (wind buffeting would have made it more difficult to precisely control the flight path), and the scene illumination was set equivalent to 12 noon regardless of the actual time of day. The first group of maneuvers was flown with the automatic flight control system (AFCS) trim engaged (the normal mode for the UH-60), and the second group was flown with the AFCS trim turned off to increase pilot workload (this system stabilizes the aircraft, making it easier to fly).

Important performance data consisted of the accuracy with which subjects maintained heading or direction (measured in compass degrees from 0 to 360 degrees), altitude or height above the ground (measured in feet above mean sea level), and airspeed or forward motion (measured in knots, with 1 knot being equivalent to 1.15 miles/h). Other important parameters indicated how well participants executed turns (by measuring variables such as degrees of aircraft roll or tilt) and how well they completed both climbs and descents (by measuring the rate of altitude change in feet/min). Steeply banked turns (greater than 3 degrees) and rapid climbs/descents (greater than 500 feet/min) tend to be very uncomfortable for aircraft occupants. A flight computer measured the performance of each pilot 2 times per second, and these data samples were averaged for each maneuver. Subjects who established and maintained flight control very close to ideal standards earned scores near 100, but those who missed the target levels by a wide margin or failed accurately to maintain a target level once that level was reached earned much lower scores. There was one composite performance score from each iteration of each maneuver during every one of the 16 test flights per subject.

EEG evaluations

During each test, volunteers were instructed to sit quietly in a sound-attenuated, electrically-shielded booth with eyes open for 2 min followed by eyes closed for 2 min. EEG data were sampled at a rate of 200 Hz and stored on optical disk. Records were scanned for three relatively artifact-free, non-overlapping 2.5-s epochs (a software-driven requirement) on which absolute power values (expressed in V^2) were calculated via a computerized Fast Fourier Transformation (FFT) algorithm which utilized a bin width of 0.4 Hz. A Hamming window was applied. This was done for each of four bands: 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). One set of power values for each of the four electrode sites under eyes closed and eyes open was analyzed. Although an effort was made to ensure that subjects remained completely awake during data collection, it obviously was not possible to eliminate brief transitions into what may have been stage 1 or 2 sleep because of the level of sleep pressure that was present due to the deprivation. Thus, there were epochs in which frank theta activity was observed; however, the technician who selected the scoring epochs was blind to the dose condition and attempted to select epochs that were representative of the entire record as a whole.

POMS

Participants were presented with 65 words which described mood states, and for each, he indicated on a computerized answer sheet how well it described the way he was presently feeling. This 5-min test yielded scores on the six scales mentioned earlier.

Testing schedule

The volunteer reported to the laboratory on Sunday, and on Monday, he completed three simulator training flights, each of which was followed by EEG and mood testing. After training sessions at 0900, 1300, and 1700 hours, he retired for the day (at 2300 hours). Following an 0700 hour wake-up on Tuesday, there were three baseline test sessions, but the aviator was not allowed to go to sleep in the evening. Instead, he was given his first drug/placebo dose at 2300 hours and a subsequent dose was given at 0300 and at 0700 hours. On Wednesday, testing began with a simulator flight 2 h 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 hours). Afterward, the aviator retired for the day at 2300 hours. On Thursday, the participant repeated the same schedule used on Tuesday; there were three test sessions during the day, after which 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 hours. On Friday, the subject repeated the Wednesday schedule, beginning with his first simulator flight at 0100 hours, and ending with an 8-h recovery sleep period in the evening (drug/placebo doses again were administered at 0300 and 0700 hours). On Saturday, the aviator was released. The schedule is shown in Table 1.

Although the amount of time from the last modafinil dose until the first baseline test on the subsequent testing day (in the case in which the drug was given on Wednesday as opposed to Friday) was insufficient for complete drug elimination, it is unlikely that this confounded the results. The reason is that, according to Cephalon's unpublished data, plasma levels of at least 2.0 µg/ml modafinil are necessary to produce measurable wake-promoting effects. Pharmacokinetics data predicted that between the last drug administration and the subsequent test session (26 h later), modafinil levels would have fallen to 0.6 µg/ml which is only 30% of the 2.0 µg/ml level. By the time of the first placebo test session on Friday morning (in the case in which modafinil was given midweek), 43 h would have elapsed since the last modafinil dose, and this would have yielded a predicted plasma concentration of less than 0.1 µg/ml, or 95% lower than the amount of drug required to produce measurable effects. In addition, comparisons between the

