Modafinil as a Replacement for Dextroamphetamine for Sustaining Alertness in Military Helicopter Pilots

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Estrada A, Kelley AM, Webb CM, Athy JR, Crowley JS. ***Modafinil as a replacement for dextroamphetamine for sustaining alertness in military helicopter pilots.*** **Aviat Space Environ Med 2012; 83:556–64.**

Introduction: Successful military aviation operations depend on maintaining continuous day-night operations. Stimulants are easy to use and popular for sustaining performance because their utility is not dependent upon environmental or scheduling modifications. Dextroamphetamine is authorized for use by the aircrews of all U.S. military services, but its potential for abuse and subsequent addiction is of aeromedical concern. Finding an alternative stimulant, such as modafinil, that displays a low affinity for dopamine uptake binding sites would prove extremely beneficial. This study sought to establish the efficacy and safety of modafinil during actual flying operations, thus providing the operational validity desired to approve the use of modafinil for helicopter flight operations. ***Methods:*** During two, 40-h periods of sustained wakefulness, 18 helicopter pilots (17 men, 1 woman, mean years of age = 29.5) each completed 15 flights and other evaluations, during which they received 2 of 3 experimental conditions: 3 doses at 4-h intervals of modafinil (100 mg), dextroamphetamine (5 mg), or placebo. ***Results:*** Statistical results showed that modafinil, like dextroamphetamine, maintained alertness, feelings of well-being, cognitive function, judgment, risk perception, and situation awareness of sleep-deprived aviators consistently better than placebo and without side effects of aeromedical concern. ***Discussion:*** Like previous research, this study strongly suggests that both drugs can maintain acceptable levels of mood and performance during sleep deprivation. The results also confirm that modafinil is well tolerated and appears to be a good alternative to dextroamphetamine for countering the debilitating mood and cognitive effects of sleep loss during sustained operations.

Keywords: modafinil, dextroamphetamine, stimulants, extended wakefulness, sustained helicopter operations, fatigue.

MUCH RESEARCH HAS been conducted on potential strategies for sustaining military performance in situations where sleep deprivation may be a factor. Some of the current strategies include manipulating the timing and duration of sleep periods (2,5,6) via sleep management programs or the administration of hypnotics (3). During times of intense operations, administrative and behavioral interventions may not be sufficient to satisfactorily preserve performance. There may be times when the only viable alternative is to sustain performance through the use of stimulants.

Stimulants are easy to use for sustaining performance because their utility is not dependent upon environmental manipulations or scheduling modifications. Drugs such as dextroamphetamine have been used in several military conflicts (16). Of the alertness-promoting compounds currently available, caffeine, dextroamphetamine, and modafinil have been shown to be effective in a variety of situations and appear to be well suited for use in aviation operations (1). Previous research indicating the potential of modafinil for use in aviation applications led to the joint funding of the present study by the U.S. Special Operations Command Biomedical Initiative Steering Committee and the U.S. Army Medical Research and Materiel Command. Despite a robust body of laboratory evidence showing modafinil to be a very well tolerated drug, the Special Operations Command Biomedical Initiative Steering Committee's goal for partially funding this project was to establish the efficacy and safety of modafinil during actual flying operations, thus providing the operational validity desired to approve the use of modafinil for military flight operations.

To date, the usefulness of modafinil, specifically for aviation settings, has been evaluated in three controlled aviation simulation studies (9,24). Caldwell et al. (9) found that three daily doses of 200 mg (given at 23:00, 03:00, and 07:00 during a 40-h period of continuous wakefulness) maintained flight performance at rested levels and attenuated the effects of 40 h of continuous wakefulness on fatigue, confusion, and physiological arousal. No adverse behavioral effects were noted; however, vertigo, nausea, and dizziness were reported as side effects by the majority of subjects.

In a subsequent simulator study, LeDuc et al. (24) found evidence that lower doses of modafinil (3×100 mg) could maintain alertness without causing the side effects reported by Caldwell et al. (9). Results from the LeDuc et al. study support the idea that the side effects reported by volunteers in the Caldwell et al. study were most likely the result of the modafinil dose [as suggested by Buguet et al. (7)]. An alternate explanation is that the side effects may be the result of fatigue, not modafinil as suggested by Eddy et al. (15).

Dextroamphetamine is a synthetic stimulant that has been marketed in the United States under the trade name Dexedrine® (SmithKline Beecham) since the 1960s.

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This manuscript was received for review in June 2011. It was accepted for publication in January 2012.

