Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness

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Accepted in revised form 7 February 2008; received 14 November 2007

SUMMARY Prolonged sleep loss impairs alertness, vigilance and some higher-order cognitive and affective capacities. Some deficits can be temporarily reversed by stimulant medications including caffeine, dextroamphetamine, and modafinil. To date, only one study has directly compared the effectiveness of these three compounds and specified the doses at which all were equally effective in restoring alertness and vigilance following 64 h of wakefulness. The present study compared the effectiveness of these same three stimulants/doses following a less extreme period of sleep loss (i.e., 44 h). Fifty-three healthy adults received a single dose of modafinil 400 mg (n = 11), dextroamphetamine 20 mg (n = 16), caffeine 600 mg (n = 12), or placebo (n = 14) after 44 h of continuous wakefulness. After 61 h of being awake, participants obtained 12 h of recovery sleep. Psychomotor vigilance was assessed bi-hourly during waking and following recovery sleep. Relative to placebo, all three stimulants were equally effective in restoring psychomotor vigilance test speed and reducing lapses, although the duration of action was shortest for caffeine and longest for dextroamphetamine. At these doses, caffeine was associated with the highest percentage of subjectively reported side-effects while modafinil did not differ significantly from placebo. Subsequent recovery sleep was adversely affected in the dextroamphetamine group, but none of the stimulants had deleterious effects on postrecovery performance. Decisions regarding stimulant selection should be made with consideration of how factors such as duration of action, potential side-effects, and subsequent disruption of recovery sleep may interact with the demands of a particular operational environment.

KEYWORDS caffeine, dextroamphetamine, modafinil, psychomotor vigilance, recovery sleep, side-effects, sleep deprivation

INTRODUCTION

Failure to obtain adequate sleep appears to be a pervasive problem in modern society, particularly among certain occupations such as medical residents, interstate truck drivers, and military personnel (Armentrout et al., 2006; Barger et al., 2005; DE Pinho et al., 2006; Lieberman et al., 2005). The deficits in cognitive performance that result from inadequate sleep are well documented and include impairments in simple reaction time (RT), mood, and some aspects of complex executive reasoning and decision making (e.g., Balkin, 2000; Belenky et al., 2003; Dingess et al., 1997; Dinges and Dingess, 2005; Kahn-Greene et al., 2007; Killgore et al., 2006a, 2007a; Mckenna et al., 2007). In the operational environment such deficits can constitute significant real world dangers, including risks of accidents and catastrophic errors (Gander et al., 2005;
Philip, 2005), often involving fatalities (Philip, 2005). While sleep itself is the most effective remedy for sleep loss-induced impairments, operational circumstances can preclude the opportunity for restorative sleep. Under such conditions, application of effective countermeasures to improve alertness, vigilance, and cognitive performance – and thus improve operational efficacy and safety – is advisable.

Some of the most commonly used and extensively studied pharmacological countermeasures for sleep loss include caffeine, dextroamphetamine, and modafinil (Caldwell and Caldwell, 2005; Eliyahu et al., 2007; Kushida, 2006). The efficacy of each for restoring and maintaining cognitive performance and alertness with sleep deprivation in healthy adults has been shown previously in number of separate studies (Beaumont et al., 2001; Caldwell et al., 2004; Smith et al., 2005). A few studies have also directly compared two of these compounds (Dagan and Doljansky, 2006; Pigeau et al., 1995; Waters et al., 2003; Wesensten et al., 2002, 2004), but a direct comparison of the efficacy of all three compounds for reversing vigilance performance has been performed in only one study to date (Wesensten et al., 2005), wherein they studied the relative efficacy of caffeine, modafinil, and dextroamphetamine for reversing performance deterioration on the psychomotor vigilance test (PVT) following 66 h of sleep deprivation. Situations requiring such extended periods of wakefulness are uncommon, however, so it is important to also determine the comparative effectiveness of these treatments for reversing deficits under conditions producing less extreme sleepiness. In the current study, the effects of caffeine, dextroamphetamine, modafinil, and placebo on psychomotor vigilance performance after 44 h of being awake and after 12 h of recovery sleep were examined. To provide more definitive benchmarks for evaluating the effectiveness of each of these stimulants during sleep deprivation, we chose to test the effects of the same dosages of stimulants used in the study by Wesensten et al. (2005).

The data presented here were collected as part of a larger study on the effects of sleep deprivation on higher order executive functions, the results of which have been presented in part elsewhere (Killgore, 2007; Killgore and Killgore, 2007; Killgore and Mcbride, 2006; Killgore et al., 2006b). Whereas the previous studies each described PVT performance for one or two time points as a comparator for a specific task, the present report provides a comprehensive analysis examining all PVT tests across the 5 days comprising the study to include predrug, postdrug, and postrecovery performance. Thus, in the present paper, we present data from tests administered during the predrug, peri-drug, and postdrug periods, as well as after drug elimination and postrecovery sleep, allowing for comparisons of each drug’s action at peak concentration as well as assessing the potential for any residual drug effects during and following recovery sleep.

