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Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature

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SUMMARY Modafinil is an alerting substance that is considered safer than amphetamine with fewer side effects. Although modafinil has been used successfully to treat narcolepsy, relatively little is known about its ability to ameliorate fatigue and declines in mental performance due to sleep deprivation (SD) in a normal population. Forty-one military subjects received either 300 mg of modafinil, 20 mg of d-amphetamine, or placebo on 3 separate occasions during 64 hours of continuous cognitive work and sleep loss. Three drug treatments were given: at 23.30 hours and 05.30 hours during the first and second SD nights, respectively, and once at 15.30 hours during the third day of continuous work. Subjective estimates of mood, fatigue and sleepiness, as well as objective measures of reaction time, logical reasoning and short-term memory clearly showed better performance with both modafinil and amphetamine relative to placebo. Both modafinil and amphetamine maintained or increased body temperature compared to the natural circadian cycle observed in the placebo group. Also, from subject debriefs at the end of the study, modafinil elicited fewer side-effects than amphetamine, although more than the placebo group. Modafinil appears to be a good alternative to amphetamine for counteracting the debilitating mood and cognitive effects of sleep loss during sustained operations.

KEYWORDS alerting substances, amphetamine, modafinil, sleep deprivation

INTRODUCTION

Fatigue due to sleep loss is a major research issue relevant to many areas of contemporary society. In a report for the National Commission of Sleep Disorders Research, Leger (1994) estimated that the total cost of accidents related to sleepiness in 1988 was over $43 billion and concluded that sleepiness, both as a primary and as a secondary cause, is a very underrated factor. Rosekind *et al.* (1994) discussed the prevalence of fatigue issues related to society's need for continuous 24 hour operations. In particular, they summarized research from the aviation environment which demonstrated the prevalence of circadian disruptions, poorer sleep quality (on the ground) and in-flight napping in both short- and long-haul commercial operations. The unique and often extreme operational conditions faced by military personnel can greatly exacerbate problems due to fatigue. For example, Neville *et al.* (1994) reported that airlift operations carried out by C-141 aircrews during Operation Desert Storm were so fatiguing that crews at times felt that they were unable to function.

Sleep loss studies have repeatedly demonstrated that sleep deprivation is associated with higher levels of (subjective) fatigue and sleepiness as well as poorer cognitive performance (Johnson and Naitoh 1974; Opstad *et al.* 1978; Haslam 1982; Naitoh 1982). However, such studies were often characterized by a paucity of behavioural tasks administered relatively infrequently. Also, the tasks were

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typically not cognitively demanding and may have been separated by long periods of leisure activity (e.g. reading or watching movies). For these reasons Angus and Heslegrave (1985) suggested that performance declines due to sleep loss reported in many studies may have been conservative and did not reflect performance impairment expected in actual work environments. Their work showed that when sleep deprivation was coupled with intensive cognitive work, performance decrements of 30–40% were found during the first night and 60–70% decrements were observed during the second night without sleep (Angus and Heslegrave 1985; Heslegrave and Angus 1985). Angus *et al*. (1992) also showed that counter measures such as physical fitness, physical exercise and reduced workload failed to inhibit the observed declines in cognitive performance. The only non-pharmacological procedure to recuperate or ameliorate the effects of sleep loss was strategically placed naps (Angus *et al*. 1992; and Naitoh and Angus 1989).

The use of alerting substances to combat sleep loss is becoming increasingly more common in military operations (Senechal and Jones 1988; Hughes 1991; Lagarde *et al*. 1991; Atkinson 1993). Although emphasis should still be placed on non-pharmacological methods for preventing or alleviating fatigue due to sleep loss (Naitoh and Kelly 1992), the exigencies of military operations may preclude such methods. Often the only alternative is the use of alerting substances.

Lagarde (1990) has divided alerting substances (or psychostimulants) into three classes: amphetaminic substances, xanthine derivatives, and new synthetics. The first (e.g. d-amphetamine) have potent pharmacological and psychological effects including feelings of euphoria, loss of appetite, increases in heart rate and blood pressure, while the second (e.g. caffeine) have fewer side-effects but also reduced potency (Newhouse *et al*. 1992; Lagarde and Batejat 1994). A new class of psychostimulants, called eugregoric, have recently become available and purport to elicit alerting properties similar to amphetaminic substances.

One of these, modafinil, is a compound (diphenylmethyl-sulfinyl-2 acetamide) that is described as maintaining wakefulness while having few side-effects (Lafon 1994). The pharmacological mechanism of modafinil is not well known. It is often described as an alpha-1 adrenergic agonistic (Rambert *et al*. 1986; Lyons and French 1991), but Mignot *et al*. (1994) have recently questioned this interpretation, reporting that modafinil had good selectivity for the dopaminergic transporter. Nevertheless, the relatively benign psychopharmacological properties of modafinil make it a good candidate to reduce or ameliorate the cognitive effects of prolonged sleep loss under continuous workload conditions. (For a more complete description of the biological–pharmacological characteristics of modafinil see our companion paper in this issue—Buguet *et al.* 1995, pp. 227–239.)

There have been few controlled studies investigating the alerting properties of modafinil using normal adult subjects (Lyons and French 1991). Modafinil has been used primarily in either clinical studies to treat sleeping disorders (Billard *et al*. 1987; Laffont *et al*. 1987; Bastuji and Jouvet 1988; Besset *et al*. 1992; Laffont *et al*. 1992) or in animal studies to investigate its pharmacological properties (Duteil *et al*. 1979; Milhaud and Klein 1985; Lagarde 1990; Hermant *et al*. 1991). Of the studies performed on healthy human adults, none has investigated the relative effectiveness of modafinil under sleep loss conditions involving more than 1 night or under continuous workload conditions (Bensimon *et al*. 1989; Lagarde and Batejat 1994; Saletu *et al*. 1986). The results of Bensimon *et al*. (1989), where healthy subjects displayed positive effects of modafinil after a single night of sleep loss with low workload, are encouraging but cannot be extended to include more extreme workload conditions. Lagarde and Batejat's (1994) study, where 200 mg of modafinil was administered to eight subjects three times a day in a 60 hour sleep loss experiment is more conclusive. Performance on a variety of cognitive tasks was maintained by modafinil, compared to placebo controls, for ≈44 h; thereafter performance declined to placebo levels. In their study, however, modafinil was not compared to other stimulants, performance was measured only intermittenly (i.e. every 6 h), and the subjects were not stressed with a continous workload.

The purpose of the present paper was to investigate the maintenance and recuperative effects of modafinil against d-amphetamine and placebo in a sleep loss experiment that required continuous cognitive work. The research paradigm was similar to those performed previously at the DCIEM laboratory where a large battery of cognitive tasks required the subjects to work continuously for 64 h without rest (except for a 15 minute break every 2 h). A drug treatment was administered after 17.5 h of wakefulness at 23.30 hours of the first night without sleep – at the circadian acrophase – to determine if modafinil and amphetamine vs. placebo would counteract the expected decline in cognitive performance. In order to investigate the recuperative effects of modafinil and amphetamine, a second drug treatment was given 30 h later at the circadian nadir of the second night without sleep (i.e. at 05.30 hours after 47.5 h of wakefulness) when cognitive performance for all three drug conditions should be at its lowest. Finally, a third drug treatment was given at 15.30 hours (10 h later) to investigate the effect of modafinil and amphetamine on recovery sleep—the results of this manipulation are reported in a companion paper.

Doses of 20 mg of d-amphetamine and 300 mg of modafinil were chosen to maximize the likelihood of observing an effect using the present experimental paradigm. Newhouse *et al*. (1989) found that 20 mg of d-amphetamine had a maximal effect on tonic arousal and cognitive performance for as long as 12 h after drug administration whereas 10 mg had a measurably smaller effect which disappeared more rapidly. For similar reasons, 300 mg was chosen for the modafinil dose (instead of 200 mg, see Lagarde and Batejat 1994).

METHOD

Subjects

Forty-one Canadian Forces reservists (19–47 y old, 39 males, 2 females) of various ranks (private to captain) participated in this study. Each subject received their regular duty wages plus a stress allowance. All subjects were pre-screened by a physician using a medical questionnaire and classified as fit to participate in the experiment if they satisfied the following criteria: (i) were healthy, (ii) were medication free for 3 weeks prior to the experiment, (iii) were not pregnant, (iv) had no history of substance abuse, (v) did not suffer from migraine headaches, and (vi) reported no sleep disturbances. Upon arrival at the laboratory, the subjects were briefed on the experiment and provided written informed consent to participate in the study. One female subject, who had been in the amphetamine group, did not complete the experiment due to illness (flu symptoms) and her data were not used. The other female subject (modafinil group) completed the experiment. A male subject in the amphetamine group did not complete the last 6 h of the sleep loss period because of a headache.

Materials

The experimental facility is a self-contained, windowless environment with subject rooms, kitchen, washrooms, relaxation areas and control rooms. The subjects worked independently in $3\,m \times 4\,m$ experimental rooms each equipped with a DEC VT100 video display terminal, IBM compatible personal computer, table, desk lamp, chair and bed. All cognitive tasks were generated and/or controlled by a DEC VAX6410 computer and were displayed on the subjects' terminal and/or personal computer. Closed-circuit televisions were used to monitor the subjects, and slave monitors were used to display to the experimenters the information present on each subject's terminal. Hence, by monitoring both the subjects and their responses, rapid detection of sleeping episodes was possible.