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DOI: 10.3357/ASEM.3129.2012

The stimulant effects of dextroamphetamine occur through widespread dopaminergic action, including high-affinity binding to the dopaminergic receptor and blocking of dopaminergic reuptake. Laboratory investigations have shown that single doses (20 mg) of dextroamphetamine can return cognitive performance to baseline levels and maintain this recovery after 48 h of total sleep deprivation (27). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, will sustain the performance of pilots for as long as 64 h (11). It is authorized for use under controlled conditions by the aircrews of all three U.S. military services.

Modafinil is a psychostimulant that has been demonstrated to sustain performance. Modafinil has been available in the United States as a schedule IV drug under the trade name Provigil® (Cephalon, Inc., Frazer, PA) since late 1998. It is approved by the FDA for treating symptoms of narcolepsy and for use in shift work disorder as well as for long-term use in obstructive sleep apnea/hyponea syndrome. Modafinil is believed to exert its stimulant effects by acting as an antagonist to the dopamine reuptake transporter. It may also act to increase the extracellular levels of dopamine (38), although the mechanism(s) by which this occurs remain(s) unclear. In contrast to dextroamphetamine (which is promoted by noradrenergic and dopaminergic actions), modafinil displays very low affinity for dopamine uptake binding sites (26). The mechanism of action for modafinil has not been fully explained by the current literature, however. In 2003, the U.S. Air Force authorized the use of modafinil for certain missions. Doses of 200 mg (not to exceed 400 mg within 24 h) can be administered to pilots of dual-pilot bomber missions greater than 12 h in duration and for F-15E missions longer than 8 h. In 2006, the U.S. Air Force authorized the use of modafinil for single-seat fighter operations.

This study included comparisons of modafinil (100 mg) to dextroamphetamine (5 mg) and placebo. Specifically, the objectives were to determine the degree to which three doses of 100 mg of modafinil or three doses of 5 mg of dextroamphetamine administered at 4-h intervals during the course of the 40-h sustained operations scenario: 1) sustained flight performance, cognitive skills, and mood; 2) produced operationally significant side effects; and 3) facilitated full recovery to baseline levels following a full night of sleep.

METHODS

The study protocol was approved in advance by the U.S. Army Medical Research and Materiel Command Institutional Review Board. Each subject provided free and informed written consent before participating. Volunteers received no monetary compensation for participation, although costs associated with travel to and from the U.S. Army Aeromedical Research Laboratory (USAARL) were reimbursed.

Subjects

There were 18 UH-60 Black Hawk helicopter rated aviators who participated in the study (17 men, 1 woman). They had flown within the previous 60 d. Their ages ranged from 22 to 38 yr of age (mean = 29.5 yr). Body weight ranged from 127 to 234 lbs with a mean of 183 lbs. Potential subjects were medically screened by a flight surgeon for disqualifying acute and chronic health and/or mental conditions [see Estrada et al. (18) for detailed exclusion criteria]. The female subject received a pregnancy test prior to drug administration.

Study Design

This study employed a double-blind, balanced, incomplete block (split-plot) design [6 condition groups (**Table I**), 3 subjects per group, for a total of 18 subjects]. During one deprivation period, subjects were given modafinil (three doses of 100 mg), dextroamphetamine (three doses of 5 mg), or placebo (three doses) at 4-h intervals.

Procedure

Fig. 1 details the activities throughout a typical week of testing. The design tested drug initial and sustained effects. The dosing procedures replicated those of previous studies (12,24). During the study, volunteers were not allowed to consume caffeine or take any medications or dietary supplements. In addition, an Actiwatch® was worn by each subject. These wrist-worn activity monitors are lightweight and collect human activity data on a minute-by-minute basis. On Day 1 following a medical exam, they were trained on the various data collection procedures and measures used in the study. Volunteers slept from 23:00 to 07:00 on Day 2. As all volunteers were on flight status, it was predetermined to be unnecessary to perform urine drug screens. Practice on all tests continued from 09:00 to 22:30. On Day 3, baseline data were collected. At 16 h post-wake (23:00), volunteers were administered the first of three doses of placebo, dextroamphetamine, or modafinil. Sleep deprivation data collection began at 23:10. The second dose was administered at 03:00 with the final dose at 07:00. Testing continued throughout the day. At approximately 22:45, volunteers were allowed to sleep from 23:00 to 07:00 on Day 5.

Testing resumed at 09:00. At 23:00, volunteers received the first of three doses of their second drug condition. At 23:10, the second sleep deprivation data collection began. The second and third doses were administered as before. Testing continued throughout Day 6. At approximately 22:45, each volunteer slept from 23:00 to 07:00 on Day 7.

TABLE I. CONDITION GROUPS (THREE SUBJECTS PER GROUP).

