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MODAFINIL, AMPHETAMINE AND PLACEBO AS ALERTING SUBSTANCES FOR SUSTAINED OPERATIONS

by

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1. INTRODUCTION

Fatigue due to sleep loss is a significant operational concern among all military forces. Neville *et. al.* (1994), for example, 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. Soldiers, particularly the commander and the maintenance personnel of a U.S. National Guard attack helicopter battalion, accrued a significant sleep debt during an annual training exercise because the sleep they received was often fragmented and intermittent (Caldwell *et al.* 1992). During an intensive 9 day Somolia re-deployment operation where numerous time zones were crossed and long working hours were logged, a Canadian CC-130 crew slept on the average only 4 hours each 24 h period (Pigeau, unpublished data). Similarly, a battery of gunners during a division level field exercise (RV'81) managed only 14-16 hours of sleep over a four day period (Angus *et al.*, 1992).

Of course fatigue due to sleep loss is not unique to the military environment. In a report for the National Commission of Sleep Disorders Research, Leger (1994) estimated that the total cost of civilian 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. Also 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.

However, the unique and often extreme conditions under which military personnel must operate greatly exacerbates problems due to fatigue — to the point where pharmacological treatments are prescribed and used. Temazepam, for example, a hypnotic for inducing sleep, was used extensively by the Royal Air Force during the Falklands campaign (Nicholson, 1984). Both Seconal and Dexedrine ('No-go' and 'go' medication respectively) was used by U.S. airman during the Libyan Air Strike in 1986 (Senechal, 1988). Dextro-amphetamine was used by almost two thirds of U.S. fighter pilots throughout both Desert Shield and Desert Storm (Emonson *et al.*, 1995; Atkinson, 1993).

The present paper describes an experiment that investigated the maintenance and recuperative effects on cognitive performance of a new alerting substance called modafinil against dextro-amphetamine and placebo during 64 hrs of sleep loss. Modafinil (diphenylmethyl-sulfinyl-2 acetamide) is a substance that is considered safer than amphetamine with fewer side effects (Lafon, 1994). It appears to produce no feelings of euphoria, does not seem to be addicting, induces no drug tolerance and in large dosages (>4500 mg) does not produce serious medical problems (Lyons and French, 1991). These features make modafinil a good candidate to reduce or ameliorate the effects of prolonged sleep loss, particularly in military operations (Hughes, 1991). The validity of these claims, however, is in question due to the very few number of controlled studies using normal adult subjects. Presently, use of modafinil in Canada is limited to scientific and/or clinical investigations.

2. METHOD

2.1. Subjects

Forty-one Canadian Forces reservists (19 - 47 years 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: (1) were healthy, (2) were medication free for 3 weeks prior to the experiment, (3) were not pregnant, (4) had no history of substance abuse, (5) did not suffer from migraine headaches, and (6) 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. Female subjects were required to take a serum beta HCG pregnancy test. 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 hours of the sleep loss period because of a headache.

2.2. Experimental Facility

The experiment was run in a self-contained, windowless facility with subject rooms, kitchen, washrooms, relaxation areas and control rooms (see Figure 1). The subjects worked independently in 3 x 4m 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.

2.3 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. During the first day in the laboratory subjects completed personality inventories and extensively trained on the battery of 30 cognitive tasks and questionnaires to be used in the experiment (see Fig. 1 for a graphical representation of the week long experimental protocol).

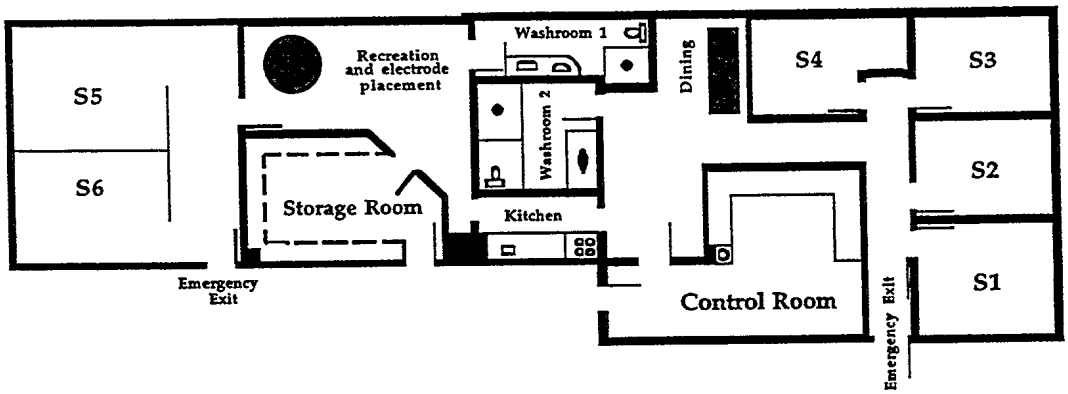

Figure 1: Diagram of windowless experimental facility. S1 - S6 are subject rooms. Subjects lived and worked in facility for 6 days without time cues.