Although night-time and daytime electrophysiology was recorded continuously from the subjects using individual, ambulatory recording devices (Oxford Medilog 9000 recording system), the present paper will not report on these results. EEG derived sleep stage scoring results for both baseline and recovery sleep is reported in our companion paper.

Core temperature was recorded using a non-invasive, surface-mounted, monitoring system (Deep Body Thermometers Limited). Gil (1992) and Tsujimoto *et al.* (1990) have shown that this system correlates well with both rectal and oral techniques for measuring core temperature. The Deep Body Thermometer interfaced with the Oxford Medilog 9000 recording system and allowed continuous core temperature readings. Oral temperature was also electronically taken once every 2 h to correlate with the surface sensor.

Procedure

Seven groups of 6 subjects were run concurrently for 6 continuous days in the laboratory (except for one of the placebo groups, which had only 5 subjects). One week prior to arriving in the laboratory, the subjects were given an information packet that broadly described the experiment, including descriptions of the drugs they may receive. Although the subjects were informed that they would receive a drug treatment three times during the experiment, they were informed neither when the treatments would be given nor which drug they would receive. The subjects were asked to remove their watches – no time cues were available during the experiment. Female subjects were required to take a serum beta HCG pregnancy test. For the remainder of the first day the subjects completed personality inventories (e.g. morningness/eveningness, need for cognition, intolerance of ambiguity) and extensively trained and practiced the battery of cognitive tasks to be used in the experiment (see Fig. 1 for a graphical representation of the week long experimental protocol).

Prior to an 8-h baseline sleep period scheduled for the first night in the laboratory, the subjects were fitted with electrophysiological recording equipment (Medilog MR-90) to measure EEG (C3, C4, P3, P4 referenced to linked ears), EOG (outer canthus), EMG (submental), ECG and core temperature. At 06.00 hours of the second day, the subjects were awakened, had their electrodes were removed, and began a full day of practice on the battery of cognitive tasks. In the evening the electrophysiological recording equipment was reattached and the subjects were allowed another 8 h of baseline sleep. At 06.00 hours of the third day, the subjects were awakened, had their electrodes checked (but kept on) and began 64 h of sleep deprivation with continuous cognitive work.

The subjects worked continuously in 1.75 h work sessions, with 15 min breaks devoted to experimental and subject related needs (e.g. checking the electrodes, eating, using the lavatory, etc.). During these breaks, oral and core temperature were recorded. At 23.30 hours of the first night without sleep, the first drug treatment was given. For the first group of six subjects (a pilot run), two subjects orally ingested 300 mg of modafinil, two ingested 20 mg of d-amphetamine and two ingested a placebo. For the subsequent 6 runs, the entire group of six subjects ingested either 300 mg of modafinil, 20 mg of d-amphetamine or a placebo[1]. The second drug treatment occurred 30 h later at 05.30 hours of the second night without sleep. The third treatment followed 10 h later at 15.30 hours. Throughout the entire experiment, administration of drugs followed double blind procedures.

[1] The procedure was changed because the placebo subjects in the pilot run, through verbal interaction with the other subjects in the group, realized that they had been given a placebo. However, since preliminary analyses showed that the results from the six pilot subjects were consistent with those from the other 6 groups, their data were included in all subsequent analyses.

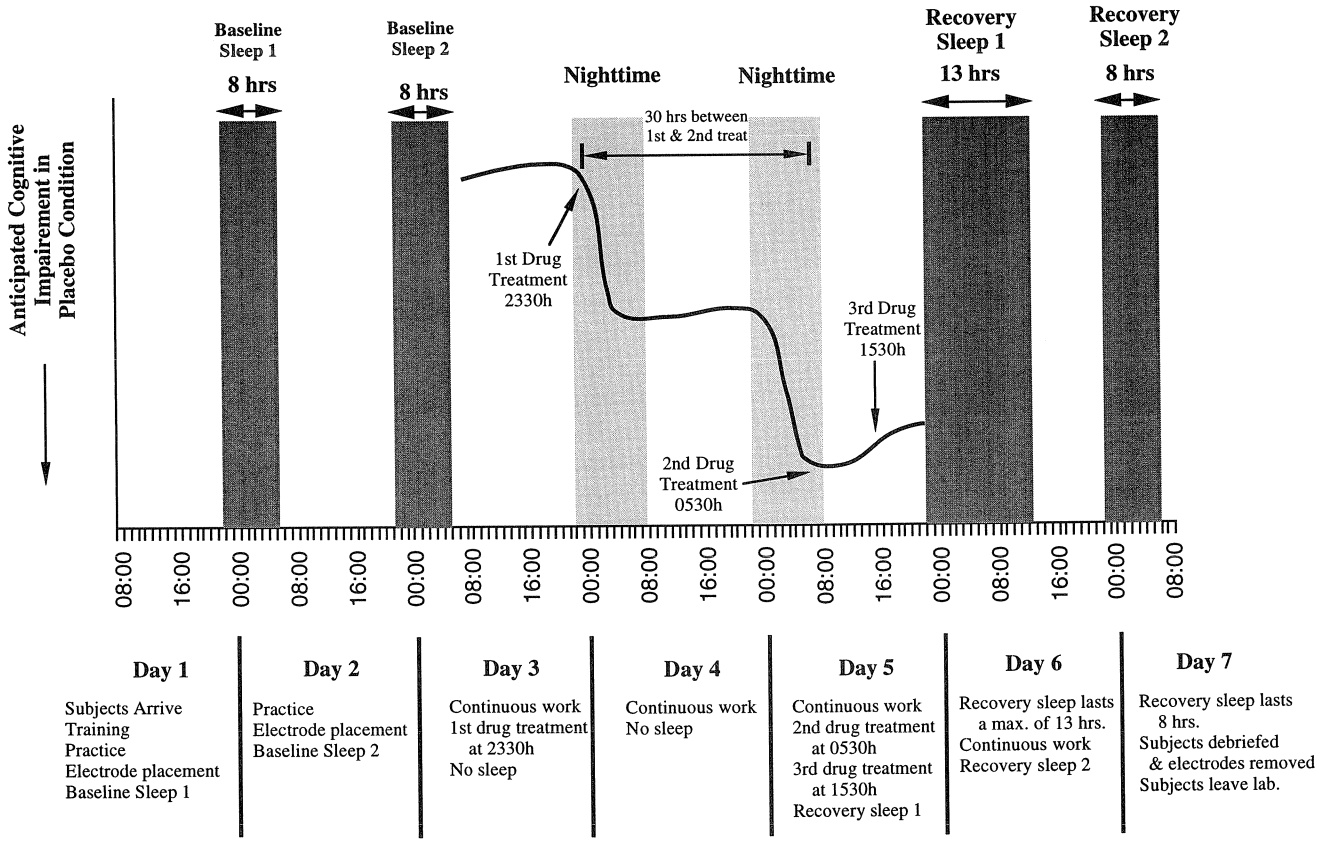

Figure 1. Graphical depiction of the experimental design. Subjects were run in groups of six. The curve represents the anticipated decline in cognitive performance expected in the placebo condition.

On the evening of the fifth day in the laboratory, at 22.00 hours, the subjects were allowed a maximum of 13 h of recovery sleep after which they were awakened and performed the cognitive tasks and subjective questionnaires until 20.00 hours that evening. A second recovery night's sleep of 8 h was allowed on the sixth day, beginning at 22.00 hours. Upon awakening on the morning of the seventh day in the laboratory, the electrodes were removed, the subjects were extensively debriefed and allowed to leave the laboratory.

Psychological tasks

In total, 17 cognitive tests and 15 subjective questionnaires were administered repeatedly to the subjects throughout the experiment. Three 2 h sessions made up a 6 hour block of tasks. This 6 hour block of tasks was then repeated until completion of the experiment. Within each 2 hour session, certain key tasks were repeated every hour, others were repeated every 2 h, and still others given only once in 6 h. Only results from a subset of these tasks (tasks used in previous DCIEM experiments) are reported here.

Subjective questionnaires. Subjects completed three subjective questionnaires each hour during the sleep loss portion of the experiment. The first was the U.S. Air Force School of Aerospace Medicine Subjective Fatigue Checklist (Harris *et al.* 1971) where subjects were presented with 10 statements, such as 'very lively' and 'petered out', and rate themselves as 'better than', 'same as' or 'worse than' each of the statements. Total scores on this scale cover a 20-point range, with lower scores indicating greater subjective feelings of fatigue.

The second scale was the 7-point Stanford Sleepiness Scale (Hoddes *et al.* 1973) where each successive point on the scale described an increasing level of sleepiness.

The third was the U.S. Naval Health Research Centre's Mood Scale (Johnson and Naitoh 1974). Subjects were presented with mood-related descriptions (e.g. active, tense, considerate, happy), and rated themselves on a 4-point scale, from 'not at all' to 'extremely'.

Cognitive tasks

Except for the short-term Memory task, the following cognitive tasks were given each hour of the experiment.

Four-choice serial reaction time task. This task required the subjects to cancel a number presented on the computer screen by pressing a spatially corresponding key on the keyboard. This adaptation of Wilkinson and Houghton's (1975) task enhanced the cognitive component of the task by requiring subjects to translate meaningful information into a spatially organized motor response.

Logical reasoning task. This task, devised by Baddeley (1968), involves understanding sentences of varying syntactic complexity. It consists of individual presentations of 16 sentences (such as 'A is preceded by B') followed by pairs of letters (either 'AB' or 'BA'). The subjects were required to indicate whether or not each sentence was a true description of the pair of letters by pressing either 'T' for true or 'F' for false.

