

Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation

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SUMMARY Stimulants may provide short-term performance and alertness enhancement during sleep loss. Caffeine 600 mg, *D*-amphetamine 20 mg, and modafinil 400 mg were compared during 85 h of total sleep deprivation to determine the extent to which the three agents restored performance on simple psychomotor tasks, objective alertness and tasks of executive functions. Forty-eight healthy young adults remained awake for 85 h. Performance and alertness tests were administered bi-hourly from 8:00 hours day 2 to 19:00 hours day 5. At 23:50 hours on day 4 (after 64 h awake), subjects ingested placebo, caffeine 600 mg, dextroamphetamine 20 mg, or modafinil 400 mg ($n = 12$ per group). Performance and alertness testing continued, and probe tasks of executive function were administered intermittently until the recovery sleep period (20:00 hours day 5 to 8:00 hours day 5). Bi-hourly postrecovery sleep testing occurred from 10:00 hours to 16:00 hours day 6. All three agents improved psychomotor vigilance speed and objectively measured alertness relative to placebo. Drugs did not affect recovery sleep, and postrecovery sleep performance for all drug groups was at presleep deprivation levels. Effects on executive function tasks were mixed, with improvement on some tasks with caffeine and modafinil, and apparent decrements with dextroamphetamine on others. At the doses tested, caffeine, dextroamphetamine, and modafinil are equally effective for approximately 2–4 h in restoring simple psychomotor performance and objective alertness. The duration of these benefits vary in accordance with the different elimination rates of the drugs. Whether caffeine, dextroamphetamine, and modafinil differentially restore executive functions during sleep deprivation remains unclear.

KEYWORDS countermeasures, executive functions, sleep loss, stimulants, vigilance

EFFECTS OF CAFFEINE, MODAFINIL AND *D*-AMPHETAMINE DURING SLEEP DEPRIVATION

In separate studies, the efficacy of caffeine, dextroamphetamine, and modafinil for restoring and sustaining cognitive performance and objective alertness during sleep deprivation in healthy adults has been established (e.g. Bensimon *et al.*, 1991; Newhouse *et al.*, 1989). Modafinil (2-[(diphenyl-methyl)-

sulfinyl]acetamide) is the newest of these three agents and is approved in both North America and Europe for treatment of the daytime sleepiness associated with narcolepsy and in the United States for treatment of sleepiness associated with shift work sleep disorder and for treatment of residual daytime sleepiness in CPAP-treated sleep apnea patients. Dextroamphetamine (*D*-alpha-methylphenethylamine) is currently approved in the United States for treatment of narcolepsy and attention-deficit disorder with hyperactivity. Caffeine (1,3,7-trimethylxanthine) is used to improve alertness and is found naturally in widely available beverages and foods including coffee, tea, and chocolate (for example, a 7-oz cup of brewed coffee contains 80–135 mg caffeine; <http://coffeedfaq.com/caffa.html#HowMuchCaff>). Caffeine also is an additive

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in widely consumed items such as soda (a 12-oz cola soda may contain 50+ mg caffeine).

Although subjective effects of caffeine, dextroamphetamine, and modafinil have been evaluated within the same study (Warot *et al.*, 1993), the relative performance-enhancing efficacy of caffeine, dextroamphetamine, and modafinil has not. In previous studies, performance-enhancing effects of two of the three compounds have been compared (e.g. caffeine versus dextroamphetamine, Magill *et al.*, 2003; Waters *et al.*, 2003; dextroamphetamine versus modafinil, Pigeau *et al.*, 1995; Saletu *et al.*, 1989; caffeine versus modafinil, Wesensten *et al.*, 2002), but a head-to-head comparison among all three agents is lacking. The purpose of the present study was to evaluate the relative efficacy of a single administration of caffeine 600 mg, dextroamphetamine 20 mg, and modafinil 400 mg versus placebo for restoring and maintaining cognitive performance and objectively measured alertness during 85 h of sleep deprivation. In addition, because sleep deprivation decreases metabolic activity in prefrontal regions of the brain (Thomas *et al.*, 2000) governing executive functions (e.g. abstract thought, critical reasoning, planning, decision-making, situational awareness, and effective judgment) – and because sleep deprivation has been shown to impair performance on some tasks of executive function (Harrison and Horne, 1998, 1999), drug effects on several tasks of executive function were also evaluated. Drug was administered just prior to midnight of a third night of total sleep deprivation to evaluate efficacy at or near operational limits and during the trough of the circadian rhythm of cognitive performance and alertness.

METHODS

This study was approved by the Walter Reed Army Institute of Research Human Use Committee and the United States Army Medical Research and Materiel Command Human Subjects Review Board of the Army Surgeon General and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Subjects

Subjects were 48 healthy non-smoking men ($n = 38$; mean age = 24.9 years, range = 19–38 years) and women ($n = 10$; mean age = 25.8 years, range = 19–39 years) who responded to advertisements posted at local universities. Informed consent was obtained, and included an explanation of all procedures as well as possible drug side effects. Subjects were screened for past and current physical health problems (complete blood cell count, blood chemistry, urinalysis, 12-lead electrocardiogram, medical history and physical examination), mental health problems [state-trait anxiety inventory (cut-off = 40), Beck Depression Inventory (cut-off = 9), and medical history], neurological problems (history), sleep problems (sleep habits questionnaire), and drug use. They were instructed to abstain from alcohol and psychoactive drugs starting 48 h prior to the study. Compliance was determined with a urine drug screen on

samples collected on the morning of the study. All subjects selected for participation reported nightly sleep onset times between 22:00 hours and 2:00 hours, total daily sleep time (nocturnal sleep + daytime naps) of approximately 6–9 h, and daily caffeine consumption of <400 mg. They were instructed to abstain from alcohol and psychoactive drugs starting 48 h prior to the study. Compliance was determined with a urine drug screen on samples collected on the morning of the study. Payment was \$1500.00 for successful completion of the study and adherence to all study procedures.

Number of volunteers per group

The number of volunteers per group (12) was selected based on power calculations conducted on Psychomotor Vigilance Task (PVT) results from a previous study comparing modafinil 100, 200, and 400 mg; caffeine 600 mg; and placebo (Wesensten *et al.*, 2002). Results of this analysis indicated that 10 volunteers per group yielded a power of approximately 0.96 [input = 5 groups, $\alpha = 0.05$, total sample size = 49, critical $F = 2.58$ (d.f. = 4, 44), $\lambda = 22.07$, output = calculated power of 0.9623, calculated effect size of 0.6711].