	1st Condition	2nd Condition
Condition Group 1	modafinil	placebo
Condition Group 2	placebo	modafinil
Condition Group 3	dextroamphetamine	placebo
Condition Group 4	placebo	dextroamphetamine
Condition Group 5	modafinil	dextroamphetamine
Condition Group 6	dextroamphetamine	modafinil

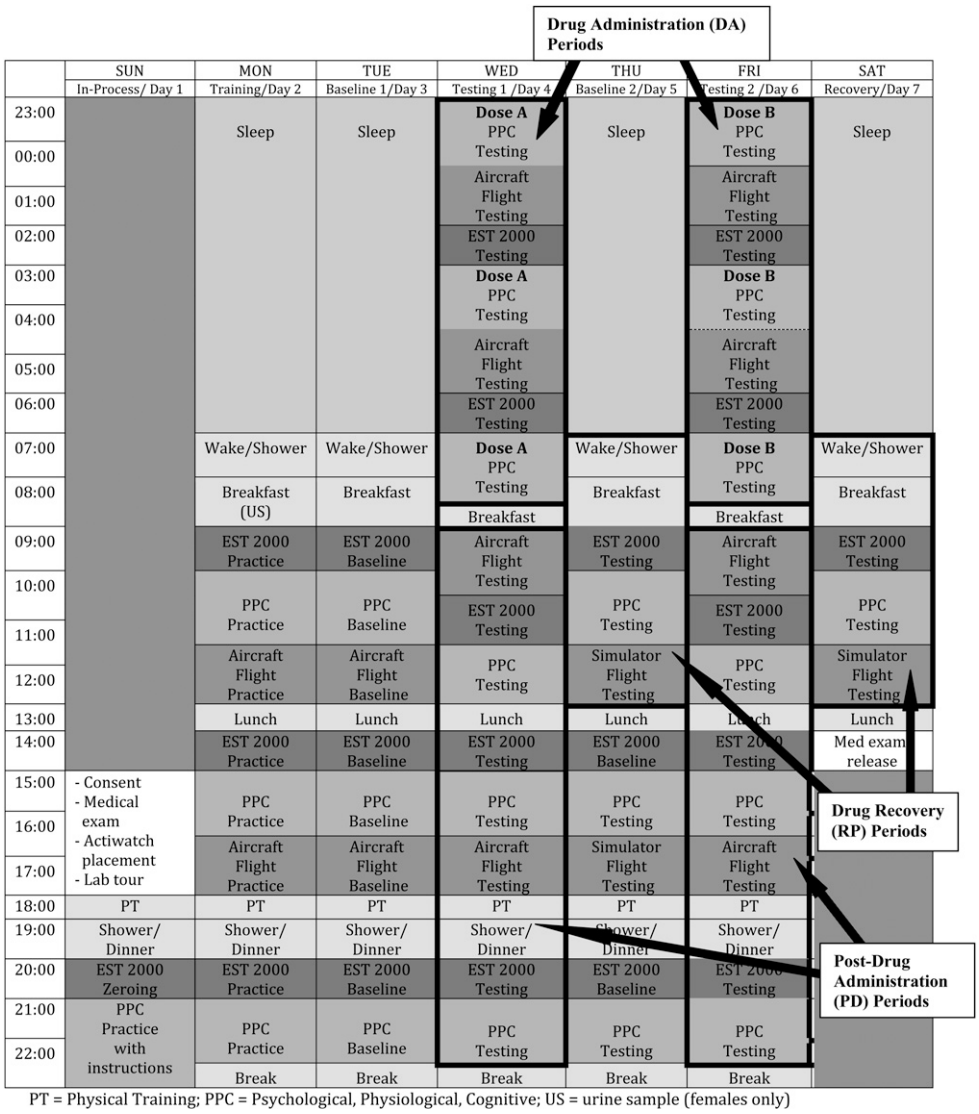

Fig. 1. Schedule of activities and testing periods.

At 09:00 on Day 7, volunteers began post-recovery sleep testing, which continued until 13:00. Volunteers were administered a brief medical examination prior to being cleared from the study. In every case, the study physician found the volunteers to be in good health and cleared them for release from the study at 15:00.

Physiological Measures

Oral temperature, blood pressure, and heart rate were recorded upon arrival on Day 1, then during each psychological, physiological, and cognitive (PPC) test period per Fig. 1. Volunteer activity data were collected through the use of the wrist-worn Actiwatch® activity monitoring system.

Questionnaires

As with all questionnaires, the 2-min Symptom Checklist (SC) was administered during each PPC period. The SC was used to determine if volunteers were currently experiencing any symptoms which corresponded to adverse effects most frequently reported following administration of modafinil and dextroamphetamine, as noted in product monographs (17). Subjective sickness symptoms were measured using the 5-min Motion Sickness Questionnaire (MSQ) (21), which is a self-report consisting of 28 items that are rated in terms of severity on a 4-point scale. The MSQ yields four scores: a nausea score, oculomotor score, disorientation score, and total motion sickness score.