Table 1 Testing schedule

Time	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
0000		Sleep	Sleep		Sleep		Sleep
		^	^	Simulator	^	Simulator	^
		^	^	EEG	^	EEG	^
		^	^	Drug/PBO	^	Drug/PBO	^
		^	^	POMS	^	POMS	^
0400		^	^		^		^
		^	^	Simulator	^	Simulator	^
		^	^	EEG	^	EEG	^
		^	^	Drug/PBO	^	Drug/PBO	^
		Wakeup	Wakeup	POMS	Wakeup	POMS	Wakeup
0800		Training	Simulator	Simulator	Simulator	Simulator	Electrode removal
			EEG	EEG	EEG	EEG	
			–	–	–	–	
			POMS	POMS	POMS	POMS	
1600							
		Training	Simulator	Simulator	Simulator	Simulator	
	Start		EEG	EEG	EEG	EEG	
			–	–	–	–	
2000	EEG hookup		POMS	POMS	POMS	POMS	
		Exercise	Exercise	Exercise	Exercise	Exercise	
		POMS		POMS		POMS	
	Bedtime	Bedtime	Drug/PBO	Bedtime	Drug/PBO	Bedtime	
2400			POMS		POMS		

Drug=200 mg modafinil; PBO=matching placebo tablets. Drug and placebo were counterbalanced between subjects. *POMS*=Profile of Mood States, *MATB*=multi-attribute task battery

modafinil and placebo baselines revealed that only two of 28 possible flight, EEG, and POMS comparisons were significantly different, and one of these was in the opposite direction of the other. Thus, it is improbable that postdrug data were confounded despite modafinil's long half-life and the relatively short interval between the modafinil and placebo conditions.

Data analysis

All data were analyzed with BMDP 4 V, repeated measures analysis of variance (ANOVA). There was a minimum of two within-subjects factors (drug and session). Significant interactions (those with P levels ≤0.05) were followed by analyses of simple effects. All results were checked for sphericity violations, and where these were found, Huynh-Feldt adjusted degrees of freedom were utilized.

Results

Flight performance data

Scores from the three baseline flights (at 0900, 1300, and 1700 hours) and five deprivation flights (0100, 0500, 0900, 1300, and 1700 hours) under placebo versus modafinil were analyzed with a three-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 except the left descending turn.

Scores from the four straight-and-levels (based on heading, altitude, airspeed, and roll control during the four iterations of this maneuver) revealed a drug-by-session interaction [$F(7,35)=3.24$, $P=0.0093$]. There were no differences during the three baseline sessions (predrug) or the first two deprivation sessions (at 0100 and 0500 hours), but control was poorer under placebo than modafinil at 0900 hours ($P<0.05$) (Fig. 1, top panel). Analysis of this maneuver also yielded an iteration main effect [$F(3,15)=15.59$, $P=0.0001$], due to superior performance on iteration 1 than on all the following iterations, and poorer performance on the fourth iteration than on all the preceding ones ($P<0.05$).

Performance on the two climbs (based on heading, airspeed, slip, roll, and vertical speed control) indicated no drug-related or session-related effects. However, iteration 1 was associated with better performance than iteration 2 [$F(1,5)=8.78$, $P=0.0314$].

Descent scores (representing the composite of heading, airspeed, slip, roll, and vertical speed scores from the three descents) revealed a drug-by-session interaction [$F(7,35)=4.13$, $P=0.0021$]. Analysis of simple effects indicated there was a difference between the conditions at the 1300 hour baseline flight (placebo better than modafinil, $P<0.05$) followed by a statistically significant reversal (modafinil better than placebo) at the 1300 hour deprivation flight ($P<0.05$) (Fig. 1, middle panel). Also, iteration 2 was associated with better performance than iteration 3 [$F(2,10)=4.91$, $P=0.0327$].

Performance on the two left standard-rate turns (based upon how well subjects maintained turn rate, airspeed, slip, roll, and vertical speed) showed a drug-by-session interaction [$F(7,35)=2.23$, $P=0.0548$]. This was

