Modafinil vs. Caffeine: Effects on Fatigue During Sleep Deprivation

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Introduction: The extent to which modafinil and caffeine reverse fatigue effects (defined as performance decrements with time on task) during total sleep deprivation was investigated. ***Methods:*** There were 50 healthy young adults who remained awake for 54.5 h (06:30 day 1 to 13:00 day 3). A 10-min vigilance test was administered bi-hourly from 08:00 day 1 until 22:00 day 2. At 23:55 day 2 (after 41.5 h awake), double-blind administration of one of five drug doses (placebo; modafinil 100, 200, or 400 mg; or caffeine 600 mg; n = 10 per group) was followed by hourly testing from 00:00 through 12:00 day 3. Response speed (reciprocal of reaction time) across the 10-min task (by 1-min block) was analyzed prior to and after drug administration. ***Results:*** A fatigue effect (response speed degradation across the 10-min task) was exacerbated by sleep deprivation and circadian rhythmicity. Prior to the drug, this effect was maximal between 08:00 and 12:00 day 3 (24–28 h sleep deprivation). Modafinil 400 mg attenuated fatigue in a manner comparable to that seen with caffeine 600 mg; these effects were especially salient during the circadian nadir of performance (06:00 through 10:00); modafinil 200 mg also reversed fatigue, but for a shorter duration (3 min) than modafinil 400 mg (8 min) or caffeine 600 mg (6 min). ***Discussion and Conclusions:*** Time-on-task effects contributed to the performance degradation seen during sleep deprivation; effects which were reversed by caffeine and, at appropriate doses, by modafinil. Because the duration of efficacy for reversing time-on-task effects was shorter at lower drug dosages, the latter must be considered when determining the appropriate dose to use during sustained operations.
Keywords: sleep deprivation, time on task, stimulants, vigilance.

UNDER REAL-WORLD conditions, sleep deprivation results from extended activity: soldiers are sleep deprived because they must remain on duty during high-tempo continuous operations; commercial motor vehicle operators are sleep deprived because they must drive long distances to make scheduled deliveries on time. Thus, individuals do not stay awake doing nothing; in fact, in the absence of a requirement to perform tasks that prevent sleep, individuals will typically fall sleep (6). The extent to which such extended activity (fatigue, operationally defined here as time on task) contributes to performance decrements during sleep loss has been well documented (6,29–31). Fatigue also increases performance variability during sleep deprivation (10). Although the terms "fatigue" and "sleep deprivation" are used synonymously, they refer to two distinct factors that potentially impact performance. Sleep deprivation is the absence of sleep. From a physiological standpoint, fatigue refers to the inability to continue performing physical work due to the depletion of energy stores (14). The analogy to cognitive performance is the inability to continue performing cognitive work, also due to the depletion of unknown but presumably neurophysiologically based energy stores. The latter may occur independently of sleep deprivation, and vice versa.

The contribution of fatigue to performance decrements during sleep deprivation has not been adequately addressed when considering pharmacological solutions to sleep-loss-induced performance deficits. For example, it is well known that caffeine improves performance during sleep deprivation (2,3,19,21,22,25,33). Caffeine's effects are mainly recognized as improvements in response speed (22). In previous studies, the effects of caffeine on fatigue (time on task) have not been addressed, although two studies showed that caffeine sustains performance on long-duration tasks, including a 60-min vigilance task, a 60-min addition task, and a 30-min logical reasoning task (2,3), thus suggesting that caffeine reverses fatigue effects as well as sleep deprivation effects. In these studies, since performance measures were collapsed across the task, caffeine's fatigue-reversing effects were not directly addressed. Therefore, whether caffeine sustains performance across an entire work period or mainly augments initial performance is still unclear.

Modafinil also improves performance during sleep deprivation (4,5,16,23). Modafinil (2-[(diphenyl-methyl)-sulfinyl]acetamide) is approved in both North America and Europe for the treatment of daytime sleepiness associated with narcolepsy, and provisional approval for treating the excessive sleepiness associated with shift work sleep disorder and obstructive sleep apnea/hypopnea syndrome was recently granted by the United States Food and Drug Administration. The

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mechanism by which modafinil promotes alertness is thought to be inhibition of the dopamine reuptake transporter (32). In contrast, caffeine acts as an antagonist at the central adenosine receptor (20). Whether modafinil ameliorates fatigue effects during sleep deprivation is unknown, although data reported in one study suggested that modafinil sustained performance across both the first and second 3-min segments of a 6-min grammatical reasoning test (4).