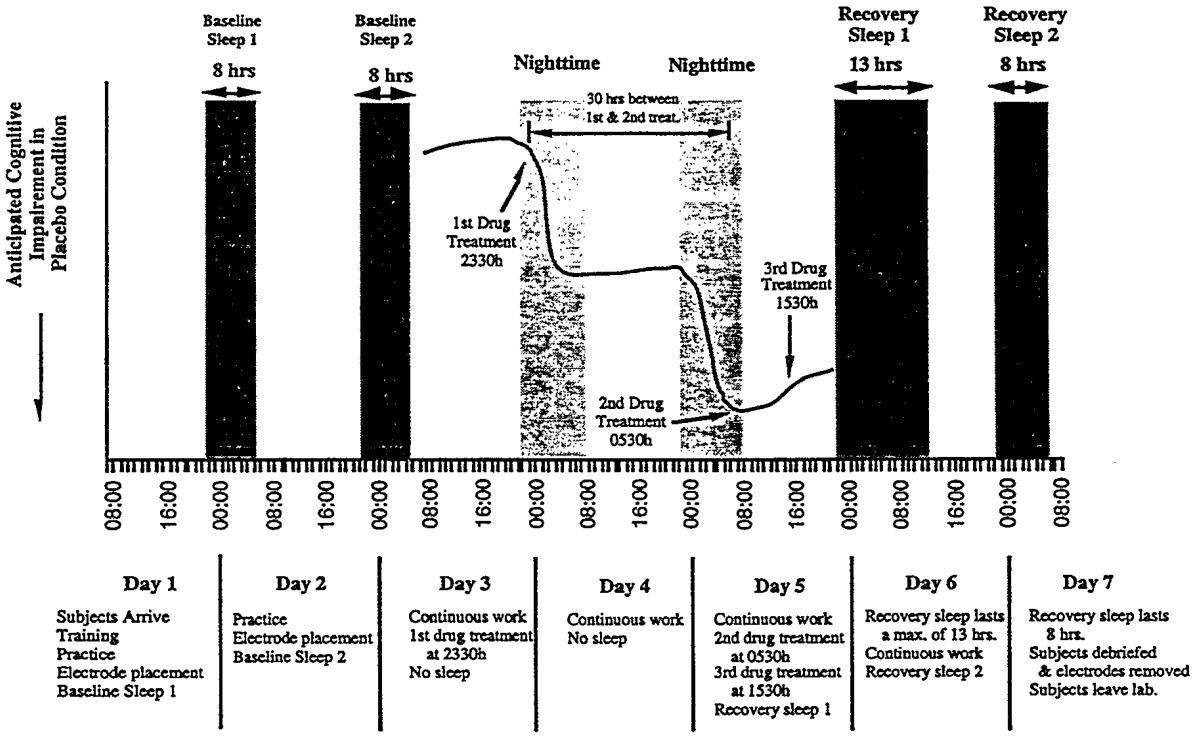

Figure 2: Experimental protocol

Prior to an 8 hour 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 h of the second day, the subjects were awakened, had their electrodes 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 hours of baseline sleep. At 06:00 h of the third day, the subjects were awakened, had their electrodes checked (but kept on) and began 64 hours of sleep deprivation with continuous cognitive work.

The subjects worked continuously in 1.75 hr 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 h 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. The second drug treatment occurred 30 hours later at 05:30 h of the second night without sleep. The third treatment followed 10 hrs later at 15:30 h. Throughout the entire experiment, administration of drugs followed double blind procedures.

On the evening of the fifth day in the laboratory, at 22:00 h, the subjects were allowed a maximum of 13 hours of recovery sleep after which they were awakened and performed the cognitive tasks and subjective questionnaires until 20:00 h that evening. A second recovery night's sleep of 8 hours was allowed on the sixth day, beginning at 22:00 h. 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.