It was hypothesized that: i) PVT performance prior to drug administration would deteriorate with sleep deprivation; ii) drug administration of caffeine, dextroamphetamine, and modafinil after 44 h of being awake would significantly improve performance compared with placebo, but their efficacy would not differ from one another at the tested doses; and iii) postrecovery performance would be comparable for all groups, including placebo.

METHODS

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

Participants

Participants were 53 healthy non-smoking, predominantly right-handed adults (29 men, 24 women) aged 18–36 (M = 23.3, SD = 4.0) who responded to advertisements posted at local universities in the metropolitan Washington DC area. Written informed consent was obtained and included an explanation of all procedures as well as possible drug side-effects. Participants were screened for past and current problems with physical, mental and neurological health, sleep history, and drug use. Participants were also excluded if they reported daily caffeine consumption above 400 mg per day and/or used tobacco products within the past 36 months. Participants were all low to moderate habitual users of caffeine based on self-reported use of coffee, tea, soft drinks, and other caffeine-containing products [i.e., their habitual caffeine intake was estimated to be 51.8 mg (SD = 65.0) per day] and there were no significant differences in average daily caffeine intake across drug groups (F[3,49] = 0.92, NS). Participants were instructed to abstain from alcohol, caffeine, and psychoactive drugs starting 48 h prior to the study. Compliance was determined with a urine drug screen on samples collected upon arrival and every 24 h throughout the study. Payment was $1600.00 for successful completion of the study and adherence to all study procedures.

The number of volunteers per randomly assigned drug group was: caffeine 600 mg (n = 12); modafinil 400 mg (n = 11); dextroamphetamine 20 mg (n = 16); or placebo (n = 14). The present study was initially designed to include four groups of 12 subjects but because of unforeseen equipment failure, six additional subjects (four dextroamphetamine and two placebo) were added in an attempt to offset the data loss. An a priori power analysis using effect sizes estimated from our previous study (Wesensten et al., 2005) suggested that a total sample size of 48 subjects equally divided amongst four groups would provide power = 0.95 to find a significant main effect of drug with z = 0.001. Participants were run in groups of two to four at a time. All volunteers who participated together as a group received the same stimulant medication to avoid noticeable differences in fatigue levels among subjects within the same session.

All volunteers were fitted with wrist actigraphs (Ambulatory Monitoring Inc., Ardsley, NY, USA) for monitoring of daily

sleep-wake activity for 7 days prior to the residential phase of the study. Sleep and wake activities were scored using automated software (action-w, version 2.6.5; Ambulatory Monitoring Inc) with custom sleep intervals created for each subject for the at-home phase of the study and pre-established ‘down-time’ intervals set for 23:00 to 7:00 hours for the in-residence baseline night. All actigraphy scoring was conducted by a trained technician (E. L. Lipizzi) blind to the drug groups. Scorable actigraphy data were available from 45 volunteers in the week preceding the study and from 48 subjects on the baseline night of the study. On average, participants obtained 6.93 h ($SD = 1.45$) of sleep per night over 7 days prior to the residential phase. The drug groups did not differ significantly in the average amount of sleep obtained during the preceding week, ($F_{3,41} = 2.17$, NS). Similarly, while sleeping overnight in the laboratory on the baseline night, volunteers obtained an average of 6.34 h ($SD = 1.25$) of actigraphically scored sleep, with no significant difference among the four drug conditions ($F_{3,44} = 0.57$, NS). In addition, valid polysomnographic (PSG) data from the baseline night were available for 37 of the participants (scored by R. M. Reichardt, a trained technician blind to drug group). These data indicated that the volunteers obtained 7.03 h ($SD = 0.86$) of sleep with no significant difference among the four drug groups at the outset of the study ($F_{3,33} = 0.59$, NS). Thus, participants in all groups began the study with essentially equivalent sleep debt.

Testing facilities

During testing and sleep periods, each subject was housed individually in a sound attenuated 8’ x 10’ room that included a bed and computer workstation. Ambient temperature was approximately 23 °C and lighting was approximately 500 lux. Background white noise was 65 dB at all times. When not engaged in testing or sleep, the participants remained within a larger lounge area to play games, eat, read, or watch television. Participants were monitored continuously by two or more laboratory technicians at all times.

Drug administration

After 44 h of continuous wakefulness, participants received a single double-blind dose of modafinil 400 mg, dextroamphetamine 20 mg, caffeine 600 mg, or placebo. The doses of drug were chosen based on previous research performed at our lab. The human pharmacokinetic properties of caffeine (Statland and Demas, 1980; Whitsett et al., 1984), dextroamphetamine (product monograph, Dexedrine®, Smith Kline Beecham Pharmaceuticals, Philadelphia, PA, USA), and modafinil (product monograph Provigil®, Cephalon Inc., West Chester, PA, USA) following a single dose 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.