It is not clear whether modafinil provides advantages over caffeine for sustaining cognitive performance during sleep deprivation. Stimulant use has been endorsed as a means for sustaining alertness in aviators (26) who, like other individuals operating complex machinery, are at risk for sleep deprivation and fatigue-induced errors and accidents associated with shift work and extended work hours (5). The extent to which modafinil has been used for the same purpose is not known; however, it is possible that some uses have included performance and alertness enhancement during sleep loss (currently an off-label use). Given caffeine's wide availability, safety, and effectiveness, for caffeine to be replaced by modafinil it would be necessary to show that modafinil is at least as efficacious as caffeine and that it displays a comparable (or more favorable) side effect profile.

In the present study, the effectiveness of modafinil vs. caffeine for attenuating fatigue effects during sleep deprivation was evaluated. Caffeine 600 mg was chosen as the comparison dose because results from a previous study indicated that this dose is effective for improving performance and alertness after 48 h of sleep deprivation, and unlike lower doses (150 and 300 mg) the 600 mg dose sustained performance for up to 12 h (21,22). Drug efficacy was evaluated using a computerized 10-min psychomotor vigilance task comparable to that described previously (9), and fatigue was operationally defined as a performance decrement across the 10-min task (10).

METHODS

The subset of data reported here was collected as part of a larger study evaluating the efficacy of modafinil (100, 200, or 400 mg) vs. caffeine (600 mg) or placebo during total sleep deprivation (28). The study was approved for implementation by the Walter Reed Army Institute of Research Human Use Committee and by the United States Army Medical Research and Materiel Command Human Subjects Review Board of the Army Surgeon General, and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Subjects were 50 healthy, non-smoking men (n = 37) and women (n = 13) (age range 18 to 30 yr, mean = 22.4) who responded to advertisements posted at local universities. Informed consent was obtained prior to inclusion in the study, and included an explanation of all procedures and possible drug side effects. Subjects were screened for past and current physical/mental health problems, sleep problems, drug use, and were excluded if reported daily caffeine consumption exceeded 400 mg. They were instructed to abstain from alcohol, caffeine, and all other drugs starting 48 h prior to the study. Compliance with abstinence from commonly abused psychoactive substances (e.g., marijuana, cocaine, nicotine) was determined with a urine drug screen on samples collected on the morning of the study. Compliance with caffeine abstinence was verified through self-report. Subjects received monetary compensation for completion of the study, plus a substantial performance bonus.

A computerized version of the task developed by Dinges and Powell (1985) was used (9). The number "000" was displayed on screen and the subject pressed a response key as soon as the number began to increment. The display then halted briefly, showing the response time in milliseconds, and then returned to zero. The delay from the response to the next incrementing stimulus was 2, 4, 6, 8, or 10 s, randomized with equal frequencies. Task duration was 10 min, and fatigue was analyzed by dividing the task into 10 1-min blocks of approximately 10 stimuli per block. There was no pause between blocks and thus this artificial division was not apparent to the subject. The dependent measure was response speed (reciprocal of response time). Lapses, defined as reaction times exceeding 500 ms (7–10), occurred infrequently and thus were not amenable to a time-on-task analysis. Descriptions of the other cognitive tasks used (for which time-on-task effects were not available) and continuous polysomnographic measures are found elsewhere (28).

During computerized testing, objective alertness testing, and sleep periods, each subject was housed individually in a sound-attenuated 10 ft × 10 ft room which included a bed and computer test station. Ambient temperature was approximately 23°C and lighting during computerized testing was approximately 200 lux, measured as the maximum value recorded at the center of the room. Subjects underwent 54.5 consecutive h of total sleep deprivation starting at 06:30 day 2 and ending at 13:00 day 4. The sleep deprivation period was preceded by 7 h of undisturbed, polysomnographically recorded sleep (23:30 day 1 to 06:30 day 2). Starting at 08:00 day 2, and continuing through 22:00 day 3, subjects performed the psychomotor vigilance task (PVT) and other tasks bi-hourly. Wakefulness during the entire sleep deprivation period (except during a modified maintenance of wakefulness test) was verified by observation and by continuous polysomnographic recordings.