3. RESULTS and DISCUSSION

The following is a summary of the results reported in Pigeau *et al.* (in press) and Buguet *et al.* (in press). The placebo group in this experiment replicated findings from previous

(non drug) sleep loss studies involving continuous work (Angus and Heslegrave, 1985; Heslegrave and Angus, 1985). Although modulated by the circadian cycle, performance on the two cognitive tasks degraded consistently as a function of sleep loss. See Figure 3 for a representative example of some of the data from this study (although these are questionnaire data, results from the cognitive tasks reported in Pigeau *et al.* (in press) show almost identical trends). 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 hours and a 55-65% percent decrease after 48 hours without sleep. In contrast, both the amphetamine and modafinil groups experienced only a 5-10% decline in cognitive performance after the first 24 hours of sleep loss (10 hours after drug ingestion). Although both groups showed performance declines comparable to the placebo group after 48 hours (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 hours post drug administration for either the first or second drug treatment.

On the morning of the last day of the experiment, a detailed debrief was carried out with all subjects. In a group, each subject responded to the following questions: 1) for each time you were given a drug, which drug do you believe you received? and 2) for each time you were given a drug, did you notice any effects? (if yes, what were they?). 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

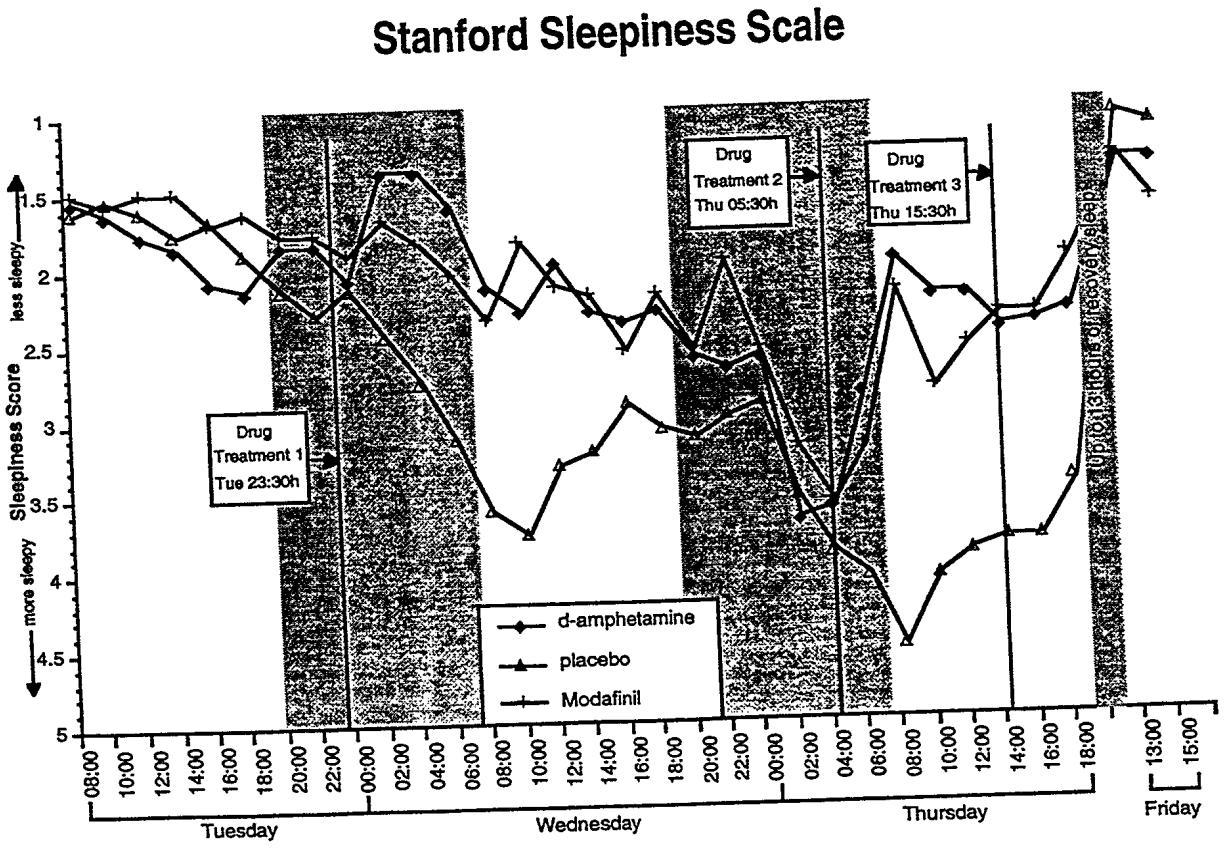

Figure 3: Stanford sleepiness scale for trials taken immediately after the 15 min break.

with anecdotal comments made by the subjects during the study. Those given amphetamine often reported positive affect 2 hours 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. However, given the subjective nature of these data, the putative safety of modafinil should be interpreted cautiously.