Short-term memory (*digit span*). In this task, given once every 6 h, subjects were presented with strings of numerical digits to learn. Each digit was presented for 1 sec, and then 0.5 s later the next digit was presented. The subject's task was to memorize the complete string of digits and recall the string immediately after the last digit was presented. Recall was requested either in the same or the opposite order to the presentation. If the subjects answered correctly, the string length was increased by 1. If the answer was incorrect, the string length was decreased by 1.

RESULTS

To facilitate exposition, the results are presented in three stages: (i) physiological circadian rhythms, where oral and core temperatures are reported; (ii) subjective questionnaires of fatigue, mood and sleepiness, and objective measures of performance during the sleep loss portion of the experiment; and (iii) drug side-effects (as reported by the subjects during the debrief). For the questionnaire and cognitive task data, mixed ANOVAs were performed. Analyses were not performed for drug treatment 3 because: (i) only four hours of data were collected before the subjects were allowed recovery sleep; (ii) two groups experienced fire alarms or power failures near the end of the sleep loss portion of the study, thus contributing to missing data; and (iii) the third drug treatment was included primarily to assess the effect that each drug condition would have on recovery sleep (see our companion paper for results).

Circadian rhythms

Figure 2 illustrates oral temperatures taken from the subjects every two hours (on their breaks) throughout the sleep loss portion of the experiment. Figure 3 illustrates core body temperature as measured by the surface mounted Deep Body Temperature sensors. [Note: although the data from all subjects contributed to the oral temperature curves seen in Fig. 2, Fig. 3 (core temperature) contains the data from only 5 amphetamine, 5 placebo and 11 modafinil subjects because the equipment was unavailable for the earlier runs.] In both Figs 2 and 3 a clear circadian rhythm is present for the placebo group. A 3-between (drug condition) by 2-within (treatments 1 and 2) by 5-within (10 h) ANOVA was performed on both the oral and core temperature data. No statistically significant differences were found for the oral temperature data because of large inter- and intra subject

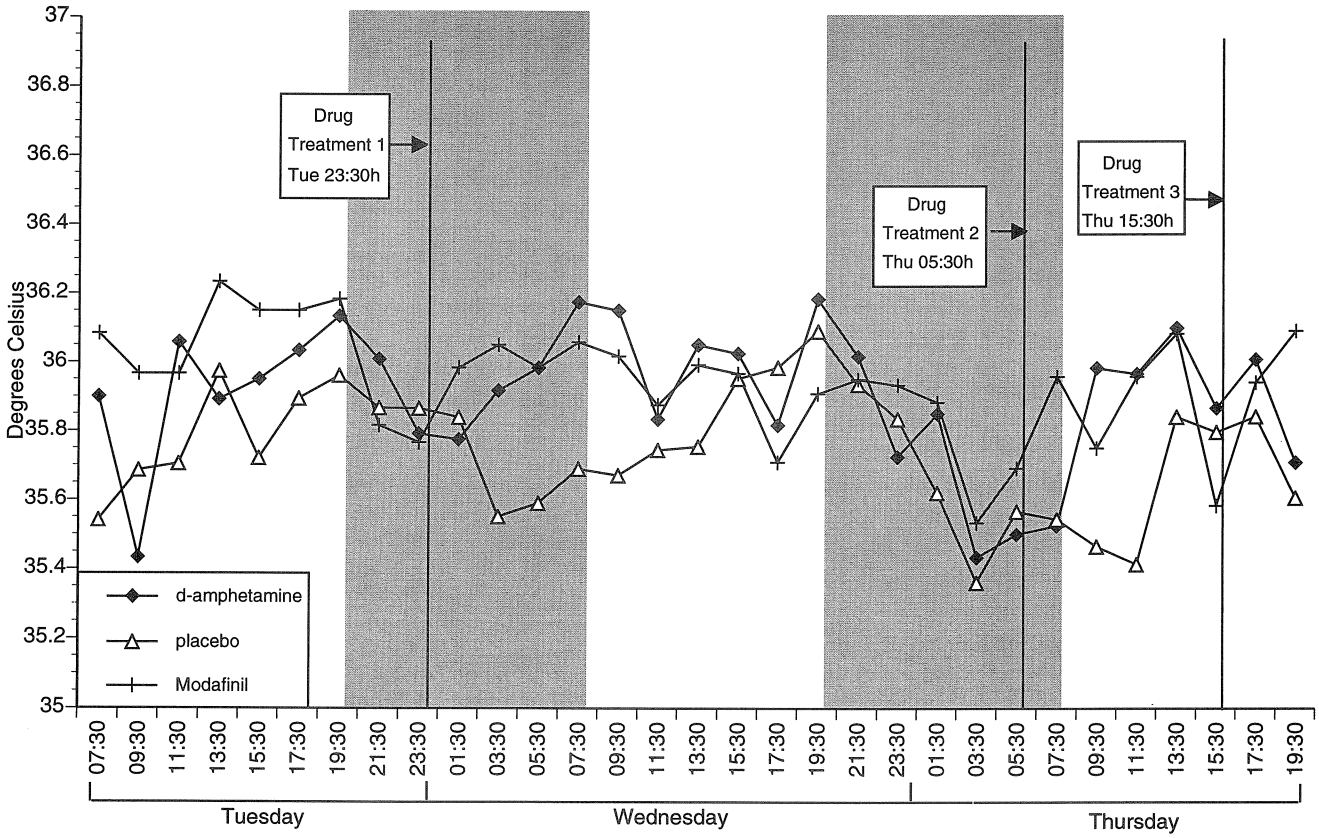

Figure 2. Mean oral temperatures taken (during breaks) every 2 h for each drug condition.

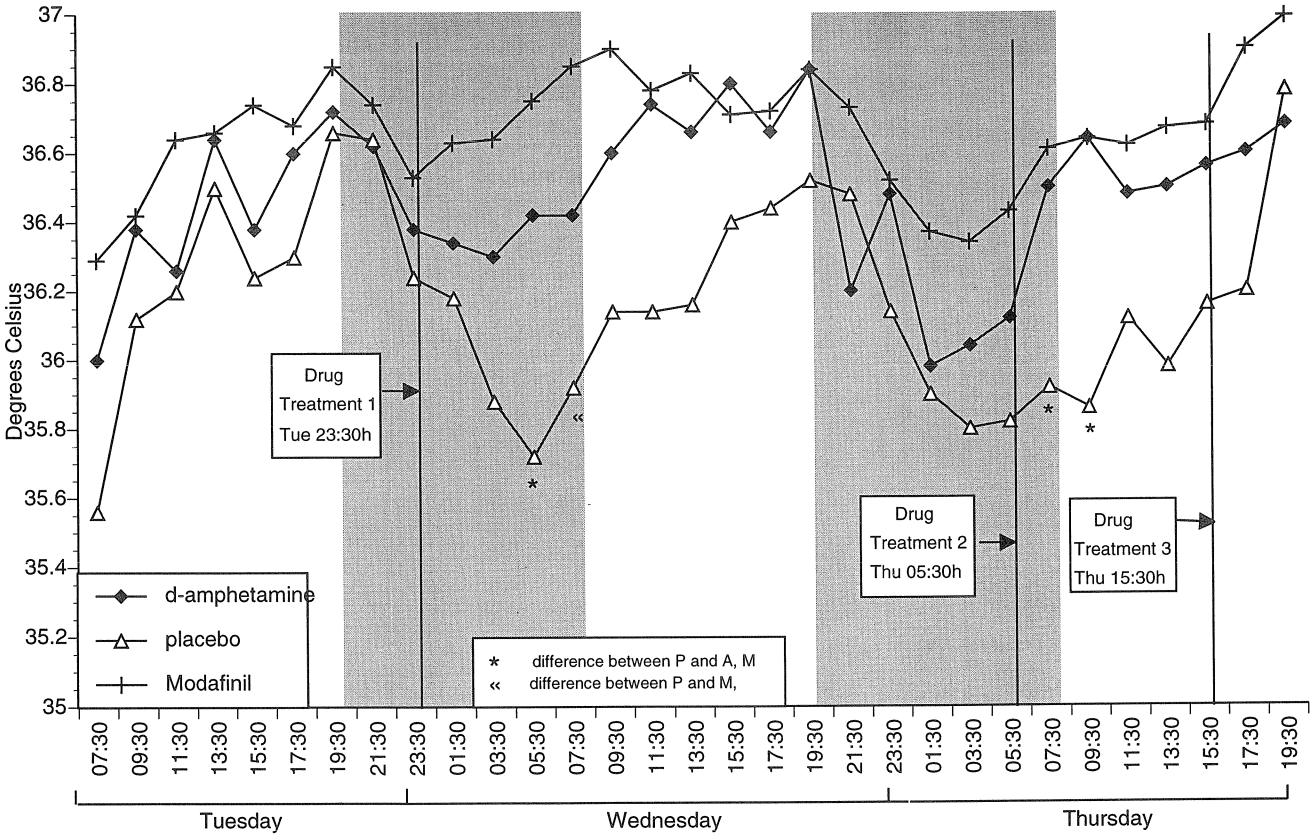

Figure 3. Mean core temperatures taken (during breaks) every 2 h for each drug condition. Newman–Keuls comparisons ($P < 0.05$) performed on values up to 10 h after drug treatments 1 and 2.

variability. A significant three-way interaction was observed for core temperatures. The interaction along with statistically significant Newman–Keuls comparison are illustrated in Fig. 3. Compared to the placebo group, the circadian rhythm for the amphetamine and modafinil groups are suppressed after administration of the first drug treatment and elevated during the second drug treatment. It appears that amphetamine and modafinil raise body temperature and thus disrupt the natural circadian rhythm.