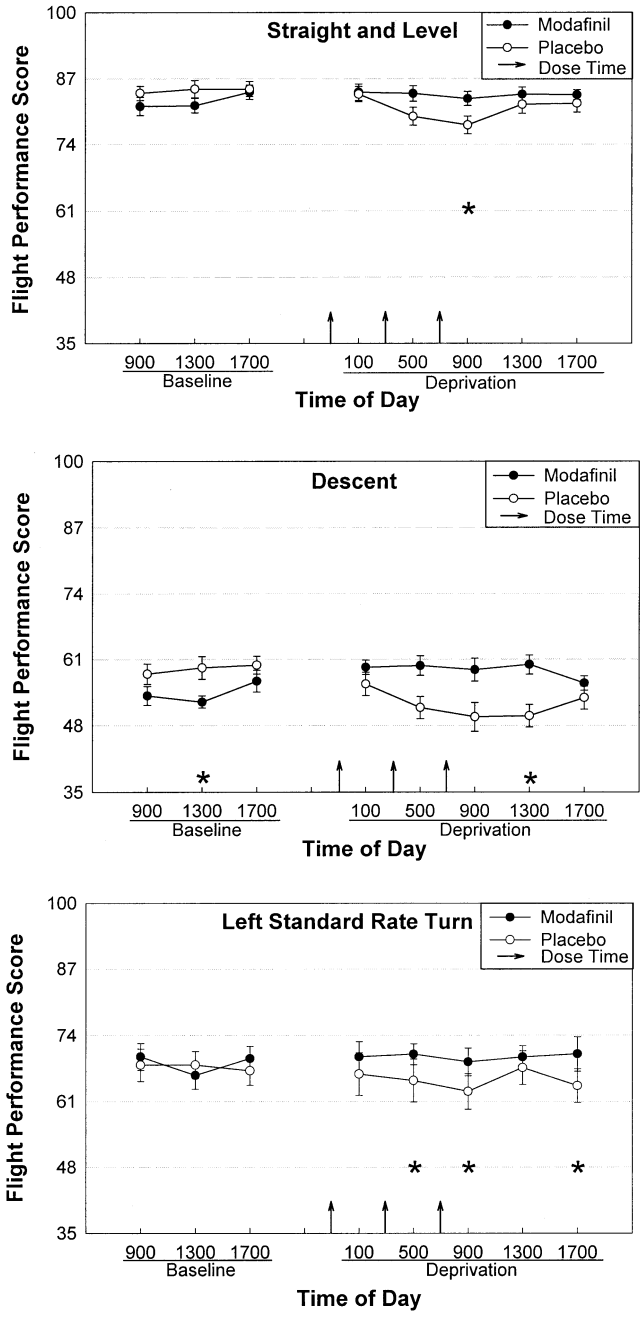

Fig. 1 The effects of modafinil versus placebo on performance of various flight maneuvers. *Top panel*: drug by session interaction for straight-and-level maneuver. *Middle panel*: drug by session interaction for descent. *Bottom panel*: drug by session interaction for left standard rate turn. *Error bars* delineate boundaries determined by SEM. *Asterisks* indicate significant simple effects for interactions

due to the absence of predrug (baseline) differences or subsequent differences at 0100 hours in the deprivation period, compared to significant decrements under placebo versus modafinil at the 0500, 0900, and 1700 hour flights on the sleep-deprivation day (Fig. 1, bottom panel). A drug-by-iteration interaction [$F(1,5)=8.35$, $P=0.0342$] was because of drug-related differences during the second turn (flown without the AFCS), but not the first. In addition, there was a drug main effect [$F(1,5)=8.65$, $P=0.0322$] due to better overall performance under modafinil than placebo (the means were 69.3 versus 66.2, respectively), and an iteration main effect [$F(1,5)=37.98$, $P=0.0016$] due to superior performance on the first than the second iteration.

Right-standard-rate-turn scores (based on the average of turn rate, altitude, airspeed, slip, and roll) revealed no drug-related effects across the three iterations of this maneuver; however, there was a tendency toward a drug main effect in which modafinil appeared to be slightly better than placebo ($P=0.0658$). There was also an iteration main effect [$F(2,10)=5.49$, $P=0.0246$], due to better performance on the second than third iteration ($P<0.05$).

Flight performance on the left descending turn (reflecting the composite of turn-rate, airspeed, slip, roll, and vertical-speed control accuracy) indicated a drug main effect [$F(1,5)=6.47$, $P=0.0516$] due to poorer performance under placebo than under modafinil. The means for the placebo and modafinil conditions were 48.2 and 51.7, respectively.

EEG

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). The ANOVAs consisted of three factors: drug (modafinil versus placebo), session (1015, 1415, and 1815 hours on the baseline day; and 0215, 0615, 1015, 1415, and 1815 hours on the deprivation day), and eyes (eyes open, eyes closed).

Delta activity

Analysis of the slowest-wave EEG revealed several effects. A drug-by-eyes interaction at Fz [$F(1,5)=8.53$, $P=0.0330$] was due to less delta under modafinil versus placebo at eyes closed, but no difference at eyes open. At Cz, a similar effect [$F(1,5)=10.30$, $P=0.0237$] was due to the fact that, while there were drug-related differences both at eyes open and eyes closed, it was larger when subjects closed their eyes (i.e., the amount of delta was much lower under modafinil versus placebo). A similar trend occurred at Pz, although it did not reach statistical significance ($P=0.0683$). There were main effects for drug at Fz [$F(1,5)=21.90$, $P=0.0054$], Cz [$F(1,5)=12.15$, $P=0.0175$], and Pz [$F(1,5)=10.45$, $P=0.0231$], all of which were due to higher delta power under placebo than modafinil. Also, a main effect of eyes was demonstrated at Fz [$F(1,5)=11.60$, $P=0.0191$], Cz [$F(1,5)=10.54$, $P=0.0228$] and Pz [$F(1,5)=14.13$, $P=0.0132$], all of which were due to higher delta power at eyes closed than at eyes open.