The propensity to engage in or avoid risky behavior and situations was assessed by a 5-min, 24-item Evaluation of Risks Questionnaire (EVAR) that has been used effectively to measure individual variability in risk assessment (32). The 3-min Visual Analog Scale consists of eight 100-mm lines centered over the adjectives 'alert/able to concentrate,' 'anxious,' 'energetic,' 'feel confident,' 'irritable,' 'jittery/nervous,' 'sleepy,' and 'talkative' (29) to measure subjective alertness and mood. The 3-min Profile of Mood States (POMS) (25) is a 65-item adjective checklist that measures current mood states along six subscales: tension-anxiety, anger-hostility, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment.

Computerized Performance Tests

During each PPC, subjects completed a series of computerized performance tests, including a 10-min psychomotor vigilance task (PVT). Using a handheld device, a pushbutton response to the visual stimulus (presented with an interstimulus duration of 1-10 s) was required. The Balloon Analog Risk Test (BART) is an 8-min computer-based risk assessment test which requires the subject to pump balloons to gain play dollars. If the balloon bursts, no money is gained. The Iowa Gambling Task (IGT) is a 20-min test involving the simple task of choosing cards from decks with differing pay/loss ratios. It measures a subject's ability to assess risk by making cost/benefit analyses and adjusting risk to his/her own benefit.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) employs touch-screen technology and rapid, language-independent cognitive tests. It is well validated and suitable for repeated measures testing. The following subtests, taking 25 min, were chosen based upon a review of published reports that have used CANTAB to assess stimulant effects.

1. The Rapid Visual Information Processing (RVP) is a test of visual sustained attention with a small working memory component.
2. The Stockings of Cambridge is a test of spatial planning.
3. The Spatial Working Memory is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory.

Engagement Skills Trainer Marksmanship Performance

The Engagement Skills Trainer (EST 2000) is the U.S. Army's primary small arms weapons simulator and is used for continuous training. Hence, it is likely that the participants had trained on an EST 2000 prior to the study. The weapons are slightly modified to interface with the system, but still maintain their form, fit, feel, and function. The USAARL EST 2000 records the usual parameters of number of rounds fired, number of hits, misses, friends killed, foes killed, and accuracy of fire, but is augmented by special data collection software which also allows shot radius, reaction time, and root mean square distance from target center of mass as a measure of aiming drift. The simulations took approximately 40 min.

Flight Performance

This study was characterized as an in-flight study because 12 of the 15 data collection flights were conducted in an actual UH-60A Black Hawk helicopter. In order to control costs, three of the flights, all occurring during the drug recovery periods, were performed in USAARL's NUH-60 Black Hawk Research Flight Simulator. The same research flight profile (**Table II**) was followed regardless of whether the flight took place in the aircraft or simulator. Repetition of the exact flight route in either the aircraft or simulator was possible due to the simulator's geo-specific visual database, which allows the pilot to see the same geographic scenes as in the real world. A set of standardized visual and instrument precision maneuvers formed a flight profile designed to provide a systematic method for detecting changes in flight performance as a function both of time and the subject's alertness. Subjects were instructed to maintain prescribed flight standards (airspeed, heading, altitude, roll, etc.) depending on the individual flight maneuvers listed in Table II. Whenever a subject was flying the aircraft, a well rested, USAARL research safety instructor pilot was in the left front seat of the aircraft with access to the flight controls. Each flight lasted approximately 35 min.

Statistical Analysis

Where appropriate, data were analyzed using mixed measures analyses of variance (ANOVAs). Post hoc pairwise comparisons were analyzed using independent samples *t*-tests and paired samples *t*-tests. Given the large number of comparisons, a Bonferroni correction was applied.

RESULTS

In this study, 18 helicopter pilots each completed 15 UH-60 flights. Of the 15 flights, 12 were conducted in an actual helicopter unless inclement weather caused the flight to be conducted in the USAARL flight simulator.

TABLE II. FLIGHT MANEUVERS.

#	Maneuver Description	Heading (degrees magnetic)	Altitude (ft)	Rate of Climb/ Descent (ft per min)	Air Speed (knots indicated)	Time (min)	Measures Scored
1	Stationary Hover	200	10 AGL	0	0	2	Heading, Altitude
2	Instrument Takeoff	200	10 AGL to 800 MSL	+500	0 to 80	1	Climb rate, Airspeed
3	Straight and Level 1	210	800 MSL	0	120	2	Heading, Altitude, Airspeed
4	Straight and Level 2	130	800 MSL	0	120	3	Heading, Altitude, Airspeed
5	Left Standard Rate Turn	From 130, full 360 degree turn	800 MSL	0	120	2	Altitude, Airspeed, Turn rate
6	Climbing Right Turn	130 to 310	800- 2000 MSL	+1000	120	2.2	Climb rate, Airspeed
7	13 DME Intercept Turn	From 310 to localizer intercept	2000 MSL	0	120	3	Altitude, Airspeed
8	Instrument Landing System	061	2000 MSL	0	120	3	Altitude, Airspeed, Localizer Course
9	Instrument Landing System	061	2000 MSL to 498 MSL	-540	120	2.8	Airspeed, Localizer Course
10	Missed Approach	061	498 MSL to 800 MSL	+500	120	1	Airspeed, Heading

DME = Distance Measuring Equipment; AGL = above ground level; MSL = mean sea level.