Study design

A two-way mixed design was employed, and included factors for drug (grouping factor with four levels: caffeine 600 mg, dextroamphetamine 20 mg, modafinil 400 mg, or placebo) and test session (within-subjects' factor with 32 bi-hourly predrug sessions and 10 bi-hourly postdrug sessions for all tasks except for executive function tasks, which were administered between one and three times (depending on the specific task).

Drug preparation and pharmacokinetics

Drug allocations were prepared by the Walter Reed Army Medical Center Pharmacy and delivered in containers which maintained the double-blind. Caffeine, dextroamphetamine, and modafinil allocations were generated from Vivarin® (GlaxoSmithKline, Pittsburgh, PA, USA), Dexedrine® (GlaxoSmithKline, Research Triangle Park, NC, USA), and Provigil® (Cephalon, Inc., West Chester, PA, USA) respectively. Following a single oral administration, the human pharmacokinetic properties of caffeine (Penetar *et al.*, 1993), dextroamphetamine (product monograph, Dexedrine®), and modafinil (product monograph, Provigil®) are as follows: time to maximum concentration = 1.5, 3.0, and 2–4 h, respectively; and elimination half-life = 6.4, 12.0, and 10–13 h respectively. As caffeine's half-life is shorter than that of dextroamphetamine and modafinil, it was anticipated that caffeine would display a shorter duration of efficacy in the present study.

Selection of drug dose

Results from a series of previous studies from our laboratory indicated that the doses chosen are equivalent for restoring

performance and alertness during sleep deprivation of up to 64 h (Newhouse *et al.*, 1989; Penetar *et al.*, 1993; Wesensten *et al.*, 2002). That is, using similar methodologies (drug administration following 48 h of sleep deprivation), Newhouse *et al.* (1989) evaluated dextroamphetamine 5, 10, or 20 mg and Penetar *et al.* (1993) evaluated caffeine 150, 300, and 600 mg. Separate analyses of these data revealed that dextroamphetamine 20 mg and caffeine 600 mg improved performance on a serial addition/subtraction task to approximately the same magnitude. Wesensten *et al.* (2002) directly compared caffeine 600 mg with modafinil 100, 200, and 400 mg and found that caffeine 600 mg and modafinil 400 mg were equivalent in terms of magnitude of performance improvement on the PVT.

Performance and subjective alertness assessments

Cognitive performance and subjective alertness tests were administered by personal computer as per the schedule outlined in Table 1 (see Procedure). The following tests were selected based on their demonstrated sensitivity to sleep deprivation and stimulants (Penetar *et al.*, 1993; Wesensten *et al.*, 2002).

Performance – Psychomotor Vigilance Task

In this task (adapted from Dinges and Powell, 1985), a time display appeared (initially set to '000'), and subjects pressed a response key as soon as the time display began to increment. A response stopped the time display and initiated the next trial. The delay between the subject's response and the next stimulus presentation was 2, 4, 6, 8, or 10 s. The delay was pseudo-randomly assigned across trials so that each of the five response/stimulus intervals was presented an equivalent

number of times during each 10-min test session. PVT was analyzed for mean speed (reciprocal reaction time, 1/reaction time × 1000).

Subjective alertness – Stanford Sleepiness Scale

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

Other measures

Components of the Walter Reed computerized Performance Assessment Battery (PAB) (running memory, 10-choice reaction time, serial addition/subtraction, and grammatical reasoning) and the Fitness Impairment Tester (FIT; Pulse Medical Instruments, Inc., Rockville, MD, USA) also were administered. Although results from these tasks appeared to be similar to those obtained with the PVT, learning effects were evident for the PAB tasks; and FIT data were considered unreliable because of substantial missing sessions when eye responses could not be captured by the device. Thus, the PVT was considered the most reliable measure among those utilized in the present study (for further discussion of the comparative utility of various metrics for monitoring sleep-loss-induced performance decrements in the operational environment, see Balkin *et al.*, 2004).

Table 1 Time line of study events

Day	Time of day	Cumulative sleep Dep (h)	Hours postdose	Events
1	23:00 hours	–	–	Lights out – baseline sleep (8 h in bed)
2	7:00 hours	0	–	Awaken
	8:00–22:00 hours	1–15	–	Bi-hourly PVT, MWT, SSS
3	00:00–22:00 hours	17–39	–	Bi-hourly PVT, MWT, SSS
4	00:00–22:00 hours	41–63	–	Bi-hourly PVT, MWT, SSS
	23:50 hours	64.5	0	Drug or placebo (double-blind, randomized)
5	00:00 hours	65	0	PVT, MWT, SSS, symptom checklist
	2:00 hours	67	2	PVT, MWT, SSS, symptom checklist
	4:00 hours	69	4	PVT, MWT, SSS, symptom checklist
	4:35 hours	69.5	4.5	Letter/category fluency; Stroop (following 4:00 hours PVT, etc.)
	6:00 hours	71	6	PVT, MWT, SSS, symptom checklist
	6:35 hours	71.5	6.5	Wisconsin Card Sort (following 6:00 hours PVT, etc.)
	8:00 hours	73	8	PVT, MWT, SSS, symptom checklist
	10:00 hours	75	10	PVT, MWT, SSS, symptom checklist
	10:35 hours	75.5	10.5	Biber Cognitive Estimation (following 10:00 hours PVT, etc.)
	12 noon–18:00 hours	77–83	12–18	PVT, MWT, SSS, symptom checklist
	20:00 hours	85	20	Lights out – recovery sleep (12 h in bed)
6	8:00 hours	0	–	Awaken
6	08:00 hours	–	–	Awaken
	10:00–16:00 hours	–	–	Bi-hourly PVT, MWT, SSS
	17:00 hours	–	–	Remove electrodes; medical exam
	18:00 hours	–	–	Release from study

Probe tasks of executive function

The following tasks of executive function were chosen to provide a broad-based assessment of executive functions believed to be subserved by the prefrontal cortex, including verbal fluency, response inhibition and conflict resolution, quantitative estimation, concept formation, abstraction, and set shifting, problem solving, and decision-making: Controlled Oral Word Association (COWA; [Benton and Hamsher, 1989](#)); Animal fluency ([Barr and Brandt, 1996](#)); Dodrill format of the Stroop task ([Lezak, 1995](#)); Biber Cognitive Estimation Test ([Bullard et al., 2004](#)); and a computerized version of the Wisconsin Card Sorting Task (WCST; [Kongs et al., 2000](#)). These tasks were administered following drug administration.