Questionnaires and cognitive tasks

Since all of the questionnaires and most of the cognitive tasks reported in this paper were performed every hour throughout the sleep loss portion of the experiment, a 'break' effect, was evident in the results due to the arousal inducing value of the 15 minute break given to the subjects every 2 h. Preliminary analyses showed that the break improved mood and performance when compared with the same task presented 1 hour later in the session. This can be seen in Fig. 4 during the first night without sleep (from 02:00 to 10:00 hours), where the mean sleepiness values for the placebo group exhibited a 'saw-tooth' shape pattern. Analysis of variance yielded a significant 'break' effect for all tasks. For ease of interpretation, separate 3-between (amphetamine, modafinil and placebo) by 2-within (drug treatment 1 or 2) by 5-within (10 h post-drug) mixed ANOVAs with Geiser–Greenhouse epsilon corrections were performed for tasks performed immediately after the 15 min break and those occurring 1 h into a session (Table 1). Newman–Keuls *post hoc* comparisons for each task were also calculated for each level of both within subject factors (i.e. for each hour), the results of which were plotted in Figs 4–10. Note that Figs 4–7 display results for each hour of sleep loss while Figs 8a,b and 9a,b plot separately the effects for those trials occurring after the break and those trials occurring 1 hour into the session. The saw-toothed 'break' effect was so large for the Serial Reaction Time and Logical Reasoning tasks (i.e. Figs 8 and 9) that important drug and treatment effects would be masked if single graphs were plotted. Figure 10 illustrates the results for each group on the short-term Memory task which was presented once every 6 h.

In general, Figs 4–10 depict a consistent pattern of results for positive and negative mood, fatigue and sleepiness as well as performance on the serial reaction, logical reasoning and short-term memory tasks[2]. During the 10 h following the first drug treatment, the placebo group demonstrated the anticipated circadian decline in mood and performance whereas both the modafinil and amphetamine groups did not. For the 10-h period following the second drug treatment, mood and performance improved for the

[2] Although Newman–Keuls post hoc comparisons were not statistically reliable for the Short Memory task, the pattern of results are consistent with those from the other tasks.

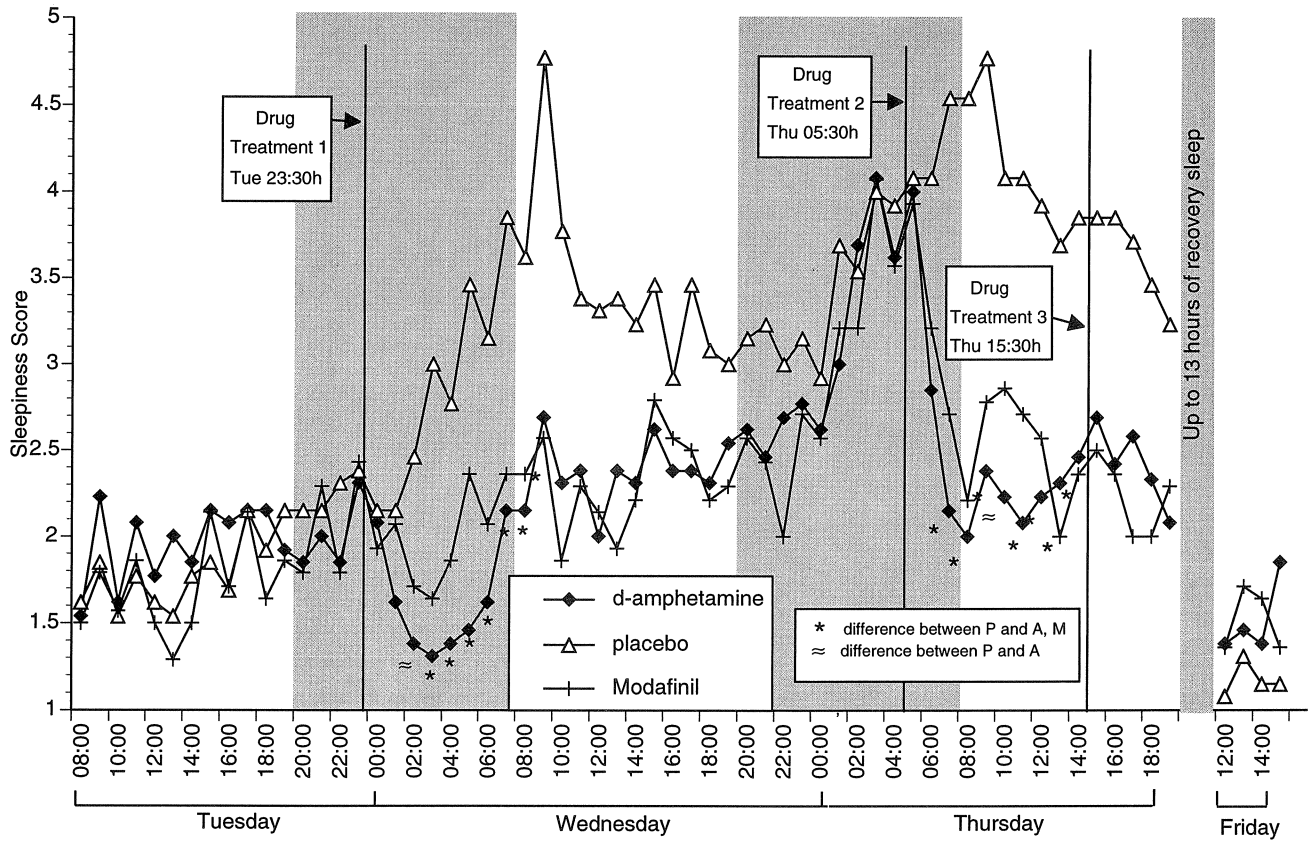

Figure 4. Mean Stanford sleepiness values taken every hour for each drug condition. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

amphetamine and modafinil groups, compared to the placebo group; no differences were observed between modafinil and amphetamine. To quantify the degree to which the three drug groups responded similarly for each task during sleep loss, intercorrelations between the drug conditions were calculated on the mean hourly values depicted in Figs 4–10. From Table 2, it can be seen that the percentage of variance shared (r^2 x 100) on each task between amphetamine and modafinil (through time) are consistently higher than those from correlations between placebo and either modafinil or amphetamine.

Statistical analyses were limited to 10 h post- treatment because (i) very little of either amphetamine or modafinil would be left in the body after 10 h, and (ii) to limit the number of statistical tests performed on the data. The following discussion of the ANOVA results (Table 1) are consistent with the general findings outlined above and observed from Figs 4 to 10.

For almost all tasks there were overall drug, treatment and time main effects. For the drug main effects, both the amphetamine and modafinil groups outperformed (and reported more positive affect) than did the placebo group. The treatment main effects illustrated that performance and mood were poorer overall during the second drug treatment when compared to the first—an effect due to increasing sleep loss. The time main effects showed that from the first to the tenth hour following drug ingestion, mood and performance declined slightly.

The main effects, however, were qualified by interactions. First, no task yielded a statistically significant drug by treatment interaction, suggesting that the three drug conditions responded in similar ways in treatments 1 and 2 (when collapsed across time). Secondly, except for the short-term memory, fatigue and serial reaction time (1 h into session) tasks, all tasks yielded significant drug by time interactions. In general (i.e. collapsed across both treatment conditions), performance and mood for the amphetamine, modafinil and placebo groups yielded similar values within 1 hour of drug ingestion, but amphetamine and modafinil progressively diverged from placebo from Hour 1 to Hour 10 post-drug. Third, almost all tasks yielded significant treatment-by-time interactions – except for negative mood (after break) and logical reasoning (1hour into session). During the first drug treatment, overall mood and performance (collapsed across drug groups) decreased from Hour 1 to Hour 10, while for treatment 2 they increased.

Some of the above main effects and two–way interactions were further qualified by a significant three–way

Table 1 ANOVA results for each task [3 drug conditions by 2 treatments by 5 trials (i.e. 10 h)]. Separate analyses performed for trials occurring immediately after a break and trials occurring 1 hour into a session. Asterisks represent significance at $P < 0.05$.