This occurred in 40 (15%) of the 270 originally planned actual helicopter flights.

Despite the randomization of individuals into the treatment groups, preliminary analyses of baseline data from the Day 3 sessions showed that there were pre-existing group differences on several of the subjective and objective test measures. To account for these pre-existing differences, data were transformed to baseline-adjusted scores for each individual as follows: the measures collected during the baseline testing period (Day 3, prior to any drug administration or sleep deprivation) were averaged for each test. This score was subtracted from each volunteer's respective test scores during the experimental periods to remove the pre-existing pretreatment bias.

In addition to the baseline testing period and for the purposes of comparing the effects of each test condition on the resulting subjective and objective baseline adjusted data, the study schedule was divided into three main testing periods (Fig. 1): the drug administration period (DA), the post-drug administration period (PD), and the drug recovery period (RP). The purpose of grouping and then averaging the tests within the three testing sessions or periods was to present an assessment that would be operationally relevant, providing military medical authorities and commanders a better characterization of drug effects during a period of active dosing vs. the period post-dosing (characterized by a peak and steady decline of drug serum concentrations) vs. the period of recovery following a full night (8 h) of sleep. Estimated serum concentration levels for modafinil were calculated and plotted based on a mean peak concentration of 4.82 mg $\cdot$ ml^{-1} at 2.3 h following a single 200-mg oral dose in healthy subjects and a $T_{1/2}$ of 15 h with zero-order elimination kinetics. Estimated levels were also calculated for dextroamphetamine on a mean peak concentration of 29.2 ng $\cdot$ ml^{-1} at 2 h following a single 10-mg oral dose in healthy subjects and a $T_{1/2}$ of 10.2 h with zero-order elimination kinetics (18). In addition, for the purposes of analysis, the construct helped minimize the variability of drug and session differences due to the many data points and the many variables (e.g., food, renal function, ethnicity) affecting serum concentration following oral administration. In most cases, the two drug test-day baseline adjusted scores were subjected to mixed measures ANOVAs using the between-subjects factor, drug group, with three levels (dextroamphetamine, modafinil, and placebo), and one within-subject factor, testing periods. In addition, the effects of a full night's recovery sleep were analyzed by comparing drug test-day scores and self-reports to those of the recovery days (Days 5 and 7).

Actigraphy and Sleep Results

Actigraphy data were analyzed using between-subjects, multivariate analyses of variance (MANOVAs) of eight output variables (e.g., sleep time, sleep efficiency, and sleep latency). The comparison sleep periods are labeled baseline, modafinil recovery, dextroamphetamine recovery, and placebo recovery. The initial night of sleep at the laboratory was not included in the analysis, given that participants were adjusting to the environment, which may have impacted their sleep. The results of the MANOVA showed a significant main effect of drug between groups [$F(24, 126) = 1.73$, $P = 0.028$]. Subsequent univariate ANOVAs showed significant between-subjects effects for actual sleep time (minutes) [$F(3, 47) = 4.06$, $P = 0.012$], sleep efficiency (percent) [$F(3, 47) = 4.08$, $P = 0.012$ $P = 0.012$], and number of sleep bouts [$F(3, 47) = 3.40$, $P = 0.025$]. Independent samples *t*-tests showed significant differences in actual sleep time between modafinil recovery and placebo recovery sleep periods [$t(20) = -2.24$, $P = 0.037$] with the placebo group sleeping an average of 15 min longer than the modafinil group. Placebo recovery and baseline sleep periods differed [$t(26) = 3.12$, $P = 0.004$], with sleep efficiency being greater under placebo. In addition, modafinil recovery and placebo recovery sleep periods differed [$t(20) = -2.175$, $P = 0.042$], with sleep efficiency greater under placebo. Finally, placebo recovery and modafinil sleep periods differed [$t(26) = -2.85$, $P = 0.009$] in the number of sleep bouts, with the placebo group averaging 10.56 more sleep bouts than the modafinil group.

Physiological, Questionnaire, and Performance Results

Tables A and B (available online*; 10.3357/ASEM.3129sd.2012) present the results of the physiological, questionnaire, and performance tests. For those measures significant for main effects, the results of the succeeding pairwise comparisons and their statistical significance are provided.