At 23:50 day 3 (just under 41.5 h of sleep deprivation), subjects ingested an oral dose of modafinil 100 mg (four women, six men), 200 mg (one woman, nine men), 400 mg (two women, eight men); caffeine 600 mg (three women, seven men); or placebo (four women, six men) in a double-blind fashion via pseudorandom assignment in blocks of five (corresponding to the five drug groups). Drugs were administered just prior to midnight in order to test efficacy across the early morning hours (i.e., at a time when individuals are most likely to incur performance deficits due to combined effects of sleep deprivation and circadian rhythmicity). Starting at 00:00 day 4 (midnight—just after drug administration), subjects performed the 10-min PVT and other

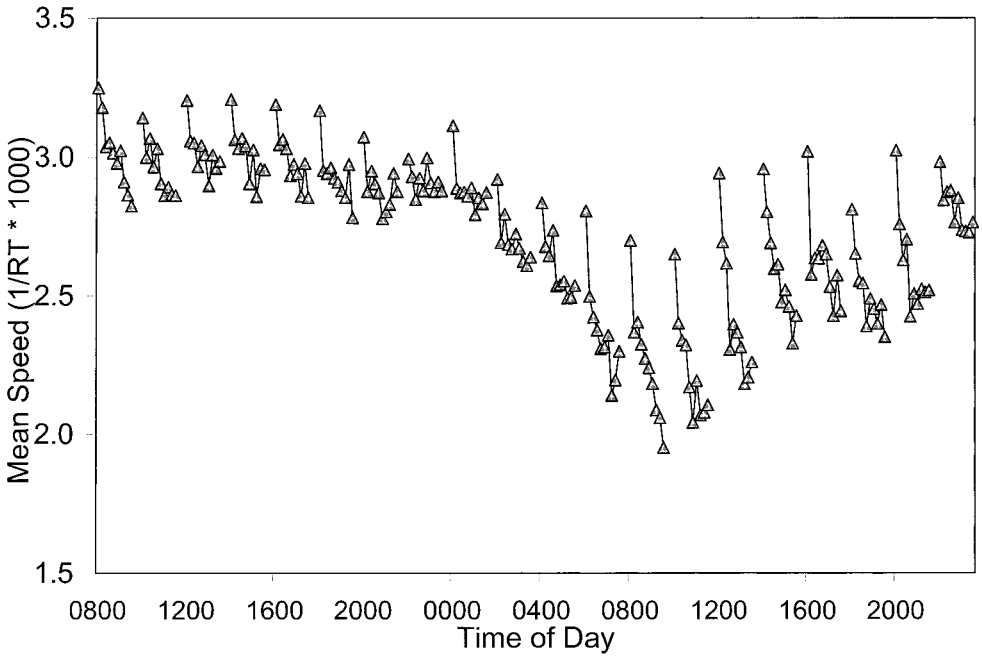

Fig. 1. Mean response speed (reaction time reciprocal) across predrug period as a function of session and block. Means are collapsed across drug groups.

tests every hour through 12:00 day 4. Subjects began a 24-h recovery sleep period at 13:00 day 4 followed by a final post-recovery sleep test session at 13:15 day 5. They were debriefed and released at 14:30.

To help maintain motivation and thereby maximize performance throughout the study, subjects were informed that they could earn a substantial bonus if their performance on the computerized test exceeded a certain criterion. They were not told the criterion (60% accuracy on one of the tests during the predrug test sessions). As anticipated, all subjects earned the bonus.

Statistical Analyses

Response speed data from the PVT were analyzed using a 3-way mixed analysis of variance (ANOVA) with drug group as a between-subjects factor (5 groups: modafinil 100, 200, or 400 mg; caffeine 600 mg; or placebo), session as a within-subjects factor, and each minute within a session or "block" (10 levels, minutes 1 through 10) as another within-subjects factor (15). The block factor served to evaluate fatigue effects across the 10-min PVT session.

Because the interval between sessions was 2 h predrug and 1 h postdrug, separate 3-way ANOVAs were conducted on the 20 predrug sessions (08:00 day 2 through 22:00 day 3), and the 13 postdrug sessions (00:00 day 4 through 12:00 day 4). Greenhouse-Geisser corrections were applied to repeated measures effects; reported p-values reflect this correction. Significant interactions were followed by simple effects analyses separately for drug group, session, or block, as deemed appropriate. In the absence of significant interactions, significant main effects (e.g., drug group) were followed by post hoc comparisons among every possible pair of groups (e.g., modafinil 100 mg v. modafinil 400 mg; modafinil 200 mg v. caffeine 600 mg) using Tukey Honestly Significant Difference (HSD) tests (15). Unless otherwise noted, statistical significance was $p < 0.05$.