Procedure

A general timeline of study procedures and testing is provided in Fig. 1. In short, participants remained awake for 61 h followed by 12 h of recovery sleep. After 44 h of continuous wakefulness, volunteers were administered one of the study medications or placebo. PVT was administered every 2 h for the duration of the waking period (30 tests total including 8 tests postdrug) and following 12 h of recovery sleep (four tests).

On the acclimation day, subjects reported to the laboratory at 18:00 hours and received a briefing on the study procedures and completed the informed consent forms. Each participant was fitted with electrodes for PSG recording and underwent familiarization with the various cognitive tasks. Participants were required to obtain 8 h time in bed within their darkened and sound-attenuated bedrooms from 23:00 to 7:00 hours, the following morning. They were awakened at 7:00 hours, engaged in basic hygiene, and were given breakfast. Decaffeinated food and beverages were allowed ad libitum throughout the study except from 23:45 hours from day 3 (approximately 3 h prior to drug administration) to 6:50 hours on day 4 (4 h postdrug administration). Water was allowed ad libitum at all times.

Starting at 8:20 hours on day 2 (first day of continuous wakefulness), subjects performed the PVT at bi-hourly intervals. During any time not occupied with testing, subjects were free to engage in reading, watching movies, and other non-strenuous activities within a common living area and under constant staff supervision. Wakefulness during the entire sleep deprivation period was verified by observation and ambulatory PSG recording.

Figure 1. The study protocol lasted for 5 days. The top x-axis indicates the hours of cumulative wakefulness and the lower x-axis is labeled in clock time. Participants received 8 h of sleep the first night, followed by 61 h of sleep deprivation, followed by a 12-h recovery sleep period. One of the study medications or placebo was administered after 44 h of sleep deprivation (indicated by the arrow and dashed line). Solid circles represent bi-hourly psychomotor vigilance test (PVT) testing sessions. The ‘baseline’ for evaluating PVT performance was derived from the mean performance of the first eight sessions.

At 2:50 hours on day 4 (after 44 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. The timing of drug administration was designed to test efficacy across the circadian trough of performance and alertness and to maximize sleep deprivation effects. Following drug administration, subjects continued bi-hourly performance and alertness testing. A 12-h recovery sleep period commenced following 61 h of sleep deprivation (17 h postdrug; 20:00 hours from day 4 to 8:00 hours on day 5). Test sessions during the postrecovery phase were administered bi-hourly from 10:20 hours to 16:20 hours on day 5. Electrodes were then removed, subjects underwent a brief physical examination, were debriefed, and released at 18:00 hours on day 5.

**Measures**

**Psychomotor vigilance test**

A 5-min variation of the PVT was administered on a palm-held computer to assess simple RT/psychomotor speed (Thorne *et al.*, 2005). PVT was analyzed for mean RT, speed (1/RT*1000), and minor (≥0.5 s) and major (≥3 s) lapses. Scores for each PVT variable were normalized as a percentage of the average score of the first eight administrations on the baseline day (testing times 8:20–22:20 hours). Higher percentage changes indicate better performance for speed and worse performance for mean RT, minor lapses, and major lapses.

**Symptom checklist**

Volunteers were screened for medication side-effects by a trained technician every 2 h during the postdrug day from 3:30 to 19:15 hours. Specifically, volunteers responded to a symptom checklist that asked whether they were experiencing any of the following symptoms: nervousness, excitement, feelings of aggression, headache, feelings of happiness or elation, pain in the abdomen or stomach area, dry mouth, pounding heart, racing heart beat, tremor, and nausea. If they responded affirmatively, they were asked to rate the severity of the symptoms as either ‘mild,’ ‘moderate,’ or ‘severe.’ To provide the maximum sensitivity to detect possible side-effects, we assessed the presence of symptoms every 2 h for the entire duration of the study from drug administration until the initiation of recovery sleep (i.e., from 3:30 to 19:30 hours on day 4). For the present report, any symptom rated as at least ‘mild’ or greater in severity was scored as present. The percentages of subjects in each drug condition who reported to be experiencing each of the 12 side-effects on one or more occasions during the postdrug period were calculated.

**Polysomnography**

Volunteers were fitted with Compumedics SIESTA PSG recording units (Compumedics USA, El Paso, TX, USA). Measures of sleep duration and sleep latency were scored for 12 h of enforced time in bed during the recovery sleep period. Records were scored by a research associate who was blind to the drug condition of the datasets. Data were scored in 30-s epochs according to the standard criteria of Rechtschaffen and Kales (1968). The following summary measures for each subject (all scored in minutes) produced were: total sleep time, time in stage 1, time in stage 2, time in slow wave sleep (SWS; stages 3 and 4 combined), time in rapid eye movement (REM) sleep, latency to first stage 1 episode, latency to first stage 2 episode, latency to first SWS episode, and latency to first REM episode. Because of technical difficulties with the recording units, valid PSG recovery sleep data were only available for 33 subjects: caffeine 600 mg (*n* = 7); modafinil 400 mg (*n* = 6); dextroamphetamine 20 mg (*n* = 11); or placebo (*n* = 9).