DISCUSSION

As mentioned above, one rationale for selecting modafinil over dextroamphetamine is the latter's reputation for addiction and abuse. Until very recently, it appeared that modafinil had less abuse potential than stimulants that target dopamine transporters (35). However, a recent study by Volkow et al. (34) found evidence that modafinil does increase dopamine in the nucleus accumbens and their report recommends heightened awareness for abuse potential in vulnerable populations.

At the dosages used, both dextroamphetamine and modafinil increased heart rate slightly above placebo, but not significantly. Other modafinil research, especially when using higher dosages, has reported significant increases in heart rate (15,24). Modafinil has been shown to increase blood pressure (usually systolic) in humans (24,33). In this study, it was not systolic, but diastolic blood pressure that showed a significant increase for session with the greatest increases by both stimulant groups occurring 5 h after the final doses.

According to Wesensten, Killgore, and Balkin (37), an important consideration when assessing the alerting properties and side effects of stimulants is the effect they

may have on the ability to obtain restorative recovery sleep. Analysis of the actigraphy data confirms that subjects were in fact inactive (asleep) during rest periods and active (awake) during wake periods. Results showed significant differences between the sleep periods of the placebo and modafinil groups. Of the 8 h (480 min) allowed for sleep, the placebo group recorded longer inactivity (recovery sleep) than the modafinil group (453.91 min versus 438.91 min, respectively). Significant differences were detected for mean sleep efficiency (the percentage of time actually sleeping), with the placebo group recording significantly greater sleep efficiency than the modafinil group (94.58% versus 91.55%). These significant differences may suggest one of two hypotheses: 1) that subjects required a longer period of rest to recover from the placebo condition and also slept more efficiently than in the recovery from the modafinil condition; or 2) that modafinil interferes with the time it takes to go to sleep. This second hypothesis is supported by the level of estimated serum concentration that remained at bedtime. This suggests that modafinil differentially impacted the need for recovery rest. A review of the mood and performance assessment results showed that the sleep effects identified had no detectable impact on recovery session performance, with nearly all measures returning to general baseline levels following recovery sleep.

When considering the use of drugs for aviation applications, knowledge of the side effect profiles is critically important. Among the most important considerations is nausea. Data from the subjective MSQ and SC showed that nausea under all drug conditions increased beyond baseline and returned to baseline levels at recovery. However, nausea was significantly lower under the stimulant conditions than under placebo. The PD period saw a significant peak in overall nausea scores that dissipated thereafter. Just as in the LeDuc et al. study (24), it appears that when compared to placebo, both dextroamphetamine and modafinil reduced the increase in nausea. The findings, like those of LeDuc et al., support the use of the lower dose modafinil regimen (3 $\times$ 100 mg) compared to the higher dose regimen (3 $\times$ 200 mg) employed by Caldwell et al. (12). As in the LeDuc et al. study, none of the serious modafinil-related side effects (vertigo, dizziness, and nausea) reported by Caldwell et al. were observed in the modafinil group. Several recent studies have suggested that symptoms such as nausea, vertigo, and jitteriness seen with modafinil are dose dependent (7,15,36). Alternatively, the side effects seen by Caldwell et al. could be fatigue-induced and the increased alertness resulted in increased awareness of these symptoms.

Other results of the MSQ showed that oculomotor difficulties and total motion sickness symptoms were significantly higher under placebo than under either stimulant conditions. In addition, greater disorientation was reported by those under placebo than those in the dextroamphetamine group during the PD period. Session differences and drug $\times$ session differences existed for these measures due to the placebo group's significantly greater adverse symptoms. In summary, participants who were administered dextroamphetamine or modafinil experienced fewer motion sickness effects than those on placebo.

Most SC measures resulted in non-significant differences, with most self-reports ranging from no symptoms to only mild severity. This is consistent with other similar research (23,24). Only two measures showed significant session differences: dry mouth and jitteriness. Self-reports of dry mouth were greater (by those under the stimulant conditions) during the DA and PD periods than during the RP. The higher scores for jitteriness reported by the modafinil group during the PD did not appear to have a deleterious effect on the group's overall comportment.

Of notable importance was the significant Visual Analog Scale finding showing that the modafinil group felt significantly less sleepy and more alert during the sleep-deprived DA and PD periods than the placebo group. Consistent with LeDuc et al. (24), modafinil tended to preserve talkativeness near baseline levels throughout the entire period of wakefulness, unlike the other conditions which appeared to suppress talkativeness.