Controlled Oral Word Association (Benton and Hamsher, 1989)

This task is an orally administered test of phonemic verbal fluency. The test requires the ability to search long-term memory for appropriate exemplars starting with the same letter and keep specific restriction conditions (e.g. no repeated words, no proper nouns) in working memory and apply them correctly. In this task, subjects were given 60 s in which to say as many words beginning with the letter 'C' as they could. They were instructed that proper names (e.g. names of people and places) and the same word with different endings would not count. The same procedure was repeated for the letters 'F' and 'L.' Administration time was approximately 4 min. Dependent measures were total number of correctly generated unique words; number of perseverative errors (repeated words) and number of intrusions (words beginning with an incorrect letter).

Animal fluency (Barr and Brandt, 1996)

This task is also an orally administered test of verbal semantic fluency that measures the ability to search long-term memory for exemplars that are members of a specific category, while still adhering to specific restriction conditions (e.g. no repeated words). Subjects were given 60 s in which to verbally generate the names of as many types of animals as possible within 1 min. Administration time was approximately 2 min. Dependent measures were total number of correctly generated unique animal names; number of perseverative errors (repeated names) and number of intrusions (non-animal words).

Wisconsin Card Sorting Task-64 Card Version (Kongs et al., 2000)

The WCST tests planning, mental flexibility, set-shifting, and concept formation. A 64-item computerized version was used (WCST-64; [Kongs et al., 2000](#)) was used. Subjects were instructed to match each response card that appeared to one of the four reference cards without being told how to match them. Following each card placement, volunteers received feedback as to whether their response was correct or incorrect.

Following standard administration procedures, cards were sorted by color, shape, or number of shapes on the card, and following 10 correct card sorts, the sorting rule was changed without notice. Administration time was approximately 15 min. Dependent measures included number of correctly sorted cards; number of errors; number of perseverative responses; number of categories completed; number of trials to complete the first category; and learning to learn, a measure of conceptual efficiency as the subject progresses through the categories.

Stroop Test (Dodrill's Format) (Lezak, 1995)

The Stroop is a test of selective attention and cognitive flexibility. Subjects were provided with a sheet of paper on which were printed a total of 176 words (16 rows \times 11 columns). Each word was the name of a color and was printed in a color of ink that either matched the word (congruent) or was different from the word (incongruent). For the first trial (word naming trial), subjects were instructed to read the words on the page as quickly as they could without making mistakes and to ignore the color of the ink. For the second trial (color naming trial), subjects were instructed to name the color of the ink that each word was printed in, and to ignore the word. Of the 176 words, nine were congruent and 167 were incongruent. The dependent measure (interference score) was calculated by subtracting the time taken to complete the word-naming trial from the time taken to complete the color-naming trial.

Biber Cognitive Estimation Test (Bullard et al., 2004)

The Biber is a test of the ability to form reasonable complex quantitative judgments about number, time, distance, and weight when sources of data are limited or ambiguous. Subjects were asked to provide a reasonable answer to each of 20 questions (e.g. 'How many seeds are there in a watermelon?', 'How long does it take to iron a shirt?'). They were allowed 10 min to complete the task and all finished within this time. Data were transformed and analyzed according to published norms ([Bullard et al., 2004](#)) as follows: responses were first transformed to *z*-scores based on a normative sample of 117 healthy, non-sleep deprived adults. *Z*-scores greater than 1.5 standard deviations from the mean were categorized as atypical responses, and subjects providing 25% or more atypical responses were classified as impaired on the task. The proportion of subjects scoring in the impaired range within each drug group was compared with the chi-square statistic. Significant between-group differences were identified using a test for the difference between independent proportions.

Symptom Checklist

The experimenter asked each subject individually whether any of the following symptoms were currently being experienced: nervousness, excitation, feelings of aggression, headache,

feelings of happiness or elation, pain in abdomen or stomach area, dry mouth, disorientation, pounding heart, racing heart beat, tremor, nausea, gastric or stomach discomfort, feeling as though the room is spinning. If the subject responded 'Yes' to an item, (s)he was then asked whether the symptom was mild, moderate or severe. The list of symptoms includes those most commonly reported for caffeine, dextroamphetamine, and modafinil as listed on the product inserts. Responses were scored as follows: no = 0; yes/mild = 1; yes/moderate = 2; yes/severe = 3. Subjects also were given the opportunity to indicate any symptoms not queried by the experimenter.

Polysomnography

Compumedics SIESTA recording units (Compumedics USA, El Paso, TX, USA) were used to record polysomnographic (PSG) signals. PSG data were used for (i) a modified maintenance of wakefulness test; (ii) recovery sleep; and (iii) verifying that subjects were awake or asleep at appropriate times throughout the study. A research associate who remained blind to drug condition scored PSG records offline in 30-s epochs according to [Rechtschaffen and Kales \(1968\)](#) criteria. Scoring reliability was within 90% of scoring conducted by a diplomate of the American Board of Sleep Medicine. PSG data were scored offline for latency to sleep onset (defined as the first epoch of sleep stage 2) and minutes of wake, stages 1, 2, slow-wave sleep (SWS, stages 3 and 4 combined), and rapid eye-movement (REM) sleep.

Objective alertness – modified Maintenance of Wakefulness Test

In order to reduce technician load associated with conducting and scoring Maintenance of Wakefulness Test (MWT) online, in the present study the MWT was modified as follows: subjects were allowed to lie down in bed, and were instructed to close their eyes but try to stay awake. Lights were then turned off, and subjects were allowed to lie undisturbed for 15 min after which lights were turned on and subjects awakened if asleep. As volunteers were undisturbed, it is possible that they accumulated sleep. Records were scored off-line for latency to stage 2 sleep (which served as the dependent variable).

Testing facilities

During testing, sleep and MWT periods, each subject was housed individually in a sound attenuated 10' × 10' room that included a bed and computer test station. Ambient temperature was approximately 23 °C, and lighting was approximately 500 lx. Background white noise was 65 dB at all times.

Procedure

A general timeline of study procedures and testing is provided in Table 1.