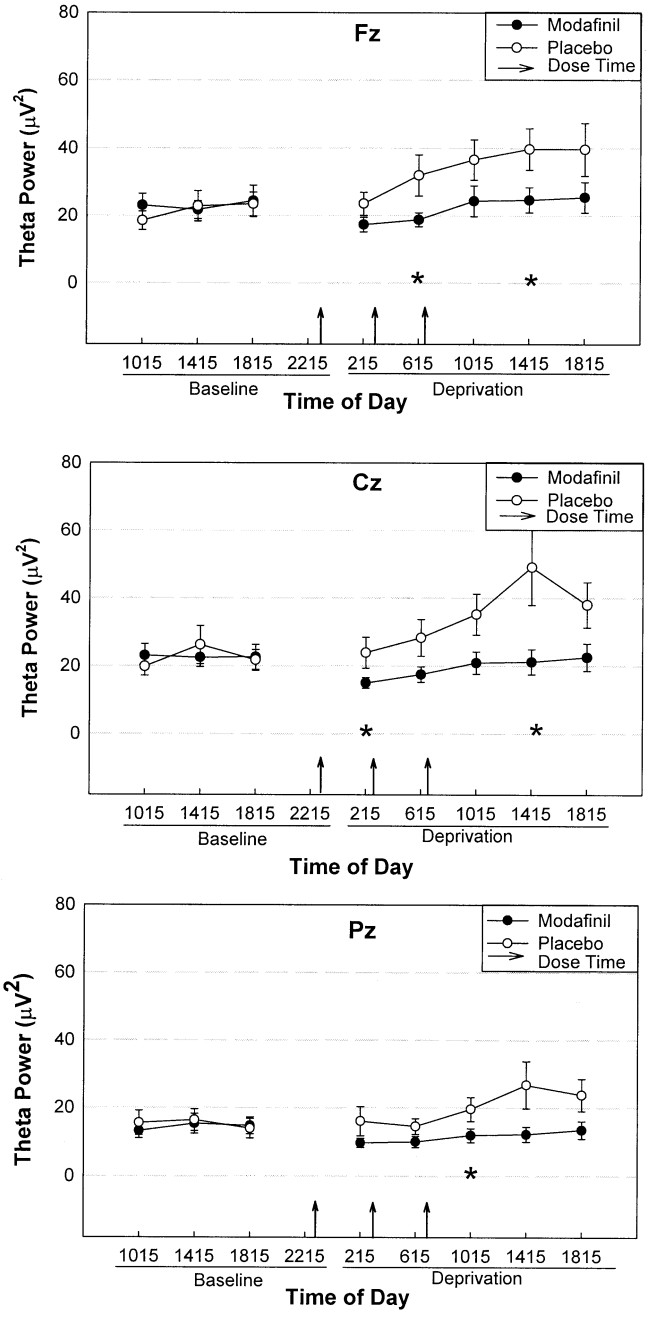

Fig. 2 The effects of modafinil versus placebo on slow-wave EEG activity. *Top panel*: drug by session interaction for theta EEG activity at FZ. *Middle panel*: drug by session interaction for theta EEG activity at CZ. *Bottom panel*: drug by session interaction for theta EEG activity at PZ. *Error bars* delineate boundaries determined by SEM. *Asterisks* indicate significant simple effects