Regarding POMS data, depression was significantly higher in the placebo group than either stimulant group. With only minor variations, the depression scores of the stimulant groups remained at their baseline levels throughout the testing. All POMS measures except anger showed significant main effects for session and drug $\times$ session. Not unexpectedly, there was greater overall fatigue, confusion, tension, depression, and less vigor reported during the DA and PD periods than during the RP. The drug $\times$ session interaction was due to higher overall fatigue, confusion, tension, depression, and less vigor from those in the placebo group. This is consistent with other research (8,30).

It is important for pilots to make sound judgments based on the weighing of potential risks. Hence, drug effects on risk propensity are important to any comprehensive assessment of stimulants intended for aviation applications. This study employed three such tests: the EVAR (subjective), and the BART and IGT (both objective). On all EVAR measures (control, confidence, risk seeking, and total score), results showed no significant differences among drug conditions and very small variations from baseline by the modafinil group. These findings are in contrast to those of Gurtman, Broadbear, and Redman (20), who conducted a simulator driving study of sleep-deprived individuals on a single 300-mg dose. Pre- and post-drive self-assessments of driving performance indicated that modafinil "may induce overconfidence." In the current study, for session, significant differences were found for each of the EVAR measures. Essentially, notable increases in control, confidence, risk propensity, and total scores of the dextroamphetamine and placebo groups in the RP caused the period to be significantly different than the DA and PD periods. It appears that the stress of the sleep deprivation periods may have weakened the feelings of control, confidence, and risk propensity of the dextroamphetamine and placebo groups, which were then restored at recovery [consistent with Killgore (22)].

BART results indicated a significantly greater risk aversion during the PD period than during the RP, with the placebo group most averse to risk, especially compared to the dextroamphetamine group. It is logical for the placebo group to feel the least capable of the groups to make risk probability judgments considering that the PD period was the most stressful in terms of sleep deprivation. However, the IGT results indicated no significant differences in risk taking among the drug conditions or sessions. These findings imply that one night of sleep deprivation may not be sufficiently stressful to impair one's ability to make cost/benefit analyses and adjustments of risk.

As in the LeDuc et al. (24) study, none of the PVT measures (reaction time, major lapses, and minor lapses) were significantly influenced by drug condition; however, all showed significant main effects for session, indicating that they were capturing fatigue-induced increases in reaction time. Significant drug × session findings for reaction time and minor lapses were due to the placebo group's generally slower reaction times and more minor lapses than the stimulant conditions during the DA and PD (sleep deprivation) periods. Several studies have shown drug effects on measures of psychomotor function. Producing the same non-significant results for drug condition as the LeDuc et al. study, the results may indicate that the use of lower doses of modafinil and dextroamphetamine may produce enough stimulation to perform at satisfactory levels while at the same time not enough to discriminate from placebo. In addition, one study by Park et al. (28) found that the PVT measures of mean reaction time and the number of lapses were the least sensitive measure of sleepiness of the three psychomotor instruments they used. Other studies suggest that modafinil's effects on reaction time may be dose dependent (4,36).

None of the CANTAB tests were significant for drug condition across all sessions. This is despite studies and reviews of studies that have reported cognitive improvements under conditions of sleep deprivation from modafinil and dextroamphetamine when compared to placebo (19). As for session, five of the eight measures were significant. Results of the RVP Hit Probability test indicated that both stimulants similarly improved detection of stimuli better than placebo during the DA and PD periods. The RVP A' test (the ability to detect sequences) found that the PD period was nearly significantly different from the RP due to the relatively poor performance of the placebo group during the PD period. The Stockings of Cambridge Thinking Reaction Time and Spatial Working Memory Total Errors also showed the RP period to be significantly different from the DA and PD periods. Again, the difference was due primarily to the lower performing placebo condition during the PD period relative to the stimulant conditions.

The cognitive tests demonstrated that during the sessions in which sleep deprivation was a factor (DA and PD), the performance effects of the stimulants were quite similar and generally superior to placebo. It is worth noting Wesensten (35), who in her detailed review of modafinil research, summarizes by writing that "overall the bulk of studies indicate that modafinil improves psychomotor and cognitive performance during sleep deprivation, most notably during the circadian nadir in performance."

Analyses of the EST 2000 marksmanship tasks produced few significant findings of questionable importance. The results of the M16 rifle prone unsupported position yielded significantly faster reaction times during the DA period than during the PD and RP periods. It is suspected that the level of arousal associated with this task being conducted during the DA period (and before significant sleep deprivation) may have contributed to this effect. In addition, there was a significant session × range difference with the furthest targets (at 250 and 300 m) being engaged more swiftly (adjusted from baseline) during the DA period than the other periods. It is suspected that closer targets were perceived as easier to hit and were more patiently engaged. Targets further away, being more difficult to sight, seem to have provoked a more urgent response.