Subjects reported to the laboratory at 18:00 hours, at which time electrodes for PSG were attached, and they were

familiarized with cognitive tasks. Lights were switched off at 23:00 hours. They were awakened the following morning at 7:00 hours and breakfast was served. Decaffeinated food and beverages were allowed *ad libitum* throughout the study except from 19:30 hours day 4 (approximately 4 h prior to drug administration) until 15:00 hours day 5 (3 h postdrug administration). Water was allowed *ad libitum* at all times, including during food abstinence.

Starting at 8:00 hours day 2, subjects performed the test battery outlined in Table 1 at bi-hourly intervals. In order to avoid sleep inertia effects on performance measures, the modified MWT was administered last during each test session; the interval between the end of a modified MWT and the next test session was 35 min. During any time not occupied with testing, subjects were free to engage in reading, watching movies, etc., within a common living area and under constant staff supervision. Wakefulness during the entire sleep deprivation period (except during the modified MWT) was verified by observation and by continuous PSG recordings. The purpose of predrug testing sessions was to verify that tasks were sensitive to sleep deprivation and circadian rhythmicity.

At 23:50 hours day 4 (after 64 h of sleep deprivation), subjects ingested an oral dose of caffeine 600 mg, dextroamphetamine 20 mg, modafinil 400 mg, or placebo in a double-blind manner. No attempt was made to assign equal numbers of men and women to each drug group. Drug was administered just prior to midnight of the third night of sleep loss in order to test efficacy across the circadian trough of performance and alertness and to amplify sleep deprivation effects. Following drug administration, subjects continued bi-hourly performance and alertness testing. In addition, periodic testing of executive functions and administration of the Symptom Checklist occurred following drug administration through 19:00 hours day 5 (19 h postdrug; 84 h of sleep deprivation) (see Table 1). A 12-h recovery sleep period commenced at 85 h of sleep deprivation (20 h postdrug) (20:00 hours day 5 to 8:00 hours day 6). Post-recovery sleep test sessions [PVT, MWT, Stanford Sleepiness Scale (SSS)] were administered bihourly from 10:00 hours to 4:00 hours day 6. Electrodes were then removed. Subjects underwent a brief physical examination, were given a meal, then were administered the symptom checklist. They were debriefed and released at 18:00 hours day 6.

Statistical analyses

Cognitive performance (PVT), MWT, and SSS data were analyzed using a two-way mixed analysis of variance (ANOVA) for drug group (caffeine 600 mg, dextroamphetamine 20 mg, modafinil 400 mg, or placebo) and session as the within-subjects factor. Separate ANOVAs were conducted on the 32 predrug sessions (8:00 hours day 2 through 22:00 hours day 4), the 10 postdrug sessions (midnight day 5 through 19:00 hours day 5), and the four postrecovery sleep sessions (10:00 hours day 6 through 16:00 hours day 6). Greenhouse-Geisser corrections were applied to repeated measures effects; reported *P*-values reflect this correction. Significant interactions were

followed by simple effects analyses for drug group. Significant drug group effects were further analysed using Tukey Honestly Significant Difference (HSD) tests comparing all possible combinations of drug groups to isolate which drug groups differed from placebo and/or each other. Significant session main effects also were further analyzed using Tukey HSD tests to isolate session differences. Executive function tasks were analyzed using a one-way ANOVA for drug group, with significant effects followed by Tukey HSD tests among drug groups. Symptom checklist data were analyzed using a contingency table analysis with the chi-square statistic for each drug group against placebo. For the latter analysis, severity rating was disregarded and symptoms were coded as 'present' or 'absent.' Unless otherwise noted, statistical significance for all analyses was $P < 0.05$.

RESULTS

Drug groups are as follows: PLA, placebo; caffeine 600 mg = C600; dextroamphetamine 20 mg = D20; modafinil 400 mg = M400. The distribution of males and females to each drug group were as follows: PLA, 11 males; one female; C600, 11 males, one female; D20, five males, seven females; and M400, 11 males, one female. Mean age was as follows: PLA = 25.8 years; C600 = 25.2 years; D20 = 25.8 years; and M400 = 24.1 years.

Prior to drug administration (day 2, 8:00 hours through day 5, 22:00 hours sessions; 1–63 h of sleep deprivation), no drug group differences were found for response speed or accuracy for any of the cognitive performance tests (all pre-drug group main effects and group \times session interactions, $P > 0.05$). Analyses for session main effects (pre-drug) were conducted to determine whether tasks were sensitive to sleep deprivation and time of day.

Psychomotor vigilance

Response speed across pre- and postdrug sessions is shown in Fig. 1. Prior to drug administration, response speed declined as a function of both time of day (trough at 8:00 hours day 3; mean speed = 1.83) and sleep deprivation (day 3 < day 2) [session $F(31,1085) = 37.41$, $P < 0.001$]. Following drug administration, speed for PLA declined until 6:00 hours (72 h of sleep deprivation). Compared with PLA, C600 and D20 improved speed until 6:00 hours [drug group $F(3,36) = 5.06$, $P < 0.01$; session $F(9,315) = 5.39$, $P < 0.001$; drug \times session $F(27,315) = 4.18$, $P < 0.001$; drug group simple effects, $P < 0.05$; Tukey HSD $P < 0.05$] and M400 improved speed until 12:00 noon (drug group simple effects $P < 0.05$; Tukey HSD $P < 0.05$). Tukey HSD comparisons among drug groups at each post-drug session revealed the following significant effects: at 00:00 hours, C600 > D20; and at 6:00 hours M400 > C600 (both effects, Tukey HSD $P < 0.05$). Otherwise, PVT speed did not differ among groups (drug group simple effects and Tukey HSD comparisons, $P > 0.05$).