**Statistical analyses**

Psychological vigilance test scores normalized to percent of baseline for each variable were analyzed separately for predrug (22 tests: day 2, 8:20 hours through day 4 to 2:20 hours; sessions 1–22 h; 1–44 h awake), postdrug (8 tests: day 4, 4:20 hours through day 4 to 18:20 hours; sessions 23–30; 46–60 h awake) and postrecovery (4 tests: day 5, 10:20 hours through day 5 to 18:20 hours; sessions 31–34: 2–10 h awake) using a repeated measures ANOVA with time (i.e., test session) as a within-subjects factor and drug group as a between-subjects factor. Greenhouse–Geisser corrections were applied to repeated measures effects; reported P-values reflect this correction. Post hoc tests were performed for significant main effects and interactions with Tukey’s honest significant differences (HSD) corrections. Statistical significance for all analyses was *P* < 0.05. Trend analyses were used to assess predrug patterns of PVT performance changes with time awake.

To assess the effects of time of day on psychomotor vigilance prior to drug administration and following recovery sleep, psychomotor vigilance scores were compared using one-sample *t*-tests against the resting baseline performance value of 100%. Because there were no significant group differences prior to drug administration, the four drug groups were combined for these analyses. Because of the number of comparisons, a Bonferroni correction (*P* < 0.05) was used to adjust the level of significance (*P* < 0.001 required for means to be considered significantly different from baseline).

The chi-squared test was used to assess drug effects on items from the symptom checklist with the criterion for significance set at *P* < 0.05. Significant drug effects were followed up by dichotomous chi-squared analyses to identify significant (*P* < 0.05) differences between pair-wise drug groups.

Polysomnographic data were analyzed using a series of one-way ANOVA’s to test the main effect of drug group on the various sleep parameters. Significant main effects were followed up with pair-wise comparisons using Tukey’s HSD post hoc tests. The statistical package spss® (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses (Version 12.0 for PC).
RESULTS

Psychomotor vigilance test

Figure 2 shows the mean values and standard error bars for a) simple RT, b) speed, c) minor lapses, and d) major lapses across time on the PVT.

Predrug

Prior to drug administration, no drug group differences were found for any PVT variable [Mean RT ($F_{1,3} = 0.39; NS$), speed ($F_{1,3} = 0.24; NS$), minor lapses ($F_{1,3} = 0.23; NS$), major lapses ($F_{1,3} = 0.82; NS$)]. Tests of the main effect of time prior to drug administration showed PVT performance deterioration for all measures as the duration of wakefulness increased [Mean RT ($F_{1,21} = 8.22, P < 0.001$), speed ($F_{1,21} = 19.40, P < 0.001$), minor lapses ($F_{1,21} = 10.04, P < 0.001$), major lapses ($F_{1,21} = 4.28, P = 0.022$)]. This deterioration followed a significantly linear trend for all variables [Mean RT ($F_{1,21} = 30.4, P < 0.001$), speed ($F_{1,21} = 45.61, P < 0.001$), minor lapses ($F_{1,21} = 25.27, P < 0.001$), major lapses ($F_{1,21} = 9.41, P = 0.004$)] and also showed a significant quadratic trend for speed ($F_{1,21} = 10.16, P = 0.003$). No interactions of drug group and time were significant for any variable [Mean RT ($F_{3,63} = 0.72; NS$), speed ($F_{3,63} = 0.80; NS$), minor lapses ($F_{3,63} = 0.82; NS$), major lapses ($F_{3,63} = 0.58; NS$)].

To examine the effects of sleep deprivation on performance, the averaged data at each time point were compared with the normalized baseline performance of 100% using one-sample $t$-tests with Bonferroni correction for the number of comparisons. These tests revealed significant differences ($P < 0.001$) from baseline emerging in the early morning hours following the first night of sleep deprivation for RT (day 3, 2:20; 4:20; 8:20; 10:20; 12:20; and 14:20 hours; day 4, 2:20 hours), speed (day 3, 2:20–14:20 hours; day 4, 00:20–2:20 hours) and minor lapses (day 3, 6:20–16:20 hours; day 4, 2:20 hours).