The kneeling position produced a significant result for shooting radius. The participants' baseline corrected shooting was significantly less precise for the 150-m targets than for the 50-m targets, a result that was expected given the higher level of difficulty in shooting targets that are more distant. The friend/foe detection task using a 9-mm pistol revealed no significant differences between any conditions (drug, session, or interactions) on any of the dependent measures. It is suspected that the level of arousal associated with this shooting task mitigated any potential differences between the drug or session conditions (31). In brief, the EST 2000 results suggest that short test sessions with the weapons simulator are not sensitive to mild-moderate sleep deprivation.

Of the 19 component measures of flight performance analyzed within the 10 flight maneuvers conducted, there were no main effects for drug or drug × session. There were, however, significant session effects observed in 14 of the 19 components, all (except takeoff climb rate) due to significantly fewer control errors (adjusted from baseline) during the RP than during the DA and PD periods. The significant main effects for the RP (for the flights between 11:30 and 13:00) indicate better control of altitude, airspeed, and turn rate (baseline adjusted) over the other test periods. This is likely because all recovery flights were conducted in the simulator, where environmental conditions remain constant (no winds, no turbulence, etc.) and when participants were well rested.

Analogous to the cognitive arousal described by De Valck, Cluydts, and Pirrera (14) and supported by comments in Caldwell, Roberts, and Jones (10), the absence of significantly different performance between the stimulant and placebo groups may be due to the stimulating nature of flying an aircraft at night, which can produce, in many aviators, a heightened state of arousal and anxiety. A similar concept emerged during a study by Ramsey et al. (31) during which the effects of stimulants, including dextroamphetamine and modafinil, were

assessed on fatigued participants undergoing rapid onset centrifuge runs. The authors were unable to draw conclusions about the impact of fatigue or of the pharmacological countermeasures due to suspicions that subject anticipation of the centrifuge ride provided cognitive arousal.

The lack of significant drug effects for flight performance may have been due to the relatively short duration of the flights. Economic constraints resulted in the helicopter flights being limited to approximately 35 to 40 min each. When possible, future studies should employ flights of greater duration (2 to 3 h), which may provide a much better opportunity to provoke more fatigue-related differences in flight performance [see Caldwell, Roberts, & Jones (10) for related discussion]. Finally, consideration should be given to testing after greater periods of wakefulness. Although more likely to be operationally relevant, one night of wakefulness may not be sufficient to produce significantly different effects in flight performance, especially considering the cognitively arousing nature of short-duration flights.

The main goals of this study were to determine the degree to which three doses of 100 mg of modafinil and three doses of 5 mg of dextroamphetamine sustained mood and performance in aviators engaged in an actual flight task, in addition to identifying operationally significant side effects during and after stimulant use. The results showed that, in most instances, dextroamphetamine and modafinil provided similar positive effects over placebo during the sleep-deprived DA and PD periods. Overall, these drugs maintained alertness, well-being, cognitive function, judgment, risk perception, and situation awareness of sleep-deprived healthy subjects at levels consistently better than placebo.

There were no clinically significant drug effects on the vital signs and, while recovery sleep after modafinil was different from placebo sleep, there was no detectable impact on performance. Although subjects' flight performance was not significantly better in either stimulant condition, neither drug produced any side effects that would be of an aeromedical concern. It appears likely that the side effects reported by Caldwell et al. (12) were possibly attributable to the higher doses used in that study.

This study, like many others before it, strongly suggest that stimulant medications can assist the pilot in maintaining acceptable levels of mood and performance when combat requirements dictate long periods of sleep deprivation. Regarding modafinil, the authors agree with the conclusions of others (13,24,30) that modafinil, at multiple doses, is well tolerated by healthy pilots at least over a short period of time. The evidence suggests that modafinil is a good alternative to dextroamphetamine for countering the debilitating mood and cognitive effects of sleep loss during sustained operations.

ACKNOWLEDGMENTS

The results of this study were presented on 22 March 2010 to the U.S. Army Aeromedical Activity's (USAAMA) Aeromedical Consultant Advisory Panel (ACAP) to support a policy permitting the use of modafinil by U.S. Army aviation forces. A detailed technical report of this study is available by contacting the USAARL Science Information Center at 334-255-6907.

The authors would like to acknowledge the dedication and professionalism of the research pilots of the Flight Systems Branch and the research staff of the Warfighter Health Division, U.S. Army Aeromedical Research Laboratory, for their contributions to the success of this project. This study was funded by the U.S. Special Operations Command Biomedical Initiative Steering Committee and the U.S. Army Medical Research and Materiel Command's Military Operational Medicine Research Program.

The opinions, interpretations, conclusions, and recommendations contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation. Citation of trade names in this report does not constitute an official Department of the Army endorsement or approval of the use of such commercial items.

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