RESULTS

Data for one subject (placebo group) were excluded from analysis because it appeared that the subject did not follow task instructions starting prior to drug administration (i.e., the subject was pressing response keys in the absence of stimuli). Analyses reported below are for 49 subjects. In text, drug groups are abbreviated as follows: placebo = PLA; modafinil 100 mg = M100; modafinil 200 mg = M200; modafinil 400 mg = M400; caffeine 600 mg = C600. The first postdrug session was at 00:00 day 4 (0 h postdrug).

Fig. 1 illustrates mean response speed across the 40-h predrug sleep deprivation period as a function of session and block. Since speed did not differ as a function of drug group across the first 40 h of sleep deprivation (prior to drug administration; drug main effect, $p > 0.05$), means presented in Fig. 1 are collapsed across drug group. With increasing sleep deprivation, speed degraded more rapidly across the 10-min PVT [session $\times$ block, $F(171, 7524) = 2.61$, $p < 0.001$]. This fatigue effect was most evident at 08:00 and 12:00 of day 3 (when the absolute decrement in speed was maximal). At both 08:00 and 12:00, speed for minutes 3–10 was significantly lower than speed during the first minute (HSD at 08:00 = 0.2486; at 12:00 = 0.2597, $p < 0.05$). The slope of decrement in speed across the 10-min task was calculated as the linear trend in speed across the 10-min session (slopes reported in **Table I**) using the formula $y = a + bx$, where b = slope and y = speed for each 1-min session. A one-way ANOVA for session conducted on slopes indicated that the maximal rate of performance decrement was observed at 12:00 day 3—significantly steeper than slopes at 10:00 day 2 through 04:00 day 3, and at 22:00 day 3 [session $F(19,912) = 7.2$, $p < 0.001$; HSD among slopes = 0.0328, $p < 0.05$].

Fig. 2 illustrates mean response speed following drug administration as a function of drug group, session, and

TABLE I. MEAN SLOPE OF SPEED ACROSS 10-MIN PSYCHOMOTOR VIGILANCE SESSIONS PRIOR TO DRUG ADMINISTRATION (COLLAPSED ACROSS DRUG GROUP).

Day–Time	Mean Slope	SE
2–08:00	−0.0411	0.0045
2–10:00	−0.0288	0.0064
2–12:00	−0.0189	0.0061
2–14:00	−0.0249	0.0050
2–16:00	−0.0288	0.0060
2–18:00	−0.0244	0.0064
2–20:00	−0.0139	0.0056
2–22:00	−0.0059	0.0065
3–00:00	−0.0173	0.0053
3–02:00	−0.0239	0.0051
3–04:00	−0.032	0.0071
3–06:00	−0.0493	0.0079
3–08:00	−0.0662	0.0086
3–10:00	−0.0546	0.0082
3–12:00	−0.0712	0.0083
3–14:00	−0.0582	0.0078
3–16:00	−0.0398	0.0076
3–18:00	−0.0386	0.0072
3–20:00	−0.0448	0.0093
3–22:00	−0.0232	0.0060

1-min block. For reference, data from the last predrug session (22:00, day 3) are illustrated at the far left of the figure (confirming that groups were similar prior to drug administration). Following drug administration, decrements in speed across the 10-min task (fatigue effect) differed as a function of drug group [drug × block, F (36, 396) = 1.98, $p < 0.05$]. Speed for PLA decreased significantly from the first to the second minute; and again from the fifth to the sixth minute; and from the sixth to the seventh minute [block simple effect for PLA, F (9,396) = 14.91, $p < 0.001$; HSD = 0.1865, $p < 0.05$]. Modafinil and caffeine maintained performance across 1-min blocks; M400 maintained response speed across the first 8 min [block simple effect, F (9, 396) = 3.24, $p < 0.05$]; C600 for 6 min [block simple effect, F (9, 396) = 2.84, $p < 0.05$]; and M200 for 3 min [block simple effect, F (9, 396) = 6.09, $p < 0.001$], compared with the first minute of performance for each drug group, respectively (HSD = 0.1865, $p < 0.05$). Although speed in the M100 group was faster than that for PLA at the first 1-min block, speed for M100 also decreased significantly across blocks [block simple effect for M100, F (9,396) = 17.18, $p < 0.001$; HSD = 0.1865, $p < 0.05$]. The three-way drug × session × block interaction was not significant ($p > 0.05$).