Recall that the third drug treatment was included to assess the effect that each drug condition would have on recovery sleep. As expected, the placebo group demonstrated slow wave sleep (SWS) and REM rebounds during the first night of recovery. SWS rebound occurred mainly during the first half of the night, while the REM rebound was distributed evenly across REM sleep episodes. Recovery sleep for the amphetamine group increased sleep latency and intrasleep wakefulness, decreased total sleep time and sleep efficiency and decreased REM sleep with a longer REM sleep latency. In fact, REM sleep rebound continued into the second night of recovery sleep. The modafinil group on the other hand, exhibited decreased time in bed and asleep suggesting a lesser requirement for recovery sleep than the other two groups. REM sleep rebound was limited to the first REM sleep episode and there were fewer disturbances than the amphetamine group during the first recovery night.

4. Further Findings

As mentioned in the procedure section (2.3), a battery of over 30 questionnaires and cognitive tasks was given to the subjects during the experiment (too many to be reported and discussed in Pigeau *et al.* ,1995). Data were collected on tasks covering a wide spectrum of cognitive capability, from simple reaction time to group problem solving. The proceedings from this conference (i.e., International Military Testing Association, 1995) contain papers from five other authors who have contributed to our understanding of the results from this experiment. These authors are: J. Baranski; C. McCann & T. Pointing; Y. Shek & R, Pigeau; M. Taylor; and M. Thompson & J.Baranski. What follows is a brief summary of their results.

Shek & Pigeau present results from an index of subjective workload (NASA TLX) as well as a physiological index of stress/arousal — i.e., salivary cortisol. Although the workload index did not differentiate among the drug conditions nor did it vary as a function of sleep loss, cortisol levels showed clear circadian fluctuations, with the amphetamine group displaying the highest levels. If cortisol is an indicator of higher organismic arousal, then these results are consistent with the anecdotal results summarized earlier in this paper where ampetamine subjects reported positive affect after drug ingestion.

The street name for amphetamine is 'speed' and it produces a generalized response that is accompanied by feelings of positive affect and euphoria (eg., 'what a kick', 'rocket fuel'). Does this increase in arousal manifest itself in improved performance on sensory-motor tasks? Although amphetamine and modafinil were equally effective in maintaining and recuperating performance on the serial reaction time task, Taylor reports better performance for the amphetamine group (over modafinil) on a pursuit and compensatory tracking task. After the first drug treatment the amphetamine group showed increased "insistence on precision" (i.e., effort expended to be precise rather than effort expended to predict the trajectories) compared to the modafinil group who maintained their "insistence" and the placebos who decreased it. Baranski should a similar effect in the comparison task.

As one ascends the cognitive continuum, where demands on higher psychological functions become greater, do the effects of sleep loss become more pronounced or are they somehow more more resistent to the effects of fatigue? The papers by McCann & Pointing and Thompson & Baranski provide evidence that a generalized sleep loss effect still occurs for such higher level tasks but that the ameliorating influence of amphetamine and modafinil is less effective. In a 10 min planning task patterned on an ammunition dumping problem, McCann & Pointing found that sleep loss degrades 1) the time taken for submitting a subject's first plan and 2) the number of attempts a fatigued subject is willing to make to improve his plan. Although effects due to drug conditions were observed, they were quite pronounced after the first drug treatment but only suggestive after the second.

Thompson & Baranski, on the other hand, found that group decision making — where subjects interacted with each other to arrive at consensus judgements — was not affected by the drug manipulation at all, even though all groups demonstrated declines in individual and group performance. It is unclear whether these reduced drug effects for higher cognitive tasks are due to the inherent difficulty in finding sensitive and reliable dependent measures (i.e., the effect may exist but our measures are unable to detect them) or whether these tasks are inherently more interesting (i.e., less boring) to the subjects and hence increase arousal levels and mask the effect.

All of the results discussed thus far have found that modafinil is as effective as amphetamine for alleviating performance declines due to sleep loss (except for Taylor's result where amphetamine was slightly better than modafinil for some aspects of the tracking task). Given it's benign psycho-pharmacological properties, modafinil seems to be an excellent alternative to amphetamine. There is one caveat to this conclusion, however. Baranski provides evidence that modafinil may actually have a negative effect on performance. Self-monitoring behaviour, where subjects were asked to assess their accuracy on both a perceptual comparison task and a mental addition task, showed clear over-confidence judgements with the modafinil group 2 hours after drug ingestion, whereas the judgements for both the amphetamine and the placebo groups remained constant throughout the sleep deprivation period. This finding may have repercussions for military personnel in positions of responsibility who, if under the influence of modafinil, may be more confident about their decisions than they might otherwise be.

Overall, the general finding from this study is that modafinil seems to be a good (and safer) alternative to amphetamine for reducing the effects of sleep loss on cognitive performance.

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