Theta activity

Analysis of theta activity, which is known to increase with sleep deprivation, showed drug-by-session interactions at Fz [$F(7,35)=2.56$, $P=0.0305$], Cz [$F(7,35)=3.00$, $P=0.0141$], and Pz [$F(7,35)=2.41$, $P=0.0402$]. No differences between the sessions were observed during baseline, but during the deprivation period, there was less theta at Fz under modafinil versus placebo at 0615 and 1415 hours. At Cz, there was less theta under modafinil than placebo at 0215 and 1415 hours, with a similar tendency at 1015 hours ($P=0.06$). At Pz, there was a difference at 1015 hours and a tendency at 1415 hours ($P=0.06$). Effects for each electrode site are shown in Fig. 2. Drug-by-eyes interactions occurred at Fz [$F(1,5)=36.20$, $P=0.0018$], Cz [$F(1,5)=13.54$, $P=0.0143$], and Pz [$F(1,5)=6.94$, $P=0.0463$] because the attenuation of theta under modafinil compared to placebo was more pronounced with eyes closed than eyes open. A session by eyes interaction occurred at electrode site Cz [$F(7,35)=2.61$, $P=0.0281$] due to more theta activity at eyes closed than eyes open at each session except the 1015 hour baseline session. A drug main effect occurred at Fz [$F(1,5)=16.26$, $P=0.0100$], Cz [$F(1,5)=18.06$, $P=0.0081$], and Pz [$F(1,5)=6.76$, $P=0.0482$] due to an overall reduction of theta activity under modafinil. A main effect also occurred for session at sites Fz [$F(7,35)=8.97$, $P<0.0001$], Cz [$F(7,35)=6.97$, $P<0.0001$], and Pz [$F(7,35)=3.60$, $P=0.0051$]. A significant linear trend at each site showed a general increase in theta activity as the day progressed. In addition, a significant quadratic trend occurred at sites Cz and Pz due to increased theta at 1415 hours on baseline, a decrease at 1815 hours, and then a steady increase in activity from 0215 until 1415 hours on the deprivation day. Significant main effects for eyes occurred at Fz [$F(1,5)=63.32$, $P=0.0005$], Cz [$F(1,5)=69.81$, $P=0.0004$], and Pz [$F(1,5)=44.92$, $P=0.0011$], all of which were due to higher theta activity during eyes closed than during eyes open.

Alpha and beta activity

There were no drug-related effects on either the alpha or beta bands. Alpha activity did demonstrate a session-by-eyes interaction at Fz [$F(7,35)=4.14$, $P=0.0021$] and Cz [$F(7,35)=2.54$, $P=0.0320$], as well as a session main effect at Fz [$F(7,35)=5.68$, $P=0.0002$] and Cz [$F(7,35)=3.85$, $P=0.0033$]. In the beta band, there was a significant session-by-eyes interaction at Pz [$F(7,35)=2.50$, $P=0.0342$], and main effects for eyes at Fz [$F(1,5)=13.86$, $P=0.0137$], Cz [$F(1,5)=19.13$, $P=0.0072$], and Pz [$F(1,5)=12.97$, $P=0.0155$]. These effects are not pursued further here, because in the absence of drug related effects, they do not bear directly on the area of interest.

POMS

The scores for each scale (vigor-activity, fatigue-inertia, confusion bewilderment, tension-anxiety, depression-dejection, and anger-hostility) were analyzed individually using two-way ANOVAs for drug (modafinil, placebo) and session (1125, 1525, and 1925 hours on the baseline day; and 0325, 0725, 1125, 1525, and 1925 hours on the deprivation day).

Vigor-activity scale

The ANOVA on these scores, which reflect energy level, revealed a drug-by-session interaction [$F(9,45)=3.19$, $P=0.0046$] and a session main effect [$F(9,45)=10.08$, $P<0.0001$]. The interaction was due to higher vigor ratings under modafinil than placebo at both the 0735 and 1135 hour testing times, while no differences existed at baseline or elsewhere during sleep-deprived testing times (Fig. 3, top panel). The session main effect resulted from linear, quadratic and cubic trends in the data ($P<0.05$ in each case). Vigor ratings fell sharply toward the end of baseline testing, then leveled off before declining again during deprivation testing.

Fatigue-inertia scale

This measure, indicative of weariness and tiredness, revealed a drug-by-session interaction [$F(9,45)=5.04$, $P=0.0001$], a session main effect [$F(9,45)=11.57$, $P<0.0001$], and a drug main effect [$F(1,5)=12.84$, $P=0.0158$]. Simple effects analysis indicated that fatigue ratings were significantly greater under placebo than modafinil at 0335, 0735, 1135, and 1535 hours ($P<0.05$). Also, there were two baseline differences, occurring at 1935 and 2335 hours ($P<0.05$; Fig. 3, middle panel). However, the mean difference between group (drug versus placebo) ratings of fatigue over these two baseline sessions (0=3.51) was less than half the size of the mean difference (0=7.75) between group fatigue ratings over the four significant deprivation sessions. The session main effect was due to linear and quadratic trends ($P<0.05$). That is, fatigue ratings increased as a function of continuous wakefulness, but also were seen to peak at 0735 hours, recovering slightly 4 h later, and then increasing again for the remainder of testing. The drug effect indicated overall greater fatigue ratings under placebo which were attenuated under modafinil.