Modified Maintenance of Wakefulness – Latency to Stage 2 Sleep

Latency to stage 2 sleep is shown in Fig. 2. Prior to drug administration, sleep latency declined as a function of time of day and sleep deprivation [session $F(31,1085) = 37.41$, $P < 0.001$]. Following drug administration, sleep latency for PLA declined until 8:00 hours and then increased thereafter. Compared with PLA, C600 increased sleep latency at 00:00 hours and 2:00 hours; and D20 and M400 increased sleep latency from 12:00 noon through 14:00 hours [drug group $F(3,39) = 21.95$, $P < 0.001$; session $F(9,351) = 9.61$,

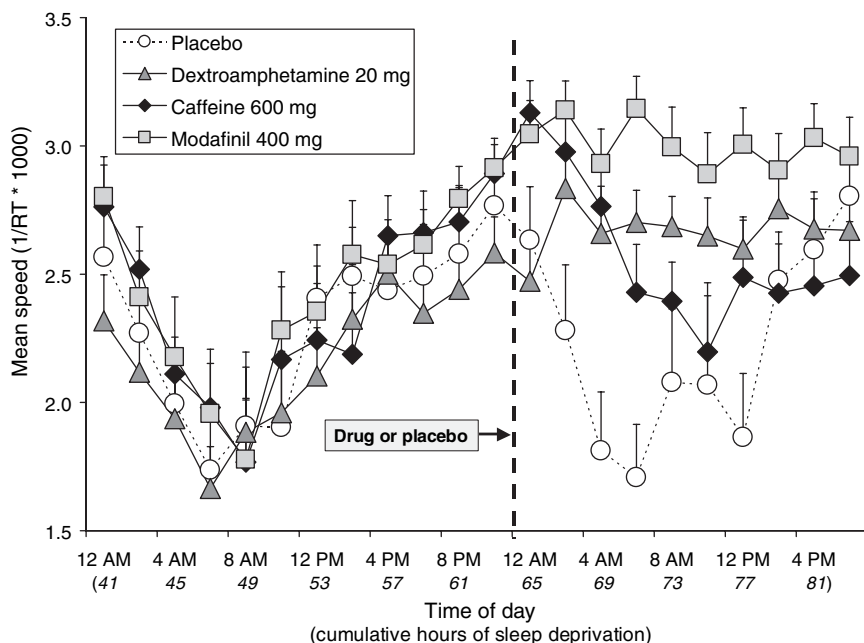


Figure 1. Psychomotor vigilance task (PVT) mean speed (1/reaction time \times 1000) and standard error across sessions as a function of drug group.

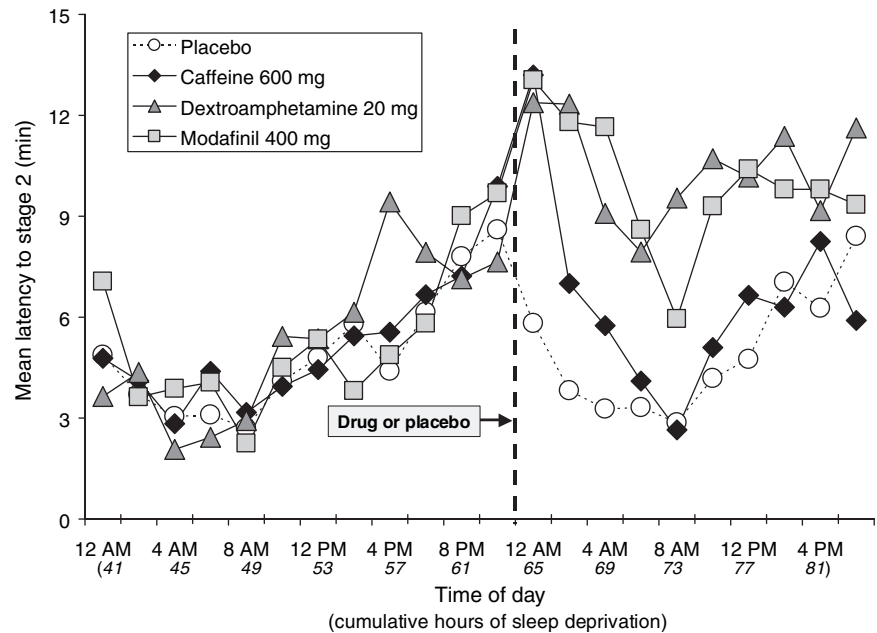


Figure 2. Modified maintenance of wakefulness (MWT) test mean latency to sleep stage 2 and standard error across sessions as a function of drug group.

$P < 0.001$; drug \times session $F(27,351) = 2.09$, $P < 0.01$; drug group simple effects 00:00 hours through 14:00 hours $P < 0.05$; Tukey HSD $P < 0.05$). Thereafter, sleep latency was not different between placebo and any drug group ($P > 0.05$). Tukey HSD comparisons also revealed the following significant effects among the three drug groups: at 2:00 hours, C600 < D20; at 4:00 hours, C600 < D20 and M400; and at 18:00 hours, C600 < D20 (all effects, Tukey HSD $P < 0.05$). Otherwise, sleep latency did not differ among groups (drug group simple effects and Tukey HSD comparisons; $P > 0.05$).

Stanford Sleepiness Scale

Subjective sleepiness increased as a function of time of day and sleep deprivation across predrug sessions [session $F(31,1364) = 32.02$, $P < 0.001$]. Highest sleepiness was reported at 6:00 hours (23 h sleep deprivation; mean score = 3.7) following the first night and at 4:00 hours (44 h

of sleep deprivation; mean score = 4.3) following the second night without sleep. Following drug administration, subjective sleepiness increased until 10:00 hours (75 h sleep deprivation) and then decreased thereafter regardless of drug group [session $F(9,396) = 4.90$, $P < .001$; drug main effect $P > 0.05$]. Although a significant drug \times session interaction was found [$F(27,396) = 2.75$, $P < 0.001$], simple effects analyses revealed a marginal drug simple effect only at 6:00 hours [drug simple effect $F(3,44) = 2.46$, $P = 0.08$] which appeared to indicate decreased sleepiness for D20 (mean sleepiness = 2.5) and M400 (mean = 2.8) compared with PLA (mean = 3.5) and C600 (mean = 3.75).

Tests of executive function

Means and standard deviations for the various dependent measures analyzed for tests of executive function are summarized in Table 2. For controlled oral word association and animal fluency, no differences among drug groups were found