		Trials immediately after a break		*Trials 1 h into session*	
Task	*Effect*	*F-ratio*	*P>*	*F-ratio*	*P >*
Positive mood score	Drug	11.27	0.0002*	13.57	0.0001*
	Treat	24.51	0.0001*	12.00	0.0014*
	Time	6.51	0.0001*	6.82	0.0002*
	Drug × Treat	2.40	0.1050	1.44	0.2492
	Drug × Time	3.40	0.0019*	2.25	0.0380*
	Treat × Time	4.15	0.0046*	8.52	0.0001*
	Drug × Treat × Time	0.99	0.4421	1.16	0.3336
Negative mood Score	Drug	0.84	0.4403	1.47	0.2440
	Treat	20.45	0.0001*	24.00	0.0014*
	Time	3.88	0.0086*	13.64	0.0002*
	Drug × Treat	0.09	0.9102	2.88	0.4984
	Drug × Time	2.30	0.0334*	4.50	0.0380*
	Treat × Time	1.24	0.2956	17.04	0.0001*
	Drug × Treat × Time	3.05	0.0074	2.32	0.6672
Fatigue score	Drug	9.50	0.0005*	11.09	0.0002*
	Treat	21.84	0.0001*	8.86	0.0051*
	Time	4.43	0.0036*	6.46	0.0002*
	Drug × Treat	0.74	0.4847	0.10	0.3972
	Drug × Time	2.05	0.0553	0.92	0.4964
	Treat × Time	4.12	0.0057*	6.05	0.0003*
	Drug × Treat × Time	1.72	0.1115	1.82	0.0887
Stanford Sleepiness Scale	Drug	7.74	0.0016*	12.82	0.0001*
	Treat	22.03	0.0001	8.59	0.0058*
	Time	4.81	0.0013*	6.54	0.0001*
	Drug × Treat	1.28	0.2907	0.43	0.6528
	Drug × Time	3.96	0.0003*	2.06	0.0552
	Treat × Time	8.01	0.0001*	13.76	0.0001*
	Drug × Treat × Time	1.85	0.0792	2.77	0.0149*
Serial reaction time	Drug	4.03	0.0261*	7.57	0.0017*
	Treat	170.91	0.0001*	193.99	0.0001*
	Time	7.85	0.0001*	11.32	0.0001*
	DrugxTreat	2.13	0.1327	1.04	0.3653
	Drug × Time	4.44	0.0002*	0.91	0.5032
	Treat × Time	22.48	0.0001*	5.92	0.0004*
	Drug × Treat × Time	5.72	0.0001*	4.34	0.0002*
Logical reasoning	Drug	0.73	0.4871	2.41	0.1054
	Treat	95.91	0.0001*	95.18	0.0001*
	Time	6.02	0.0003*	8.85	0.0001*
	Drug × Treat	0.03	0.9716	0.33	0.7213
	Drug × Time	3.62	0.0013*	2.54	0.0169*
	Treat × Time	3.22	0.0222*	1.49	0.2147
	Drug × Treat × Time	3.42	0.0030*	1.71	0.1122
		Overall ANOVA (every 6 h, no break effects)			
Short-term memory	Drug	4.73	0.0161*		
	Treat	66.05	0.0001*		
	Time	0.96	0.3357		
	Drug × Treat	1.66	0.2062		
	Drug × Time	0.26	0.7746		
	Treat × Time	6.35	0.0171*		
	Drug × Treat × Time	0.07	0.9280		

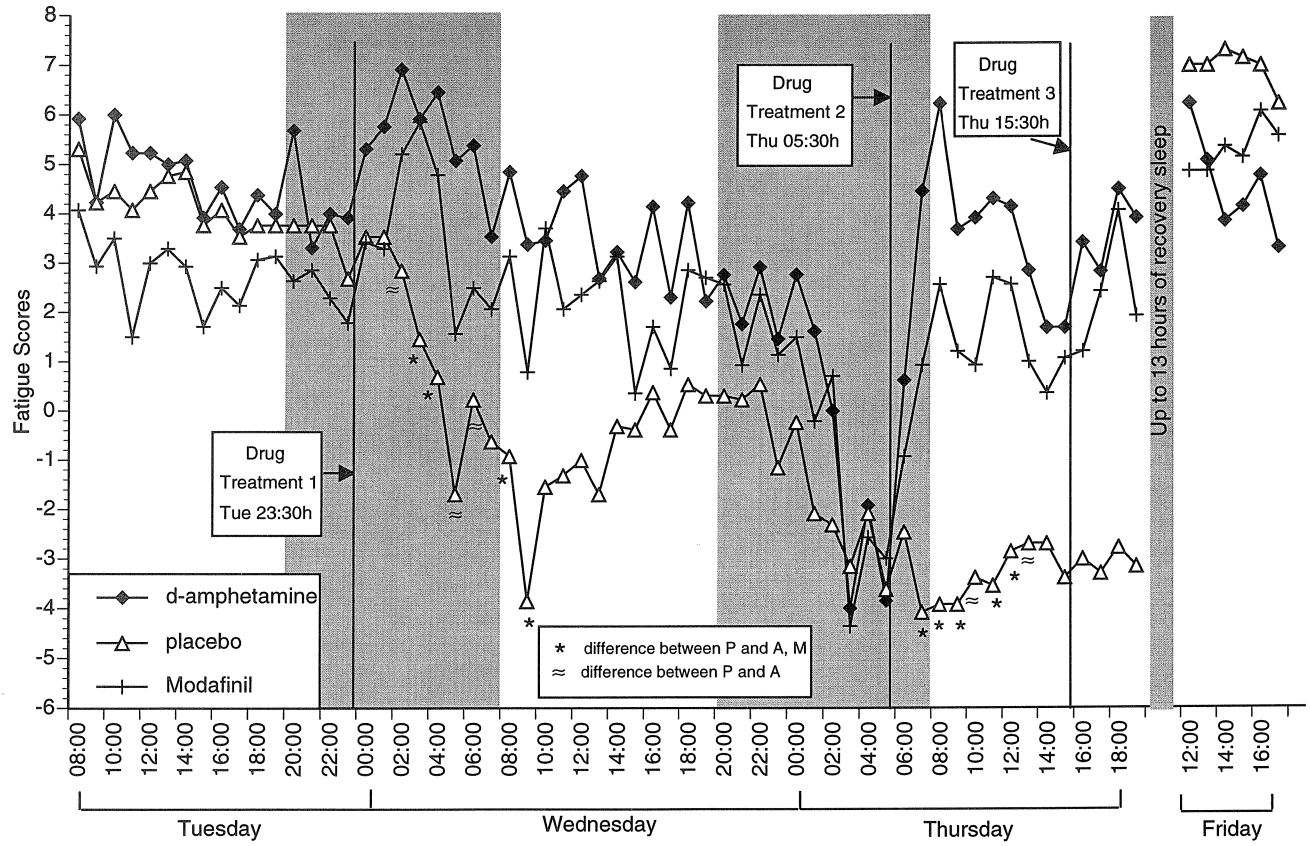

Figure 5. Mean fatigue scores taken every hour for each drug condition. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

interaction – specifically, serial reaction time, Stanford sleepiness (1hour into session) and logical reasoning (after break). From Hours 1 to 10 after the first drug treatment, the placebo group demonstrated degraded mood and performance when compared to the amphetamine and modafinil groups (who were less affected). From Hours 1 to 10 for the second drug treatment, however, the placebo group's mood and performance remained largely unchanged while those of both the amphetamine and modafinil groups increased.

When the mean subjective estimates for mood and fatigue were correlated with each of the performance tasks, the percentage of variance shared between the two were consistently high for all three drug conditions (amphetamine: 33–92%; modafinil: 44–86%; placebo: 60–92%). This suggests that hour-by-hour estimates of subjective mood, fatigue and sleepiness were good estimators of varying cognitive performance throughout the 64 h of sleep loss.

Subjective drug effects

Saturday morning, at the end of the experiment, a detailed debrief was carried out with all subjects. In a group, each subject responded to the following questions: (i) for each time you were given a drug, which drug do you believe you received? and (ii) for each time you were given a drug, did you notice any effects? (if yes, what were they?). After enduring a week-long, intensive experiment together, each group of six subjects answered the questions willingly and were eager to share their experiences with the others.

Table 3 displays, for each drug treatment and for each drug condition, the subjects' estimates of the drug taken. It was evident from their responses that the subjects did not realize they had received the same drug on all three occasions. From the column totals in Table 3, for subjects given amphetamine, 53% indicated they had received amphetamine, 31% said modafinil, 16% said placebo and 0% did not know. For subjects given modafinil: 26% said they had received amphetamine, 39% modafinil, 27% placebo and 7% did not know. For the placebo group the distribution was: 19% amphetamine, 17% modafinil, 49% placebo and 15% did not know. Subjectively, 84% of the amphetamine group felt that they had received some alerting substance (either modafinil or amphetamine), vs. 65% for the modafinil group and 36% for placebo subjects. A Chi-squared analysis of the column totals from Table 3 yielded a statistically significant difference ($\chi^2_{(6)} = 25.3$,