DISCUSSION

Results of the present study can be summarized as follows: as sleep deprivation increased, speed declined more rapidly across a 10-min simple vigilance task. This effect was not monotonic: fatigue effects were exacerbated during the circadian trough (for this study population, approximately 06:00 to 10:00), followed by some improvement thereafter despite increasing sleep deprivation. C600 and M400 attenuated the fatigue effect; M200 and M100 were less effective, although in both groups overall speed was higher across all blocks compared with placebo.

The present results indicate that fatigue contributes to the performance deficits seen during sleep deprivation, confirming results reported previously (7,8,10,29–31). In addition, there appears to be some interdependence among fatigue, sleep deprivation, and circadian rhythmicity (time of day). That is, the rate of decrement across the 10-min task was maximal during those sessions when initial performance also was decremented; sessions which occurred during the circadian performance trough (08:00–09:00 in this study population). However, the present results also suggest that fatigue is, to some extent, independent of sleep deprivation: fatigue effects are reversed by simple rest, whereas sleep deprivation effects are reversed only by sleep. For example, PVT speed improved on day 3 from minute 10

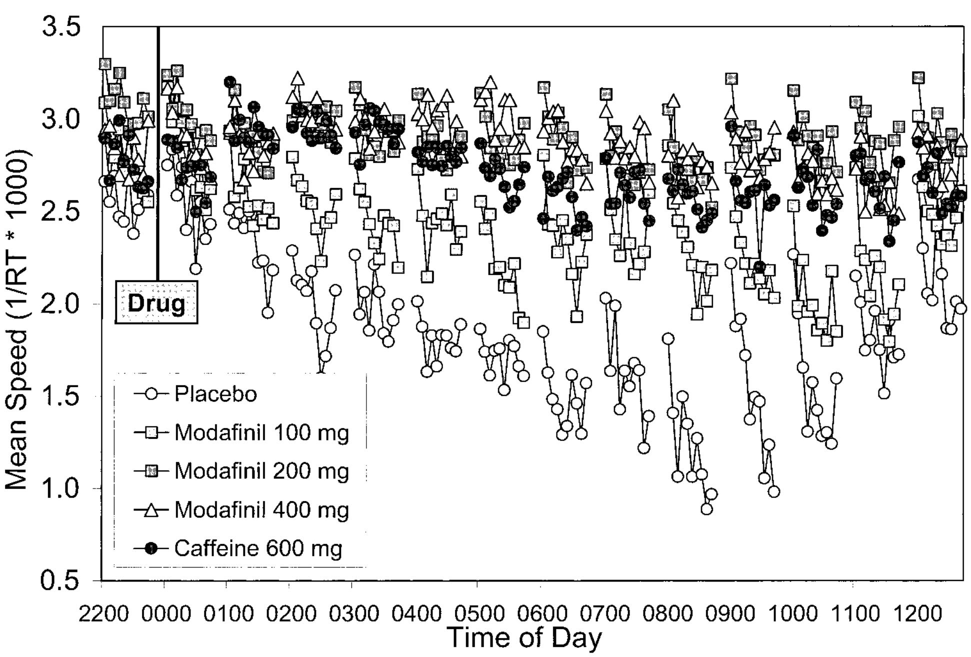

Fig. 2. Mean response speed (reaction time reciprocal) across postdrug sessions by 1-min blocks of the 10-min vigilance task as a function of drug group. For comparison, data from the last predrug session (22:00 day 4) are displayed to the left of the vertical dashed line on the figure.

at 06:00 to minute 1 at 08:00—an improvement occurring despite the fact that there was no intervening sleep (in fact, sleep debt increased by 2 h and the circadian alertness drive decreased).

Fatigue effects were found despite the fact that the psychomotor vigilance task lasted only 10 min. This finding contrasts with earlier work in which it was assumed that only long-duration tasks [e.g., 30 or more min (29)] would show fatigue effects during sleep deprivation. Whether fatigue effects would be apparent on tasks tapping cognitive functions other than simple psychomotor vigilance (memory, executive functions, etc.) and whether the rate of degradation on such tasks would be similar to or steeper than those for simple psychomotor vigilance remains to be determined. Evaluation of time-on-task effects across a broader array of cognitive tasks would also be useful for determining the nature of these effects. For example, in the present study we did not address whether reduced motivation accounted for fatigue effects. These issues could be addressed in future studies by obtaining volunteer subjective ratings of motivation and effort, or by placing a greater emphasis on performance reward contingencies to minimize motivation effects.