Table 2 Mean (standard deviation) values for tasks of executive function

Task	Variable	PLA	C600	D20	M400
COWA	Correctly generated unique items	39.0 (7.9)	39.4 (7.9)	39.3 (11.4)	43.4 (9.9)
COWA	Perseverative errors	0.7 (1.0)	1.6 (2.3)	1.0 (1.1)	1.0 (1.5)
COWA	Number of intrusions	0.8 (0.8)	1.4 (1.2)	0.8 (0.8)	1.0 (2.0)
Category fluency	Correctly generated unique items	21.7 (5.7)	20.5 (6.4)	18.9 (3.5)	20.4 (4.8)
Category fluency	Perseverative errors	0.3 (0.5)	0.4 (0.9)	0.1 (.3)	0.2 (0.6)
Category fluency	Number of intrusions	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)
WCST	Learning to Learn	-12.8 (3.8)	-2.7 (3.2)	-3.3 (3.1)	-1.4 (0.4)
WCST	Number of correctly sorted cards	44.8 (1.9)	45.8 (3.3)	50.4 (1.3)	48.1 (3.1)
WCST	Number of errors	19.2 (1.9)	16.8 (3.6)	13.6 (1.3)	15.9 (3.1)
WCST	Number of perseverative responses	10.3 (1.2)	12.8 (4.4)	7.5 (1.0)	9.6 (2.6)
WCST	Number of categories completed	2.8 (0.3)	3.2 (0.4)	3.4 (0.4)	3.0 (0.4)
WCST	Number of trials to complete the first category	14.2 (1.5)	20.0 (5.0)	18.4 (2.8)	23.0 (5.4)
Stroop	Interference score	111.7 (10.0)	111.2 (15.7)	132.6 (13.2)	98.6 (10.0)
Biber	Prop. of impaired subjects	58.3 (N/A)	8.3 (N/A)	58.3 (N/A)	25.0 (N/A)

for number of correctly generated unique items, number of perseverative errors, or number of intrusions ($P > 0.05$). For the WCST, C600, D20 and M400 appeared to improve learning to learn [drug $F(3,35) = 2.92$, $P = 0.047$]. However, *posthoc* Tukey HSD comparisons failed to reveal significant differences among drug groups ($P > 0.05$). No significant drug group effects were found for number of correctly sorted cards, number of errors, number of perseverative responses, number of categories completed, or number of trials to complete the first category ($P > 0.05$). For the Stroop word and color naming, no drug group differences were found for interference score ($P > 0.05$). For the Biber cognitive estimation task, the proportion of subjects categorized as impaired (i.e. those eliciting 25% or more responses with Z-scores greater than 1.5 standard deviations from the mean) as

significantly less for C600 ($z = 7.5$, $P < 0.0001$) and M400 ($z = 4.8$, $P < .0001$) compared with PLA (chi-squares = 9.6, $P < 0.05$).

Symptom checklist

Number of subjects reporting each symptom (collapsed across ratings of mild, moderate, and severe) at each postdrug session are listed in Table 3. Significant results of the chi-square analyses of symptom ratings for each drug group versus PLA for each postdrug session are highlighted in bolded text. Onset of symptoms was most rapid with C600 (symptoms significantly different from PLA at 00:35 hours; approximately 40 min postdrug, approximately 65.5 h sleep deprivation). By 2 h and 40 min postdrug (approximately 67.5 h sleep

Table 3 Frequency of symptoms at each post-drug session

Time	Nervousness				Excitation				Aggressive Feelings				Headache			
	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400
00:35 AM	1	4	1	0	1	4	1	2	0	2	0	0	1	0	0	1
2:35 AM	0	4	3	0	0	4	5	5	1	2	0	1	1	1	0	2
4:35 AM	0	3	1	1	0	0	5	0	1	1	0	0	1	1	0	1
6:35 AM	0	2	1	1	0	0	1	0	0	0	0	0	2	0	0	1
8:35 AM	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0
10:35 AM	0	1	1	0	0	0	0	0	1	0	0	1	0	0	0	0
12:35 PM	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
14:35 PM	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1
16:35 PM	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	1
18:35 PM	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Time	Happiness				Pain in stomach or abdomen				Dry mouth				Pounding heart			
	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400
00:35 AM	0	2	1	1	1	2	1	0	2	3	2	0	0	3	1	0
2:35 AM	1	2	5	3	4	2	0	1	2	4	6	2	0	4	5	2
4:35 AM	0	0	1	1	1	1	1	0	1	2	4	2	0	2	3	1
6:35 AM	0	0	1	0	0	2	1	1	0	0	2	1	0	2	2	3
8:35 AM	0	0	0	0	0	1	1	2	1	0	5	2	0	0	4	0
10:35 AM	0	0	0	0	0	1	0	0	0	0	3	1	0	0	4	1
12:35 PM	1	0	1	0	0	0	0	0	0	0	2	0	0	0	3	0
14:35 PM	0	0	0	0	0	1	0	0	0	0	3	0	0	0	2	1
16:35 PM	0	1	0	0	0	1	0	0	0	0	2	0	0	0	2	1
18:35 PM	0	0	1	0	0	0	0	0	0	0	1	0	0	0	2	0

Time	Racing heartbeat				Tremors				Nausea				Jitteriness			
	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400	PLA	C600	D20	M400
00:35 AM	0	3	1	2	1	8	1	0	0	4	2	0	1	8	0	1
2:35 AM	0	5	3	1	1	3	1	2	0	5	1	0	0	7	6	2
4:35 AM	1	2	2	1	1	3	2	3	0	4	1	5	0	5	6	2
6:35 AM	0	1	1	1	1	1	1	2	0	5	0	5	0	2	2	1
8:35 AM	0	0	1	1	0	0	1	1	0	3	3	4	0	2	2	1
10:35 AM	0	0	1	1	0	0	1	1	0	2	2	3	0	1	3	0
12:35 PM	0	0	1	0	0	1	0	0	0	3	2	2	0	0	1	0
14:35 PM	0	0	1	1	0	0	1	0	0	2	1	3	0	0	2	0
16:35 PM	0	0	1	1	0	0	1	0	0	3	1	0	0	0	2	0
18:35 PM	0	0	1	0	0	0	1	0	0	2	2	0	0	0	3	0

Frequencies significantly different from placebo (PLA) are given in bold. PLA, placebo; C600, caffeine 600 mg; D20, dextroamphetamine 20 mg; M400, modafinil 400 mg.

deprivation), some symptoms were evident in all drug groups, and this continued until 8 h and 40 min postdrug (approximately 73.5 h sleep deprivation), at which point significant effects were no longer found.

Recovery sleep

No differences among drug groups were found for mean total sleep time (TST; sum of stages 2, SWS, and REM) or minutes of individual sleep stages (drug main effects; $P > 0.05$). TST minutes (and standard deviation) for PLA = 585.8 (74.8); for C600 = 611.1 (71.9); for D20 = 597.6 (63.0); and for M400 = 577.9 (108.9).

Postrecovery sleep performance and alertness

Postrecovery sleep PVT performance and MWT latency to stage 2 appeared to return to presleep deprivation baseline levels and did not differ among drug groups at any test session (all effects; $P > 0.05$).