Confusion-bewilderment scale

The ANOVA on this scale, which indicates difficulties in mental abilities, showed session [$F(9,45)=7.42$, $P<0.0001$] and drug [$F(1,5)=7.67$, $P=0.0394$] main effects. The session effect was due to linear and quadratic trends ($P<0.05$) which resulted from a gradual deprivation-related increase in confusion ratings that was punctuated by a peak in confusion scores at 0735 and 1135 hours. The drug effect was due to a general elevation in confusion scores under placebo versus modafinil (Fig. 3, bottom panel).

The remaining three scales revealed no drug-related effects. The tension-anxiety scale, reflecting heightened musculoskeletal tension, and the depression-dejection scale, measuring despondence and sadness, each yielded a session main effect [$F(9,45)=8.83$, $P<0.0001$ and $F(9,45)=2.11$, $P=0.0487$, respectively]. These were due to gradual deprivation-related increases throughout the wakefulness periods. The anger-hostility scale yielded no significant effects.

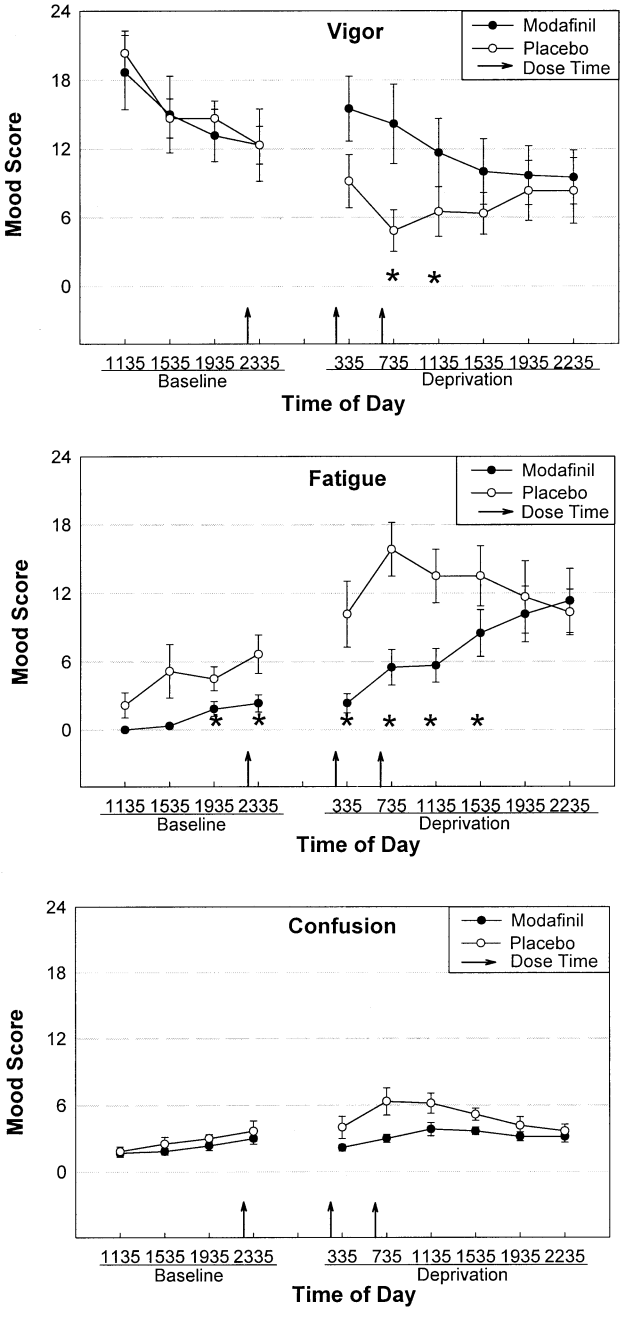

Fig. 3 The effects of modafinil versus placebo on self-reported mood scales from the Profile of Mood States Questionnaire. *Top panel*: drug by session interaction for vigor ratings. *Middle panel*: drug by session interaction for fatigue ratings. *Bottom panel*: main effect of drug condition for confusion ratings. *Error bars* delineate boundaries determined by SEM. *Asterisks* indicate significant simple effects

Vital signs

Temperatures, pulses, and blood pressures were taken throughout the baseline and deprivation periods, and