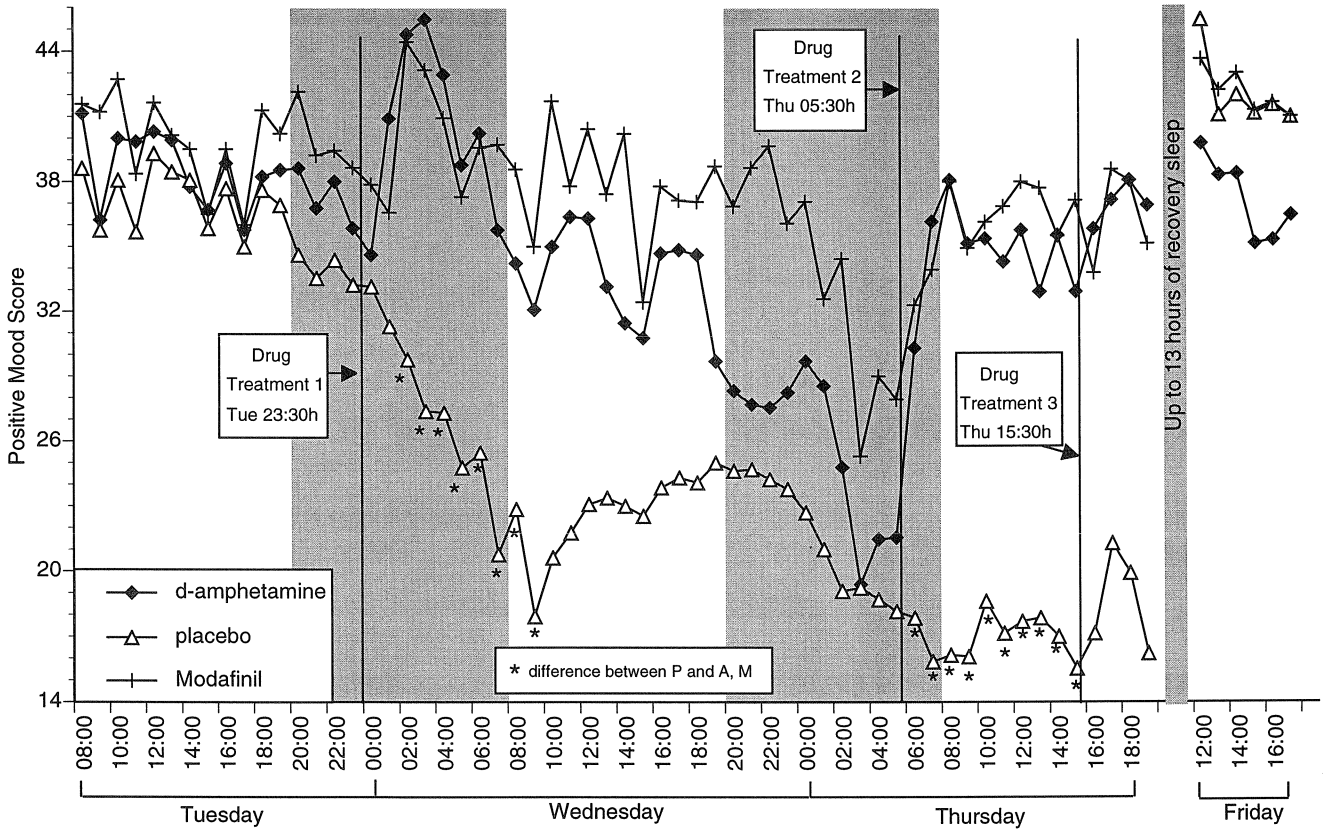

Figure 6. Mean positive mood values taken every hour for each drug condition. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

$P > 0.001$) between the three drug conditions, confirming that the subjects responded differently to the drug conditions.

Of the total number of physical and psychological symptoms reported by the subjects during the debrief (Table 4), 45% were experienced by the amphetamine group, 35% by the modafinil group, and 20% by the placebo group. Table 4 also lists a few of the more noteable symptoms reported by the subjects in each drug condition, as well as the total number of symptoms reported by each group. An increase in the frequency of urination was reported 13 times by the modafinil group but only once by the amphetamine group and 3 times by the placebos. All groups reported hallucinations, but only the amphetamine group experienced subjective changes in ambient illumination.

In summary, the circadian rhythm, as reflected by core and oral body temperatures for the placebo group, were disrupted in the amphetamine and modafinil groups. Body temperature remained high for both drug conditions after the first treatment (compared to placebo) and increased after the second treatment. Similar results were found for all subjective measures of mood and fatigue as well as for the objective measures of cognitive performance. For the most part, subjects were able to tell (*post hoc*) whether or not they had ingested an alerting substance (either amphetamine or modafinil) or had received a placebo.

DISCUSSION

The results for the placebo group in this experiment replicated findings from previous (non drug) sleep loss studies involving continous work (Angus *et al.* 1985; Heslegrave *et al.* 1985). Although modulated by the circadian cycle, subjective estimates of fatigue, sleepiness and mood as well as objective measures of cognitive performance varied consistently as a function of sleep loss. Taken as a percentage of the level of baseline performance (i.e. from the beginning of the experiment), the placebo group demonstrated a 30–40% decrement in performance after the first 24 h and a 55–65% percentage decrease after 48 h without sleep. In contrast, both the amphetamine and modafinil groups experienced only a 5–10% decline in cognitive performance after the first 24 h of sleep loss (10 h after drug ingestion). Although both groups showed performance declines comparable to the placebo group after 48 h (i.e. 55–65%), the second drug treatment improved performance to a level 20–30% below baseline for both the amphetamine and the modafinil groups. There were no differences between modafinil and amphetamine in their ability to either ameliorate or recuperate mood and performance during the 10 h post drug administration for either the first or second drug treatment. This conclusion is supported by both the non-significant Newman–Keuls *post*

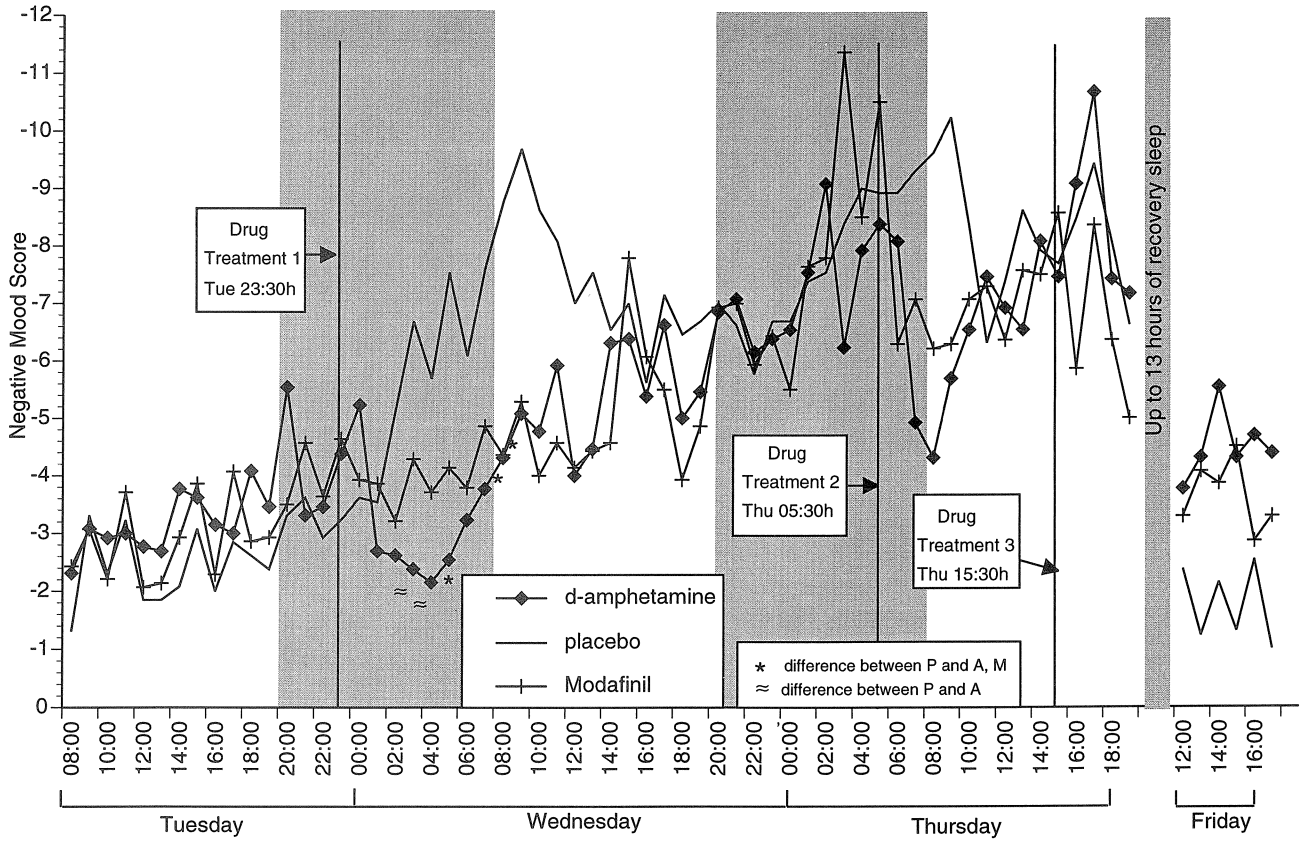

Figure 7. Mean negative mood values taken every hour for each drug condition. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

hoc comparisons between modafinil and amphetamine and the consistently higher percentage of variance shared by the two drug groups vs. placebo for all of the tasks.

There was good correspondence (i.e. high percentage of shared variance) between mean subjective estimates of mood-fatigue and mean objective measures of performance across the entire sleep loss period for each of the drug conditions. This supports a large body of evidence showing that subjective measures of sleepiness and performance decrements are the two most common effects of fatigue and covary as a function of the circadian cycle (Glenville and Broughton 1979; Herscovitch and Broughton 1981; Babkoff *et al.* 1991; Gillberg *et al.* 1994). These effects, however, were influenced by the presence of the 15 minute break, as the significant main effect for break (for all tasks) demonstrated. Mood, fatigue and performance were moderately ameliorated after a short rest period, when compared with results one hour later after continuous cognitive work. This finding is consistent with previous (non-drug) studies from our laboratory (Angus *et al.* 1992).