Postdrug

All PVT variables showed a significant main effect of drug group for postdrug analyses [Mean RT ($F_{1,3} = 7.58, P < 0.001$), speed ($F_{1,3} = 14.39, P < 0.001$), minor lapses ($F_{1,3} = 11.82, P < 0.001$), major lapses ($F_{1,3} = 6.11, P = 0.001$)]. Tukey’s HSD corrected post hoc tests showed each of the drugs to be better than placebo overall for each PVT variable ($P < 0.05$) but no significant differences were found among any of the three drug groups when evaluated using Tukey’s HSD paired comparisons.

Analyses for main effects of time (postdrug) were significant for speed ($F_{1,7} = 9.48, P < 0.001$), suggesting slower speeds with greater duration of time since drug administration, but not for any other PVT variable [Mean RT ($F_{1,7} = 2.53, NS$), minor lapses ($F_{1,7} = 1.62, NS$), major lapses ($F_{1,7} = 2.25, NS$)].

The interaction of drug group and time was significant for mean RT ($F_{7,21} = 2.16, P = 0.049$) and major lapses ($F_{7,21} = 1.98, P = 0.043$), but not for speed ($F_{7,21} = 1.70, NS$) or minor lapses ($F_{7,21} = 1.18, NS$). Significant interactions were determined by examining the drug group differences at each time point using one-way ANOVAs with Tukey’s HSD corrections for pair-wise post hoc comparisons. As evident in Fig. 2, relative to placebo, the effects of dextroamphetamine emerged within the first 90 min of administration and generally sustained mean RT for 11.5 h (until 14:20 hours on day 4) and speed for 13.5 h after administration (until 16:20 hours on day 4). Significant improvement in lapses emerged 3.5 h after administration of dextroamphetamine and was generally sustained up to 11.5 h after administration relative to placebo. The effects of modafinil relative to placebo became evident after 3.5 h and were sustained until 11.5 h after administration for speed, whereas mean RT and lapses showed only sporadic improvement with modafinil relative to placebo during that time period. The effects of caffeine relative to placebo were first evident for mean RT, speed, and lapses by 3.5 h after administration were no longer significant by 5.5 h, but re-emerged briefly at 7.5 h during late morning (at 10:30 hours on day 4). Caffeine was not significantly different from placebo after that time.

Postrecovery

After recovery sleep, no drug group differences were found for any PVT variable [Mean RT ($F_{3,63} = 2.24; NS$), speed ($F_{3,63} = 0.24; NS$), minor lapses ($F_{3,63} = 1.30; NS$), major lapses ($F_{3,63} = 2.04, NS$)]. Analyses of time main effects (postrecovery) were significant for mean RT ($F_{1,3} = 7.68, P < 0.001$), speed ($F_{1,3} = 9.48, P < 0.001$), and minor lapses ($F_{1,3} = 3.15, P = 0.032$), but not for major lapses ($F_{1,3} = 0.67, NS$). No interactions between drug group and time were significant for any variable [Mean RT ($F_{3,9} = 0.01; NS$), speed ($F_{3,9} = 0.87; NS$), minor lapses ($F_{3,9} = 1.79; NS$), major lapses ($F_{3,9} = 0.48; NS$)].

It was also of interest to compare postrecovery performance to typical resting baseline performance. One-sample $t$-tests with Bonferroni correction comparing each time point against the null hypothesis of no change from baseline levels ($P < 0.001$) showed significant improvement for RT (day 5, 8:20 hours) and speed (day 5, 8:20 and 14:20 hours). Performance was comparable to baseline levels for all other time points and for minor ($\geq 5$ s) and major ($\geq 3$ s) lapses.

Symptom checklist

The symptom profile showing the percent of subjects reporting various side-effects for each stimulant group and significant drug effects are shown in Fig. 3. Chi-squared analyses revealed significant differences among the drug groups for six of the twelve symptoms assessed. Most notably, a significantly higher percentage of the caffeine group reported symptoms of nervousness, excitation, happiness, abdominal pain, nausea, and jitteriness compared with placebo; higher nervousness, excitation, nausea, and jitteriness compared with modafinil;
and higher abdominal pain and nausea compared with dextroamphetamine. The dextroamphetamine group more frequently reported feelings of excitation and happiness compared with placebo and modafinil. In contrast, the modafinil group did not differ significantly from placebo for any of the symptoms assessed here. Time courses for the reporting of each symptom are shown in Fig. 4. From the figure, it is apparent that most side-effects emerged within