DISCUSSION

The purpose of the present study was to evaluate the relative efficacy of a single administration of caffeine 600 mg, dextroamphetamine 20 mg, and modafinil 400 mg versus placebo for restoring and maintaining cognitive performance and objectively measured alertness during 85 h of sleep deprivation. The results indicated that caffeine 600 mg, dextroamphetamine 20 mg, and modafinil 400 mg were comparable for improving response speed on a simple vigilance task for up to 6 h postadministration. The three drugs were also comparable for improving the ability to maintain wakefulness under sleep-conducive conditions for 2 h postadministration. These findings are consistent with results from previous studies suggesting that at appropriate doses, all three agents are efficacious for improving performance and alertness during sleep deprivation (e.g. [Caldwell et al., 2000](#); [Penetar et al., 1993](#); [Wesensten et al., 2002](#)).

Duration of action: performance enhancement and implications for recovery sleep

The longer duration of action on PVT speed seen after a single dose of modafinil 400 mg or dextroamphetamine 20 mg versus placebo, compared with caffeine 600 mg versus placebo, could be explained by the different half-lives of the drugs: whereas modafinil ([Wong et al., 1999](#)) and dextroamphetamine (Dexedrine® product monograph) possess half-lives of at least 10 h, caffeine's half-life is 4–6 h ([Penetar et al., 1993](#)). Despite its shorter half-life, caffeine improved performance and alertness during the circadian trough, which in this study was 6:00 hours for PVT speed (placebo group). Although they possess longer half-lives, modafinil 400 mg and dextroamphetamine 20 mg did not impair recovery sleep (compared with placebo – nor did caffeine 600 mg). The recovery sleep period commenced

20 h postdose, at which point drug effects may have dissipated sufficiently to allow for sleep. Sleep periods commencing closer to drug administration might reveal drug-induced effects on recovery sleep. For example, in the same study as [Pigeau et al. \(1995\)](#), [Buguet et al. \(1995\)](#) evaluated the effect of modafinil 200 mg versus amphetamine 20 mg or placebo on recovery sleep. The first recovery sleep session commenced at 22:00 hours – after 64 h of total sleep deprivation and 6.5 h after the third drug administration. [Buguet et al. \(1995\)](#) reported significantly decreased total recuperative sleep time (sum of stages 2; SWS, stages 3 and 4; and REM) in both the modafinil and amphetamine groups (9.78 h and 9.37 h respectively, compared with 11.43 h for placebo). In a study by [Lagarde et al. \(1995\)](#), volunteers maintained sleep logs for 5 days following participation in a study involving sleep deprivation and modafinil or placebo. [Lagarde et al. \(1995\)](#) reported that sleep duration increased on the first recovery sleep night for the placebo group but not for the modafinil group (10 versus 8.5 h, respectively), compared with baseline sleep. However, on the second night, the situation was reversed – placebo subjects reported 8.1 h of sleep whereas modafinil subjects reported sleeping for 10 h. It has been suggested that modafinil actually reduces the extra 'sleep need' driven by sleep deprivation ([Buguet et al., 1995](#), in which amphetamine-induced decreased recovery sleep time was ascribed to a deleterious effect of drug whereas modafinil-induced decreased recovery sleep time was ascribed to a reduced need for recovery sleep). However, these same results ([Buguet et al., 1995](#)), those of [Lagarde et al. \(1995\)](#), and results from the present study suggest a more parsimonious explanation, i.e. that drug half-life and dosage determine whether a given stimulant will likely interfere with recovery sleep.

Viewed this way, caffeine's shorter half-life (relative to modafinil and dextroamphetamine) could be seen as a potential benefit: should an opportunity for sleep arise shortly after taking caffeine, dextroamphetamine, or modafinil, sleep would be more likely following caffeine than following either modafinil or dextroamphetamine. Alternatively, caffeine dosing could be repeated to sustain performance for extended periods ([Kamimori et al., 2004](#); [Wyatt et al., 2004](#)). Although in the present study MWTs were not analyzed for TST, the shorter sleep latencies seen in the caffeine group relative to the modafinil and dextroamphetamine groups suggests that volunteers would have accumulated more sleep time during the MWTs. The latter further implies that in the present study, the effects of short naps as well as the combination of naps and drug in the caffeine group was evaluated. If so, short naps appeared to have little benefit as performance degraded in the placebo group.

In the present study, postrecovery sleep performance did not differ among drug groups – and for all groups, performance appeared to be restored to presleep deprivation levels. These results correspond to those reported by [Pigeau et al. \(1995\)](#) in which postrecovery sleep performance in both the modafinil and dextroamphetamine groups was restored to baseline levels (despite the decreased recovery sleep time relative to placebo).

The recovery sleep period in this study was relatively long (12 h) as was that in the [Pigeau et al. \(1995\)](#) and [Buguet et al. \(1995\)](#) study. [Rosenthal et al. \(1991\)](#) found that when an enforced recovery sleep period of 24 h was imposed following a 0, 24, or 48-h sleep deprivation period, volunteers sleep deprived for 48 h accumulated significantly more TST than nonsleep-deprived volunteers for up to 16 h. Thereafter, however, the effects were reversed, suggesting little or no additional benefit to extending recovery sleep beyond 16 h. The latter results suggest that the 12-h period utilized in the present study was adequate to allow for maximal or near-maximal amounts of recovery sleep. Although in the present study it is not known whether volunteers were sufficiently recovered to withstand another cycle of sleep deprivation (an issue which has implications for the use of stimulants and 'recycle rates,' that is, the degree to which administration affects the rate at which the operator recovers from sleep loss, and is ready for re-insertion into the operational environment), performance did appear to be fully restored.

Dosage

In the present study, single administrations of caffeine, dextroamphetamine, and modafinil were administered at dosages which are higher than what would likely be used (caffeine) or prescribed (dextroamphetamine, modafinil) under most circumstances. For example, individuals would likely use over-the-counter caffeine to sustain alertness and performance during shorter-term (e.g. one night) sleep loss, and they would likely self-administer multiple, smaller (e.g. 100–200 mg) doses. However, because the goal of the present study was specifically to address relative efficacy at or near operational limits of sleep deprivation and during the trough of the circadian rhythm of cognitive performance and alertness, relatively large doses were chosen. Nonetheless, a limitation of the present study is that only a single dose of each drug was tested and therefore dose-dependent effects were not evaluated. The dose-dependent efficacy of caffeine ([Penetar et al., 1993](#)) and dextroamphetamine ([Newhouse et al., 1989](#)) have been demonstrated previously – i.e. efficacy of lower dosages of either drug is not maintained beyond several hours post-administration. Results from other studies also suggest some dose-dependency for modafinil ([Baranski et al., 1998](#); [Wesensten et al., 2002](#)).