Newhouse *et al.* (1989) found that 20 mg of d-amphetamine after 48 h of sleep deprivation returned performance to baseline levels whereas in our study performance was still degraded by 20–30% after the second drug treatment. A likely explanation for this discrepency is the high work-to-rest ratio in our experiment (≈0.8) compared to that used by Newhouse *et al.* which ranged from ≈0.2 for the first 48 h to ≈0.4 for the following 12 h. There were two reasons why a high work-to-rest ratio was considered important for our study. First, a high ratio tends to 'increase physiological sleep tendency, which the boring tasks unmask even with sleep loss of less than 24 h' (Babkoff *et al.* 1991; p. 538); hence, it was important to induce cognitive fatigue during the first night of sleep loss in order to study the possible ameliorative effects of amphetamine and modafinil during this time. Second, it would have been unrealistic to expect, in actual military environments, that personnel would not sleep if they were not continually tasked. Since continuous and sustained operations are at times expected from military personnel, high work-to-rest ratios are operationally relevant and need to be investigated.

The modafinil results presented here compare favourably with those of Lagarde and Batejat (1994) despite differences in sample size, drug administration and testing frequency. In their study, 8 military subjects were given 200 mg of modafinil 3 times a day throughout 60 h of sleep deprivation. Compared to the placebo condition (where subjects served as their own controls), modafinil maintained performance until the 44th hour of sleep loss and thereafter declined toward placebo levels. Although performance was measured only once every 12 h, circadian differences were observed at 03.00 hours. In our study, performance declined to placebo

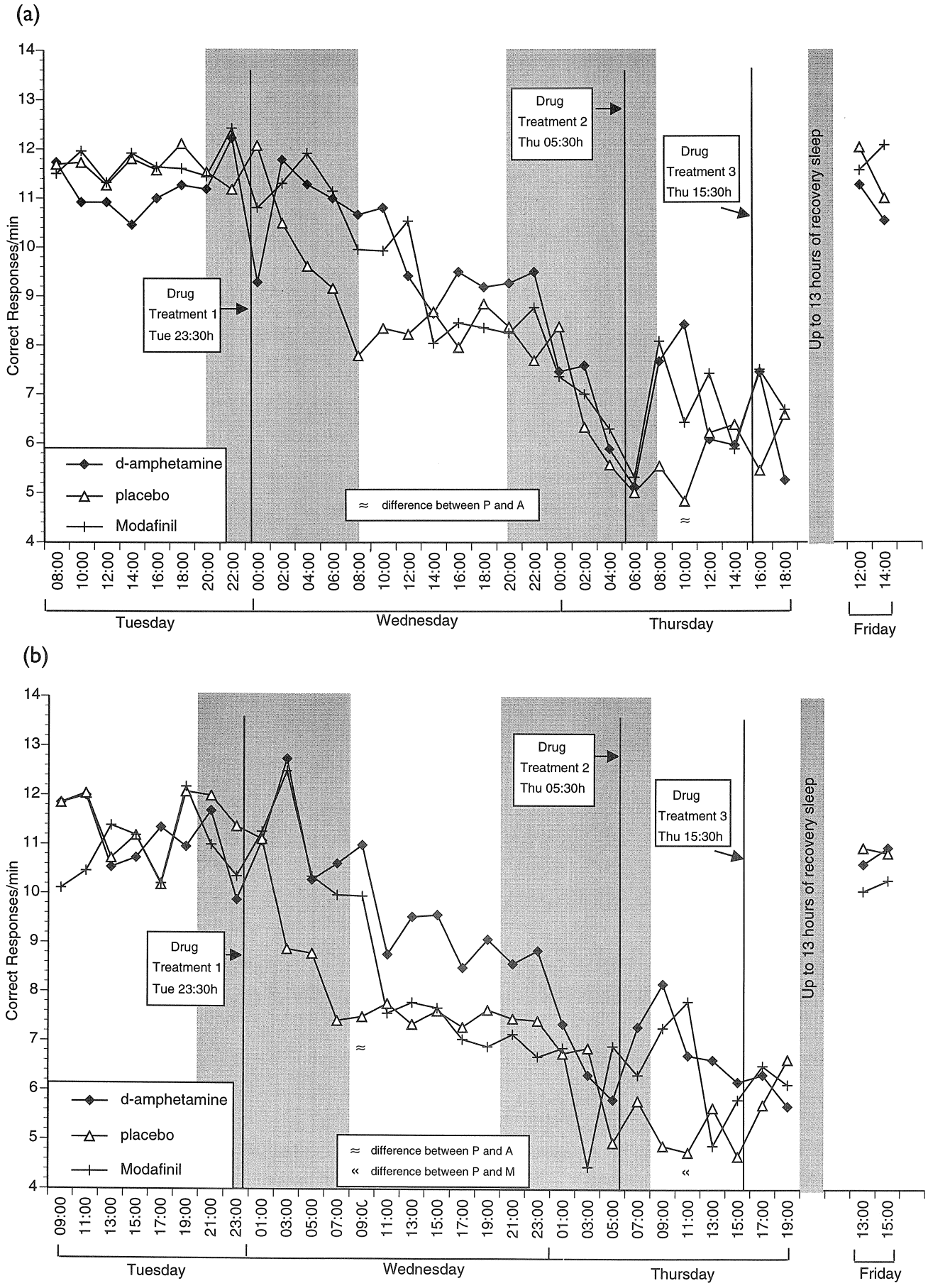

Figure 8. Mean no. of correct responses per minute for hourly trials of the logical reasoning task occurring (a) immediately after a break, and (b) 1 hour into a session. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

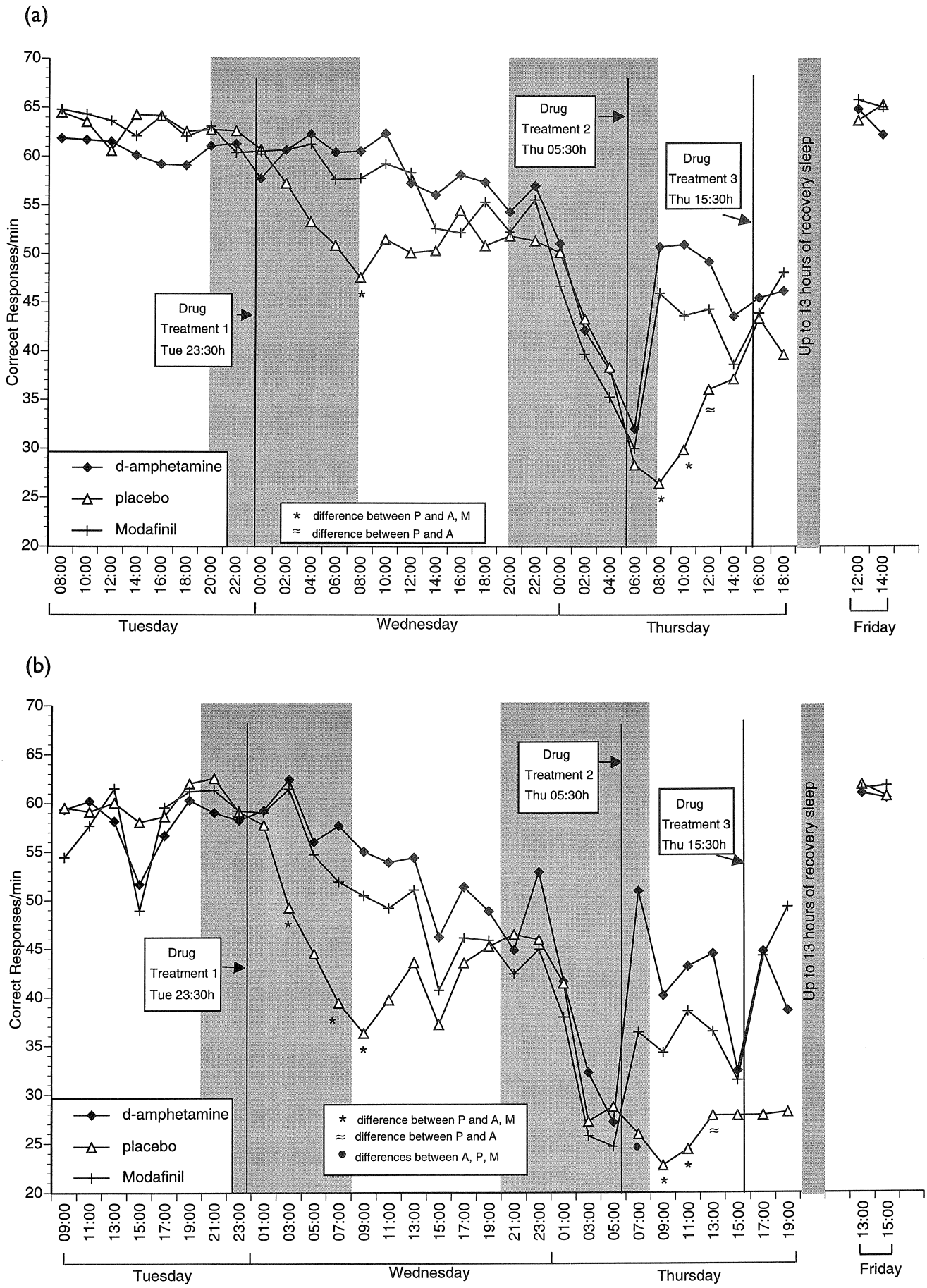

Figure 9. Mean number of correct responses per minute for hourly trials of the serial reaction time task occurring (a) immediately after a break, and (b) 1 hour into a session. Newman–Keuls ($P < 0.05$) comparisons performed on values up to 10 h after drug treatments 1 and 2.