Figure 2. Mean percent of baseline and SE for (a) mean reaction time (RT), (b) speed, (c) minor lapses, and (d) major lapses are displayed for placebo (solid black square), caffeine (solid gray triangle), modafinil (x), and dextroamphetamine (open circle) conditions for the psychomotor vigilance test. Percent of baseline values for each are labeled on the y-axis. Clock time is labeled on the x-axis; drug administration occurred at 2:50 hours on day 4, approximately 44 h after waking, indicated by vertical dashed line. Crosses indicate significant ($P < 0.001$) differences of averaged group performance from baseline during the predrug and postrecovery periods. Letters 'c', 'd', and 'm' indicate significant post hoc ($P < 0.05$) differences for caffeine, dextroamphetamine, and modafinil, respectively, compared with placebo.
Figure 3. Symptom profile showing the percent of subjects reporting various side-effect symptoms for each stimulant group. Subjects were queried on a standard list of symptoms every 2 h during the postdrug assessment period from 3:30 (35 min after drug administration) to 19:15 hours (16 h 25 min after drug administration). A symptom was scored as present if it was rated as ‘mild,’ ‘moderate,’ or ‘severe’ at least one or more times during the postdrug assessment period. *Symptoms labeled with asterisks indicate a significant (P < 0.05) main effect for drug group. a,b,c,dWithin each symptom, drug conditions sharing the same superscript indicate significant (P < 0.05) pair-wise differences.

Recovery sleep

The mean sleep durations and latencies to enter each stage of sleep are shown in Fig. 5. There was a significant difference among the four groups in total sleep time (F3,29 = 3.49, P = 0.028). Tukey’s post hoc analyses suggested that this effect was driven by a significant difference between the caffeine group which received an average of 694.14 min (SD = 16.96) of recovery sleep and the dextroamphetamine group which received only 564.77 min (SD = 39.66) of sleep. In contrast, there were no significant main effects of drug condition on other measures of sleep duration, including time in stage 1 (F3,29 = 1.16, P = 0.34), stage 2 (F3,29 = 2.39, P = 0.09), in SWS (F3,29 = 0.55, P = 0.65), or in REM (F3,29 = 0.70, P = 0.59).

The stimulant medications had significant effects on the latency to enter SWS, there was a significant main effect of drug group (F3,29 = 3.446, P = 0.031) which was driven primarily by a significantly longer latency for dextroamphetamine relative to placebo (P = 0.04). Finally, for latency to enter the first episode of REM sleep, there was also a significant effect of drug group (F3,29 = 3.66, P = 0.024), with the dextroamphetamine group taking significantly longer than the modafinil group (P = 0.05) to reach this sleep stage.

DISCUSSION

The relative efficacy of a single dose of caffeine 600 mg, dextroamphetamine 20 mg, modafinil 400 mg, and placebo for restoring and maintaining PVT performance during 44–61 h of continuous wakefulness was compared. Sleep deprivation produced significant decrements in PVT performance, decrements that were essentially reversed (i.e., to near baseline levels) by administration of each of the three stimulant medications, albeit for different durations of sustained performance. The present findings are therefore consistent with those of previous studies in which these three compounds have been shown to be significantly more effective than placebo for restoring alertness during sleep deprivation (Baranski et al., 2004; Caldwell et al., 2000; Kamimori et al., 2005; Mclellan et al., 2005; Silber et al., 2006; Walsh et al., 2004; Wesensten et al., 2004, 2005).

To our knowledge, there has been only one previous study that has included a direct head-to-head comparison of the effectiveness of all three stimulants within the same study. In that study, Wesensten et al., 2005 reported that caffeine 600 mg, modafinil 400 mg, and dextroamphetamine 20 mg were all equally effective in restoring alertness and psychomotor vigilance during sleep deprivation. However, that study was designed to test the effectiveness of these stimulants at rather extreme levels of sleep deprivation (i.e., 64–85 h awake), whereas the purpose of the present study was to evaluate the effectiveness of these countermeasures during a less extreme (and more commonly experienced in operational environments) period of sleep loss of 44–61 h awake. Interestingly, despite the different durations of sleep loss between the two studies, the psychomotor vigilance findings are highly comparable. Together, the two studies suggest that at the doses reported here, all three stimulants are significantly more effective than placebo and produce similar vigilance-promoting effects during periods of sleep loss extending from 44 to 85 h. None of the stimulants emerged as clearly superior to its counterparts in restoring PVT performance, however, suggesting that the decision about which stimulant to be chosen for a particular operational
setting will require consideration of other factors, such as the duration of action, unwanted side-effects, and the potential impact on recovery sleep.

**Alerting effects of stimulants**

Administration of stimulant medications on the second night of sleep deprivation essentially reversed the observed decrements in psychomotor vigilance performance relative to placebo. Whereas the placebo group showed dramatic worsening of simple RT during the early morning hours with average responses taking more than 300% longer than baseline performance when tested at their lowest point at 7:20 hours in the morning, the performance of those receiving any one of the three stimulant medications did not differ significantly from baseline levels and were generally sustained throughout much of the day.