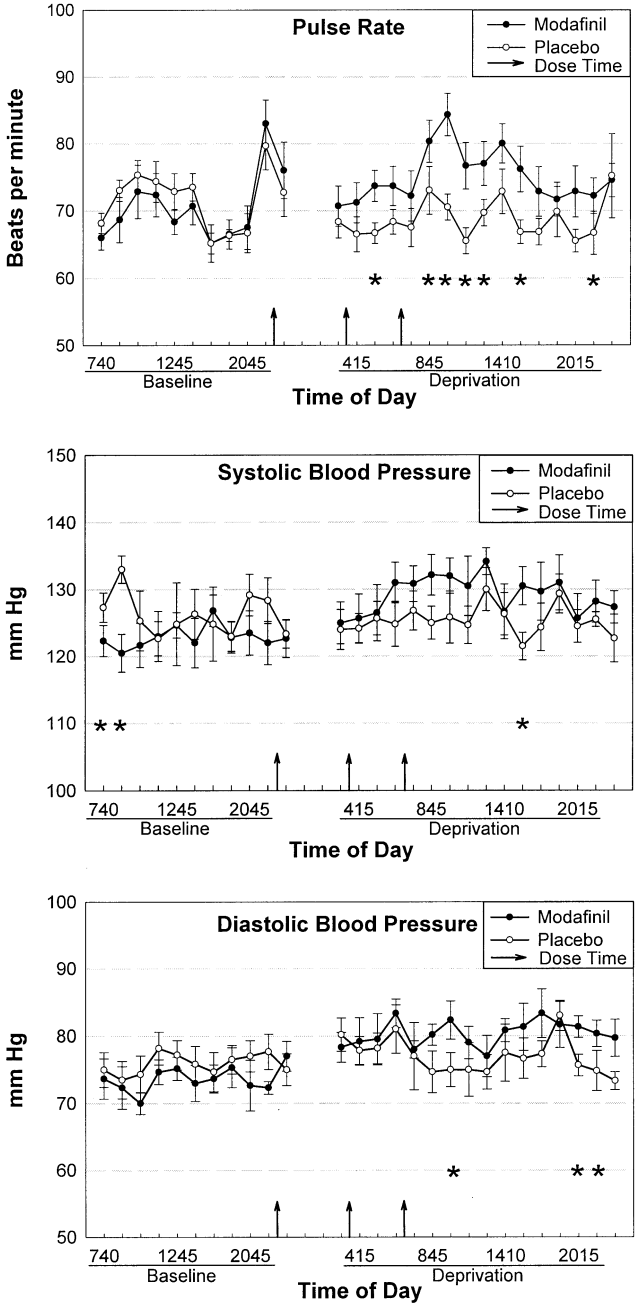

Fig. 4 The effects of modafinil versus placebo on vital signs. *Top panel*: drug by session interaction on pulse rate. *Middle panel*: drug by session interaction on systolic blood pressure. *Bottom panel*: drug by session interaction on diastolic blood pressure. *Error bars* delineate boundaries determined by SEM. *Asterisks* indicate significant simple effects

these data were analyzed in two-way ANOVAs for drug (placebo versus modafinil) and time (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 min of data collection. Steps were taken to minimize this problem, but because of constraints in the testing schedule (sometimes subjects had only 5–10 min between tests), it was difficult to avoid some contamination.

There were no drug-related effects on oral temperature, but there was a time main effect [$F(26,130)=2.91$, $P<0.0001$] due largely to a combination of circadian factors (low temperatures in the mornings) and physical activity (higher temperatures following the evening exercise period). On the pulse measure, there was a significant drug-by-time effect [$F(26,130)=2.91$, $P<0.0001$] because, although pulse rate was not different between the two conditions at baseline, it was elevated under modafinil versus placebo at 0445, 0845,1010, 1215, 1245, 1615, and 2045 hours on the deprivation day (Fig. 4, top panel). There also was a time main effect [$F(26,130)=5.42$, $P<0.0001$] due to quadratic and cubic trends in the data ($P<0.05$). There was a drug-by-time interaction on systolic blood pressure [$F(26,130)=1.65$, $P=0.0360$] which analysis of simple effects revealed was due to an initial baseline difference (with placebo greater than modafinil at the 0740 and 0820 hour assessments) followed by an increase under modafinil versus placebo. The apparent later elevations under modafinil during the deprivation sessions attained significance only at 1615 hours ($P<0.05$), but not earlier (Fig. 4, middle panel). A time main effect on systolic blood pressures [$F(26,130)=1.85$, $P<0.0133$] resulted from general cubic and quadratic trends which were not pursued because they are superfluous in the presence of the higher-order interaction. There was a drug-by-time interaction on diastolic blood pressures [$F(26,130)=1.88$, $P<0.0113$] due to increases at 1010, 2015, and 2045 hours on the deprivation day ($P<0.05$), but not elsewhere (Fig. 4, bottom panel). There also was a time main effect [$F(26,130)=3.39$, $P<0.0001$] which was not analyzed further in light of the higher-order interaction between drug and time.

Discussion

The general finding from this investigation was that modafinil attenuated a number of performance and mood-based problems associated with sleep loss. The benefits of modafinil were especially noticeable from approximately 0330 hours until 1200 hours 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 (vigor and fatigue).