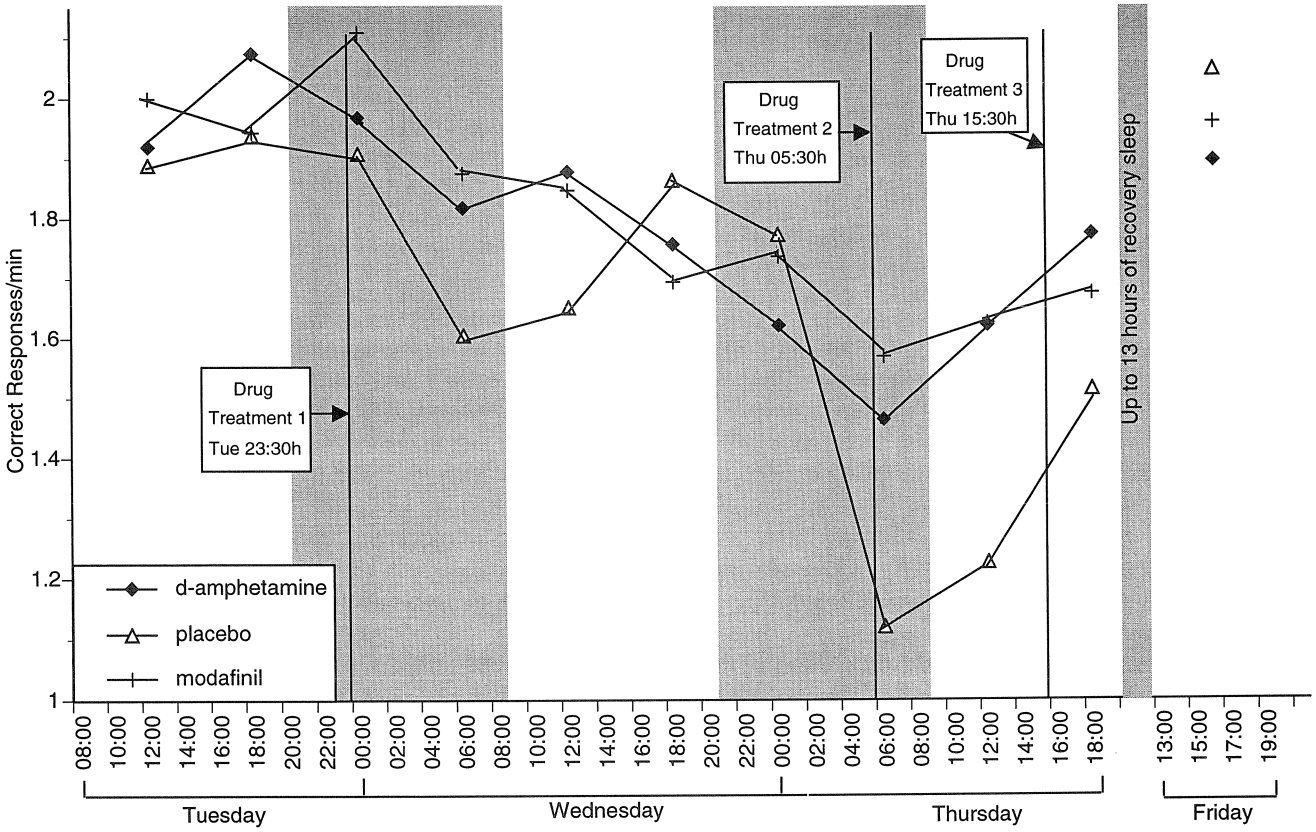

Figure 10. Mean number of correct responses per minute for trials of the short-term memory task taken every six hours.

levels after 48 h, but 300 mg of modafinil (at Hour 48) improved performance to levels observed 24 h before – but not back to baseline levels.

Lagarde and Batejat (1994) reported neither core nor oral temperatures in their paper. Bourdon *et al.* (1994), in a thermoregulation study, found that modafinil subjects had lower rectal temperatures compared to placebos during 3 h of 10°C cold exposure. From these findings they cautioned that 'modafinil could be detrimental by decreasing the

Table 2 Correlations squared (×100) for each task on the results presented in Figs 4–10 between pairs of drug conditions.

	Placebo with amphetamine (%)	*Placebo with modafinil* (%)	*Amphetamine with modafinil* (%)
Positive mode	23.63	31.05	56.25
Negative mood	40.34	52.33	61.86
Fatigue score	22.14	24.42	74.55
Stanford Sleepiness Scale	23.28	45.7	67.42
Short-term Memory	62.69	58.43	73.81
Logical reasoning task	66.18	72.66	79.67
Serial reaction time	62.81	74.1	87.37

Table 3 Subjects' responses (during debrief) to the question: 'For each of the three times you were given a drug to take, which drug do you think you received?' Results are summarized for each of the drug conditions. If subjects could not decide between two responses (e.g. 'I got either modafinil or amphetamine') 0.5 was scored for each category (e.g. 0.5 for modafinil and 0.5 for amphetamine).

Which Drug?	*1st*	*2nd*	*3rd*	*Total*
Amphetamine group				
Amphetamine	8	6.5	6.5	21
Modafinil	3	4.5	4.5	12
Placebo	2	2	2	6
Dont't know	0	0	0	0
Total	13	13	13	39
Placebo group				
Amphetamine	3.5	2.5	1.5	7.5
Modafinil	0.5	2.5	3.5	6.5
Placebo	8	6	5	19
Dont't know	1	2	3	0
Total	13	13	13	39
Modafinil group				
Amphetamine	7	2	2	11
Modafinil	3	7.5	6	16.5
Placebo	3	3.5	5	11.5
Dont't know	1	1	1	3
Total	14	14	14	42

Table 4 Total no. of symptoms reported (during debrief) for each drug conditions. Four notable symptoms are also presented.

Symptoms	*Amphetamine*	*Modafinil*	*Placebo*
Frequency of urination	1	13	3
Hallucinations	19	16	14
Changes in lighting	18	0	0
Headaches	5	8	4
Total symptoms reported	189 (45%)	147 (35%)	82 (20%)

metabolic heat production' (p. 1003) if taken to combat fatigue during the night when body temperatures naturally decline. The present authors' results do not support this claim. Compared to the placebo group, modafinil inhibited rather than promoted the decline in body temperature during the first night without sleep. In fact, modafinil responded much like amphetamine with respect to core temperature (Newhouse *et al.* 1989); it raised body temperature after both drug administrations.

During the debrief, 53% of the subjects who actually received amphetamine responded that they thought they had been given amphetamine. Similarly, a large portion (49%) of the placebo group felt that they had not received any drug. Subjects in the modafinil group, however, were much more equivocal about their estimates: 26% amphetamine, 39% modafinil, 27% placebo and 7% did not know. These results are consistent with anecdotal comments made by the subjects during the study. Those given amphetamine often reported positive affect 2 h after drug administration—e.g. 'feeling great', 'what a kick'; placebo subjects on the other hand were often sullen; while modafinil subjects were neutral in their comments—'fine', 'feel ok', 'no problem'. The affective difference that best described the two drug conditions was that amphetamine subjects experienced heightened arousal whereas the modafinil subjects simply felt less fatigued. This conclusion agrees with that made by Warot *et al.* (1993) in their study comparing amphetamine (15 mg), modafinil (300 mg), caffeine (300 mg) and placebo for 8 h after a single dose administration taken at 09.00 hours. Based on results from the Visual Analog Scales they found that 'modafinil was significantly different from amphetamine on many items ('relaxed', 'drowsy', 'alert', 'energetic', 'happy', 'sad', and 'depressed') suggesting that modafinil does not induce well-being and euphoriant effects at the dose studied' (p. 206). It should be cautioned however, that the anecdotal differences in effect that we report between modafinil and amphetamine occurred only during the debrief; affective differences between modafinil and amphetamine were not observed in the hourly mood, fatigue and sleepiness results. This inconsistency between the present results and those of Warot *et al.* (op. cit.) may be due to the fact that their subjects neither worked continuously nor were sleep deprived. To the sleep-deprived modafinil subjects in our study, the experience of 'not feeling tired' may have been as positive as the experience of 'feeling great' reported by amphetamine group. Another possible explanation is that the Visual Analog Scales is a psychometrically more sensitive test than either the fatigue checklist or the mood scale used in our study.

Unlike Warot *et al.* only a marginally higher incidence of headaches was observed for the modafinil group in this study. The only side-effect of note for modafinil was the reported increase in frequency of urination. Subjects in the amphetamine condition reported the highest number of symptoms overall (45%) with marginally more reported hallucinations and markedly more experiences in changes of lighting. Modafinil subjects reported 35% of the total number of symptoms and the placebo group 20%. From these results, modafinil elicits fewer side-effects than amphetamine, though more than the placebo condition. However, given the subjective nature of these data, the putative safety of modafinil should be interpreted cautiously.

In conclusion, modafinil appears to be as effective as amphetamine in maintaining mood and cognitive performance during the first night without sleep, and partially recovering mood and performance after 48 h without sleep. Although research must be performed to study the long-term effects of modafinil on normal subjects, long-term clinical studies on narcoleptics suggests that modafinil does not induce tolerance or drug dependence, nor does it have severe side-effects (Bastuji and Jouvet 1988; Billiard 1988). The present results, as well as those reported in our companion paper on recovery sleep, suggest that modafinil may be an attractive alternative to amphetamine for maintaining or recovering performance during periods of continuous work and sleep loss.

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