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**Figure 4.** Time courses showing the percentage of subjects reporting each of the 12 symptoms on the symptom checklist for each drug group separately. Caffeine, modafinil, dextroamphetamine, or placebo was administered in a double-blind manner at 2:50 hours in the morning and the first symptoms were assessed at 3:30 hours. Symptoms were assessed approximately every 2 h until recovery sleep was initiated at 20:00 hours. As evident in the figure, most symptoms were apparent soon after administration and dissipated over the next 6–8 h.
of the postdrug period. Speed performance was similarly sustained by all three stimulants relative to placebo. The three stimulant groups remained at 90% of baseline performance or better for the entire postdrug period, whereas the placebo group dropped to nearly 60% by 7:20 hours and remained significantly below the other drug groups throughout most of the postdrug period. The frequency and severity of lapses also showed a comparable pattern. When assessed near the circadian nadir at 7:20 hours, the minor lapses (i.e., ≥0.5 s) of the placebo group exceeded 650% of baseline frequency and major lapses (i.e., ≥3 s) exceeded more than 400% of baseline frequency. In contrast, all three stimulant groups showed significantly fewer lapses than the placebo group, generally performing near baseline levels for the entire postdrug period.

Statistically, the three stimulants were equally effective in restoring PVT performance, showing no significant differences.
from one another when the drug groups were compared directly. This finding is consistent with previous work by Wesensten et al. (2005), which found that caffeine, dextroamphetamine, and modafinil, at the doses used here were equally effective in sustaining PVT speed following 66 h of continuous wakefulness. Other studies comparing various paired combinations of the three stimulants have also suggested relative equivalence in effectiveness for restoring alertness (Dagan and Doljansky, 2006; Pigeau et al., 1995; Waters et al., 2003; Wesensten et al., 2002, 2004). However, it should be noted that in the current study, while the stimulants did not differ statistically among themselves, there was a clear tendency for dextroamphetamine to show the most consistent and sustained effectiveness throughout the postdrug period when compared with placebo. The dextroamphetamine group differed reliably from placebo for up to 13.5 h after administration, consistent with its relatively long half-life of greater than 10 h (Dexadrine® product monograph). While not statistically different from the other two stimulants, the performance of the modafinil group was less consistently sustained relative to placebo during this same time frame, although differences were generally observed for up to 11.5 h postadministration, consistent with the reported half-life of the drug (Provigil® product monograph). Caffeine with its reported half-life of 4–6 h (Statland and Demas, 1980; Whitsett et al., 1984) was found to be more effective than placebo in sustaining mean RT, speed, and reducing lapses between 1.5 and 3.5 h after administration, but differences were generally not sustained in any consistent manner beyond that point. Because of its shorter half-life, a single large dose of caffeine may be less effective than multiple smaller doses or the use of a slow release formulation of caffeine. Some evidence suggests that repeated doses of 200 mg of caffeine every 2 h can be effective in sustaining alertness (Kamimori et al., 2005) as does slow release caffeine administered once or twice a day (Beaumont et al., 2001; DE Valck and Cluydts, 2001; Patat et al., 2000).

Side-effects of stimulants

While one of the main considerations in choosing a stimulant countermeasure is its effectiveness in sustaining alertness and performance, another consideration that is perhaps just as important is the side-effect profile of the compound. Therefore, for the present study, we collected data regarding the occurrence and severity of 12 commonly experienced side-effect symptoms every 2 h over the course of the entire postdrug period. For that analysis, a symptom was identified as ‘present’ if it was endorsed by a subject at least once during the 17-h postdrug period. That analysis showed clearly that a single 600 mg dose of caffeine was associated with significant elevations of several symptom complaints relative to placebo, including feelings of nervousness, excitation, happiness, abdominal pain, nausea, and jitters. Moreover, several of these symptoms were reported at significantly higher rates than modafinil 400 mg or dextroamphetamine 20 mg. Dextroamphetamine only showed elevated rates of excitation and feelings of happiness relative to placebo, and modafinil did not differ significantly from placebo on any symptom queried. Overall, symptoms for most stimulants were notable within 30 min and peaked at about 2.5 h after administration, although some symptoms such as abdominal pain, racing heartbeat, and nausea were still common up to 6 h postadministration for caffeine. These findings suggest that at the doses used here, caffeine may have significant unwanted side-effects relative to other stimulants and clearly argue against the use of a single bolus of caffeine, such as the 600mg dose used here. There is promising evidence suggesting that slow release caffeine (e.g., 300 mg slow release preparation every 12 h) can effectively sustain performance without unwanted side-effects (Beaumont et al., 2001; DE Valck and Cluydts, 2001; Patat et al., 2000). By distributing the concentration of caffeine throughout the course of the day, it appears possible to sustain the advantageous alerting aspects of caffeine while avoiding many side-effect symptoms. The effectiveness of slow release caffeine should be compared directly with that of other candidate stimulants in future research. Finally, dextroamphetamine was associated with more frequent reports of feelings of happiness and excitation compared with modafinil, raising concerns regarding the potential for addiction and/or abuse of this stimulant.