Flight performance

Of the six flight maneuvers conducted in the UH-60 simulator, there were drug-by-session effects on three and a drug main effect on one. Performance under modafinil was maintained at or near baseline levels throughout the deprivation period whereas performance under placebo suffered. The times at which modafinil most clearly at-

tenuated the problems associated with sleep loss ranged from as early as 0500 hours to as late as 1700 hours. However, the largest differences tended to occur at about 0900 hours (after 26 h of continuous wakefulness). 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 Lagarde and Batéjat (1995) and Pigeau et al. (1995).

EEG

The EEG 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. Note that delta activity is often found in waking EEG records via signal processing techniques despite the fact that traditional delta waves are not observed in visually-scored records (Ray 1990). Nonetheless, FFT-scored delta activity has been reported in several studies, to include those of sleep deprivation (Lorenzo et al. 1995). Generally speaking, sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (Pigeau et al 1995), 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, elevated slow-wave brain activity, particularly noticeable under the placebo condition, tended to coincide with flight performance decrements.

POMS

Self-reported vigor declined the most under placebo at 0735 hours (concomitant with most of the observed performance decrements), and then recovered somewhat toward the end of the deprivation period. An analogous trend was seen in which ratings of fatigue increased around this same time (0735 hours) before improving later in the day. Visual inspection of the data revealed that modafinil tended to preserve vigor at baseline levels until approximately 1135 hours (after almost 29 h of continuous wakefulness), while attenuating ratings of fatigue at these and later times. Most such effects were seen between 0735 hours and 1535 hours, which is consistent with the results reported by Pigeau et al. (1995), that modafinil significantly diminished 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 consistent with what was found in the performance data.

Vital signs and side effects

Modafinil in comparison to placebo significantly increased the heart rates of the volunteers in this study, but the effect on blood pressure was minimal. The most common side effect reported by participants was nausea or related symptoms, and less common were vertigo (or related complaints), jitteriness or nervousness, dizziness, heartburn, and headache. When symptoms of vertigo, including dizziness, were reported, they most often occurred around the times the simulator flights were conducted, while nausea usually occurred during the flight and/or immediately afterward. Both tended to occur most at times when modafinil levels in the blood were at their highest.

Our data do not support previous observations that modafinil has no side effects (Batéjat and Lagarde 1999), however, it is possible that side effects were more numerous than expected in this study because of: 1) the relatively high dosage of modafinil that was used in comparison to other investigations (a single 200 mg versus a 600-mg divided dose), and/or 2) the use of a moving flight simulator with computer-generated visual scenery, rather than a static laboratory test. A follow-on study of the efficacy of a lower dose of modafinil may determine whether the vertigo and nausea will subside without overly reducing the stimulant effect, while in-flight testing would address the "simulator sickness" concerns. If explanations can be attributed to high dose or simulator properties such that actual in-flight use would not be contraindicated, then modafinil should not be discounted as a fatigue countermeasure because it reportedly has a number of desirable characteristics (e.g. low abuse potential, low toxicity).

Study limitations

A couple of study limitations should be noted. First, some of the volunteers failed to follow instructions to discontinue caffeine use several days prior to the protocol, and this resulted in instances of headaches on the training day (and sometimes on the first baseline day) which may have been associated with other unreported symptoms. However, since the number of headaches (thought to be associated with caffeine withdrawal) was roughly equivalent in those who received modafinil first and in those who received placebo first, it is doubtful that this confounded the results. Second, although the present results indicate that modafinil was effective for sustaining the alertness of normal sleep-deprived subjects, it should be noted that additional research (with a variety of doses) should be performed to characterize completely the efficacy of this compound. Future studies are currently being formulated for this purpose.

Summary and conclusions

The results of this study showed that modafinil was moderately effective for sustaining both the perfor-

mance and alertness of aviators in a helicopter flight simulator. On four of the six instrument maneuvers modafinil significantly attenuated the sleep-deprivation problems which were observed under placebo. Both EEG activity and self-reports indicated that alertness was better under modafinil than placebo. All six volunteers reported they were able to determine when they were on modafinil versus placebo, and five of the six thought modafinil helped their performance. The greatest drug-related effects occurred between 0330 and 1200 hours when the impact of fatigue was most profound due to extended wakefulness and circadian factors. There were side effects, particularly nausea and vertigo, which must be explored further. It is possible that these were at least exacerbated by the motion-base testing. Also, they might have been dose-related, and a simple reduction in the amount of modafinil from 600 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. In the meantime, the present results indicate that modafinil holds promise for its alerting effects, and that subsequent research is warranted to establish the best dosage level to be used for sustaining the real-world performance of sleep-deprived personnel.

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