Results of previous studies showed that modafinil and caffeine maintain or improve performance during sleep deprivation (2–5,16,19,21–23,25,33). Results from the present study expand on these findings by showing that modafinil and caffeine improve performance not just by enhancing initial performance but by sustaining within-task performance (i.e., modafinil and caffeine counteract fatigue). Importantly, modafinil and caffeine attenuated fatigue during the circadian nadir in performance (when such effects were maximal in the placebo group). The present results also indicate that modafinil's fatigue-countering effects are dose-dependent, with a longer duration of within-task improved performance at higher doses. Compared with initial speed (first minute of the 10-min task), modafinil 400 mg maintained response speed for 8 min while modafinil 200 mg maintained speed for 3 min; modafinil 100 mg failed to maintain speed across blocks (although initial speed was faster than that for placebo). The 400 mg dosage of modafinil compared favorably to caffeine 600 mg, which maintained speed for 6 min. These findings indicate that choice of drug dosage depends not only on anticipated hours of sleep deprivation, but also on length of task. Finally, the lack of a three-way drug × session × block interaction implies a lack of a "drug time course by fatigue" interaction. That is, despite caffeine's relatively shorter half-life (5–12 h) compared with that of modafinil (10–13 h), caffeine's fatigue-reversing effects did not dissipate across sessions. The latter was likely a function of the dose of caffeine administered; caffeine's fatigue-reversing effects may have dissipated across sessions at lower doses (as was the case for the 100-mg dose of modafinil).

In the present study, response speed during a simple psychomotor vigilance task was used to evaluate the effects of caffeine and modafinil. This measure has not been validated against operationally relevant functions such as decision making and identifying friend from foe. However, it could be argued that most (if not all) operationally relevant tasks have a temporal component: in effect, the operator must make a correct decision in a limited amount of time, and operational failure results when the operator comes to a correct decision too late (or never). In this respect, the speed of the response (in particular, the correct response) is essential to all successful operations.

Both modafinil and caffeine can be characterized (at least behaviorally) as somnolytic; that is, they inhibit sleep and promote wakefulness, but do not induce hyperlocomotion in animals (11). Caffeine is a potent central adenosine receptor antagonist (20), and adenosine receptor activation plays a role in sleep promotion (1,24). The mechanism by which modafinil promotes alertness appears to be inhibition of the dopamine reuptake transporter (32). Despite their different mechanisms of action, in the present study both drugs exerted similar effects on performance; other results indicated that both drugs exert similar and mild side effect profiles (e.g., headache and nausea, neither of which interfered with task performance) (28). Thus, results from the present study failed to indicate the advantages of one drug over the other.

Performance is determined by a number of factors, including sleep/wake history, time of day (circadian rhythmicity), and fatigue (via time on task). It is reasonable to speculate that somnolytic drugs affect one or more of these factors via underlying neurobiology. Evidence that modafinil increases c-fos expression (a marker of neuronal activation) in the suprachiasmatic nucleus (12,17) suggests that modafinil initiates a cascade that ultimately results in increased suprachiasmatic nucleus output, translating into greater alertness consolidation and improved performance during the circadian trough. Such a hypothesis remains speculative. Because modafinil has been shown to affect neurotransmitter levels and to increase c-fos expression in hypothalamic nuclei associated with sleep and wakefulness (13,17,27), it has also been suggested that modafinil's alerting effects may be mediated via the hypothalamic arousal system. This hypothesis also remains speculative. Nonetheless, if certain drugs, by virtue of their neurobiological mechanisms of action, are selective for homeostatic (sleep/wake) vs. circadian processes, it may be possible to obtain pharmacological control over wakefulness/performance by selectively targeting these processes. The neurobiological processes underlying fatigue effects have yet to be elucidated.

CONCLUSIONS

Modafinil 400 mg and caffeine 600 mg are comparably efficacious for reducing fatigue during performance of a 10-min vigilance task in sleep-deprived normal healthy adults, particularly during the early morning hours. The efficacy of modafinil for attenuating fatigue (and sleep deprivation effects) varied in a dose-dependent fashion. Thus, both duration of sleep deprivation and task duration should be considered when devising pharmacological strategies for coping with short-term sleep loss. That is, with a single night (less than 24 h) of

sleep loss in operators performing short-duration (2–3 min) tasks, low doses of caffeine or modafinil may be sufficient. However, with more than one night (greater than 24 h) of sleep loss and with longer time-on-task requirements (e.g., sentry duty), higher drug doses (or repeated lower doses) will likely be required to adequately sustain performance. Finally, the failure to find measurable advantages for modafinil suggest that caffeine should remain the drug of choice for reversing performance decrements resulting from the combined effects of sleep loss and fatigue.

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