Effects on recovery sleep

In addition to the alerting properties and potential side-effect symptoms of the various stimulants, another important consideration is the effect they may have on the ability to obtain restorative recovery sleep when the opportunity arises (Wesensten et al., 2005). It is well known that when recovery sleep is attempted shortly after administration of stimulants, particularly during the time of peak plasma concentration, such sleep may be significantly disrupted or difficult to obtain (Carrier et al., 2007; Jay et al., 2006; Lajambe et al., 2005). For example, Buguet et al. (1995) showed that recovery sleep was significantly disrupted relative to placebo when it was attempted within 6.5 h after administration of either dextroamphetamine 20 mg or modafinil 200 mg, even when participants had been sleep deprived for 64 h. Similarly, when individuals attempt to sleep within 3 h of taking caffeine 200–300 mg, there is significant disruption in sleep onset, quality, and quantity (Carrier et al., 2007; Lajambe et al., 2005). It also appears that the effect of stimulants on recovery sleep may depend heavily on the half-life of the particular stimulant and the relative timing of the recovery sleep period. Wesensten et al. (2005) recently showed that when recovery sleep is not attempted until 20 h after the last stimulant administration, modafinil 400 mg, dextroamphetamine 20 mg, and caffeine 600 mg were not significantly different from placebo with regard to the duration of total sleep time, stage 2 sleep, SWS, and REM. It was of interest in the present study to evaluate whether recovery sleep was disrupted by stimulants.
when the duration of sleep deprivation was one night less than that of Wesensten et al.

In the present study, the recovery sleep period was initiated 17 h after the administration of the stimulant medications. As mentioned previously, equipment failure led to data loss for approximately 1/3 of the recovery sleep recordings. Consequently, we present the remaining data tentatively, recognizing that such a significant loss may have limited our power to detect effects on some variables. Nevertheless, we found that total sleep time was significantly affected by some of the stimulants. Dextroamphetamine 20 mg was associated with significantly less total sleep time than the caffeine 600 mg group. Similarly, dextroamphetamine was also associated with a longer latency to stage 2 than caffeine, a longer latency to enter SWS than placebo, and a longer latency to enter REM sleep than modafinil 200 mg. Dextroamphetamine has been suggested to have a relatively long half-life of approximately 10 h or more (Dexadrine® product monograph), whereas caffeine has a much shorter half-life of 4–6 h (Statland and Demas, 1980; Whitsett et al., 1984); it is conceivable that the residual effects of dextroamphetamine may still be present enough to adversely impact recovery sleep up to 17-h postdrug administration. No other drug effects were evident but the lack of significant effects should be interpreted cautiously in light of the reduced statistical power of these analyses. Despite this limitation, the present findings provide further evidence that the effects of stimulant medications on recovery sleep are dependent on the half-life of the particular stimulant and the amount of time that has passed since ingestion until sleep is attempted (Wesensten, 2006). It should be noted, however, that postrecovery performance on the PVT in the dextroamphetamine group was at baseline levels or higher, so any changes in the amount or quality of prior recovery sleep associated with dextroamphetamine did not appear to impact subsequent psychomotor vigilance performance.

Summary and conclusions

The present findings suggest that all three stimulants at the doses tested presently have significant alerting effects and are effective at countering deficits in PVT performance induced by sleep deprivation for 44–61 h when compared with placebo. The consistency of performance, however was generally most stable and long-lasting for dextroamphetamine 20 mg, while the effects of caffeine 600 mg were relatively short-lived. The three stimulants also produced significantly different side-effect profiles, with the greatest number of symptoms evident for caffeine 600 mg, whereas modafinil 200 mg yielded a symptom profile that was statistically indistinguishable from placebo. Finally, only dextroamphetamine 20 mg showed mild adverse effects on recovery sleep relative to the other stimulants or placebo, although these sleep effects did not impact postrecovery PVT performance. The doses of drugs administered in this study were high (approximately two times the amount generally prescribed), thus findings of effectiveness, symptom severity and impact on recovery sleep may differ at lower doses. Given the specific dosages and sleep deprivation parameters used here, it is difficult to definitively specify the best stimulant for all operational settings. Such decisions will require full consideration of the duration of alerting action desired, the level of symptom tolerance that is acceptable, and the possibility that the opportunity to obtain recovery sleep will arise on short notice. Furthermore, some emerging evidence suggests that while stimulants may be effective in restoring simple alertness and vigilance, they may not be as effective in restoring higher order cognitive processes (Gottselig et al., 2006; Killgore et al., 2007b), a question that clearly requires additional research. Further investigation of drug effects with varying amounts of sleep deprivation and dosage is needed to provide a more comprehensive picture of the performance-enhancing effects these drugs and to inform decisions concerning their use.

Acknowledgements

This material has been reviewed by the Walter Reed Army Institute of Research, and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the authors and are not to be constructed as official or as reflecting the position of the Department of the Army or the Department of Defense.

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