Effects on executive functions

Although all three stimulants tested in the present study have been shown to improve performance on simple psychomotor tasks (e.g. [Newhouse et al., 1989](#); [Penetar et al., 1993](#); [Wesensten et al., 2002](#)), their effects on executive functions during sleep deprivation have received little attention. A notable exception is a study by [Walsh et al. \(2004\)](#). In that study, modafinil 200 mg or placebo ($n = 16$ per group) was administered at 22:00 hours for four consecutive 'night shifts' (23:00 to 07:30 hours) followed by daytime sleep (6–8 h time in bed

commencing at 08:00 hours). Compared with placebo, modafinil 200 mg significantly improved performance on verbal fluency, flexibility, and originality as measured by the Torrence Test of Creative Thinking-Verbal. Modafinil also improved performance on the WCST and Haylings Sentence Completion (which measures the ability to inhibit verbal responses). Performance on other executive function tasks either did not show drug effects (tasks administered once post-drug including Thurstone's Word Fluency; Anagram Task; Category Test; Letter-Number Sequencing) and/or did not appear to be sensitive to sleep deprivation (tasks repeated over the course of the study including Optimal Telegram and Torrence Test of Creative Thinking – Figural). There is some evidence in nonsleep-deprived volunteers that modafinil generally enhances higher-order cognitive performance ([Turner et al., 2003](#)); however positive effects on cognitive performance have not consistently been found ([Randall et al., 2003, 2004](#)). For example, [Turner et al. \(2003\)](#) compared a single dose of modafinil 100 mg versus 200 mg on tasks of digit span, a battery of eight tasks from the Cambridge Neuropsychological Test Automated Battery tapping visual memory, working memory/planning and attention; a gambling task; and response inhibition. Of the 30 dependent variables analyzed, 10 showed statistically significant effects of modafinil versus placebo. Several of these included measures tapping executive function, including mean attempts on the New Tower of London; deliberation time on a gambling task, and stop-signal reaction time and number of errors on a Stop-signal task (the latter two dependent measures also showed dose-dependent effects of modafinil). In a double-blind, placebo-controlled parallel groups design ($n = 45$; $n = 15$ per group) [Randall et al. \(2004\)](#) found significant performance-enhancing effects with modafinil 200 mg (but not modafinil 100 mg) in middle-aged adults but only for time to complete the color-naming phase of the Stroop test. [Muller et al. \(2004\)](#) evaluated effects of modafinil 200 mg versus placebo on a numeric working memory task, a delayed matching-to-sample task, letter cancellation, and trail-making using a double-blind crossover design ($n = 16$; 1-week wash-out). Modafinil decreased errors on the numeric working memory task, particularly for the most difficult condition (all four digits re-ordered: e.g. 1–2–3–4 to 3–1–4–2); further analyses indicated that subjects who were the poorest performers at baseline benefited most from modafinil.

Results from the present study (in which a limited battery of tests of executive function were used) indicated that all three drugs improved some aspects of executive function (e.g. learning to learn on WCST). Other aspects were either selectively impaired by one drug (e.g. Stroop performance impaired by dextroamphetamine) or selectively improved (e.g. Biber Cognitive Estimation performance improved by caffeine and modafinil). For the most part, few significant drug effects were found on tasks of executive function. As tasks of executive function are generally non-repeatable, in the present study those tasks for which multiple versions did not exist were administered only after sleep deprivation plus drug (a similar

approach was used by Walsh *et al.*, 2004). Although placebo-controlled, with this design it is not possible to differentiate whether lack of effects are because of lack of drug effects (only a single dose of each drug was examined) or lack of sensitivity of the tasks to sleep deprivation effects. Further, neither the present study ($n = 12$ per drug group) nor the Walsh *et al.* (2004) study ($n = 16$ per group) may have been adequately powered to reveal drug-induced differences on the tasks of executive function-tasks which although sensitive to relatively large CNS perturbations may not be sensitive to more subtle effects because of sleep loss.

Stimulant selection for operational use

For reversing sleep deprivation effects, adequate sleep is always the countermeasure of choice. However, as outlined in the introduction, certain operational contingencies (shift work, emergencies) may preclude adequate sleep. In those instances, short-term use of stimulants (which delay sleep but do not replace sleep) may be necessary to sustain safe performance. In the present study, volunteers were deprived for sleep for 64 h prior to drug administration in order to assess the extent to which tested doses restore performance. In practical use, an alertness-enhancing substance would most likely be administered during the first night of sleep loss.

As results of the present study indicate that at the dosages tested caffeine (600 mg), dextroamphetamine (20 mg) and modafinil (400 mg) are equally effective for reversing sleep loss-induced alertness and psychomotor performance decrements in otherwise normal healthy adults, and because evidence indicating that these stimulants differentially restore higher-order executive functions is lacking, decisions regarding which stimulant to use for this purpose could be based on considerations including (i) side-effect profile at equivalent doses; (ii) intermediate effects (e.g. subsequent sleep – an issue relevant to recycle rates); and (iii) tolerance/dependence effects (i.e. at equivalent dose levels, which stimulant is most likely to cause tolerance and/or dependence effects?) and abuse potential. Results of the present study suggest equivalent and relatively mild side-effect profiles of caffeine, dextroamphetamine, and modafinil at equivalent doses administered once, and no effects on recovery sleep when sleep is initiated 20 h after drug administration. Issues not addressed in the present study include tolerance/dependence/abuse potential and other side effects arising from chronic use.

CONCLUSIONS

All three stimulants tested in the present study have some costs associated with them, particularly in terms of side effects (which in some operational settings may be more salient). However, the currently available data suggest that caffeine is safe and effective – and its efficacy may be enhanced by infrequent use. Based on this, its low cost, and its wide availability, judicious/well-informed use of caffeine may

constitute a reasonable ‘first line of defense.’ Modafinil is effective and appears to have a good side-effect profile. Given its status as a scheduled medication and its cost, this would seem like the compound to try if response to caffeine is inadequate. Dextroamphetamine would constitute the third line of defense, only used acutely, and when there is reason to believe that caffeine or modafinil would not be effective.

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